PIMAVANSERIN FOR THE TREATMENT OF HALLUCINATIONS AND DELUSIONS ASSOCIATED WITH ALZHEIMER'S DISEASE PSYCHOSIS

SPONSOR BRIEFING DOCUMENT

ACADIA PHARMACEUTICALS INC.

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
5-HT_{2A} receptor	5-hydroxytryptamine (serotonin) receptor subtype 2A
Acadia	Acadia Pharmaceuticals Inc.
AD	Alzheimer's disease
AD pool	Alzheimer's disease parallel group, placebo-controlled pool
ADP	Alzheimer's disease psychosis
AE	adverse event
AUC	area under the concentration-time curve
CGI-I	Clinical Global Impression–Improvement
CI	confidence interval
C_{max}	maximum (peak) observed drug concentration
CRL	complete response letter
CSR	clinical study report
DB	double-blind
DLB	dementia with Lewy bodies
DRP	dementia-related psychosis
DSMB	data and safety monitoring board
EPS	extrapyramidal symptoms
E-R	exposure-response
ESRS-A	Extrapyramidal Symptoms Rating Scale–Abbreviated
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTD	frontotemporal dementia
HR	hazard ratio
IA	interim analysis
IRR	incidence rate ratio
MMSE	Mini-Mental State Examination
NDD	neurodegenerative disease
NDD pool	Neurodegenerative disease parallel group, placebo-controlled pool
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association
NNT	number needed to treat
NPI-NH PS	Neuropsychiatric Inventory–Nursing Home Version Psychosis Score
OL	open-label
PD	Parkinson's disease

Term	Definition
PDD	Parkinson's disease dementia
PDP	Parkinson's disease psychosis
PG	parallel-group
PMC	postmarketing commitment
PY	person-years
QD	once daily
QT interval	QT interval on ECG
QTcF	corrected QT interval using Fridericia's correction method
SAPS-H+D	Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (20-item)
SAPS-PD	Scale for the Assessment of Positive Symptoms in Parkinson's disease
SE	standard error
sNDA	supplemental new drug application
TEAE	treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
UTI	urinary tract infection
VaD	vascular dementia

1 EXECUTIVE SUMMARY

1.1 Introduction

In April 2016, pimavanserin was approved by the United States (US) Food and Drug Administration (FDA) under the tradename NUPLAZID® for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). Unlike available multi-receptor acting antipsychotic drugs, that primarily act via dopamine receptor blockade, pimavanserin selectively targets serotonergic 5-HT_{2A} receptors as an inverse agonist/antagonist. The FDA designated pimavanserin a Breakthrough Therapy Drug based on clinical study data demonstrating that pimavanserin 34 mg once daily (QD) treatment improved psychosis symptoms without adversely impacting motor function (a core feature of Parkinson's disease [PD]), addressing a medical need in patients with PDP that was not met by available antipsychotic drugs used "off-label".

Acadia Pharmaceutical Inc. (Acadia) is now seeking approval for pimavanserin 34 mg QD in the closely-related condition of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP).

To support pimavanserin's effectiveness for the newly proposed treatment of ADP indication, Acadia will present clinical study data from three independent placebo-controlled clinical studies:

- A positive study in patients with ADP, ACP-103-019 (Study 019), in which pimavanserin 34 mg QD demonstrated on the primary efficacy endpoint statistically significant and clinically meaningful improvement in psychosis symptoms as compared to placebo,
- Confirmatory evidence of effectiveness from a positive study in patients with PDP, ACP-103-020 (Study 020), in which pimavanserin 34 mg QD demonstrated on the primary efficacy endpoint statistically significant and clinically meaningful improvement in psychosis symptoms as compared to placebo. Study 020 was a pivotal study that supported the approval of pimavanserin for the treatment of PDP, and the pimavanserin treatment effect in ADP patients will be evidenced in the presented clinical study data as being consistent with that observed in ADP patients.
- Supportive evidence of efficacy from a positive randomized withdrawal study in patients with dementia-related psychosis (DRP), ACP-103-045 (Study 045) in which patients with DRP showed a statistically significant reduction of risk of psychosis relapse. Patients with ADP were the largest dementia subgroup evaluated (66% of all patients) and showed consistent and clinically meaningful reduction of risk of

psychosis relapse. Parkinson's disease patients *with dementia* and psychosis (PDD) were the second largest dementia subgroup evaluated in Study 045 and showed robust reduction of risk of psychosis relapse.

Taken together, these clinical study data support the addition of the proposed treatment of the ADP indication to the NUPLAZID label and constitute substantial evidence of effectiveness consistent with the FDA regulatory guidance '*Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (*draft; 2019*)'. Specifically, the guidance states that one adequate and well-controlled clinical study on a new indication for an approved drug, supported by existing adequate and well-controlled clinical study(ies) that demonstrated the effectiveness of the drug for its other, closely related approved indication(s), can establish effectiveness. In this case, Study 019 demonstrated pimavanserin reduced psychosis symptoms in patients with ADP. Study 020 demonstrated pimavanserin reduced psychosis symptoms in patients with PDP, was the basis of the FDA approval of this closely-related indication, and serves to provide confirmatory evidence of effectiveness. This evidence is further supported by a positive randomized withdrawal study (Study 045) in DRP patients, that included patients with ADP (the largest dementia subgroup evaluated), that demonstrated a consistent and clinically meaningful reduction of risk of psychosis relapse and also had the benefit of evidencing maintenance of pimavanserin's efficacy in the context of the two studies that had already demonstrated improvement of psychosis symptoms.

Historical Context Between Approval for PDP and the Proposed ADP Indication

Shortly after the approval of pimavanserin for the treatment of PDP in April 2016, positive Study 019 efficacy results in patients with ADP became available. Similar to the profile that was the basis of the Breakthrough Therapy Designation for PDP, the demonstrated improvement of psychosis in patients with ADP was not associated with an adverse impact on cognition, a core feature of Alzheimer's disease (AD). With positive study results in both patients with PDP (Study 020) and patients with ADP (Study 019), at an End of Phase 2 meeting, Acadia discussed with the FDA and aligned on a development plan to support a broad indication for pimavanserin for the treatment of DRP. Study 045 had the goal of demonstrating pimavanserin's efficacy for treating psychosis in this broad DRP indication regardless of the underlying dementia diagnosis. As acute response for improving psychosis symptoms had already been demonstrated in Studies 020 and 019, the randomized withdrawal Study 045 design had the benefits of (1) mimicking the way in which patients with DRP were treated in the "real world", (2) limiting the duration of potentially ineffective (and placebo) therapy, and (3) being a recognized design to establish maintenance of efficacy. The primary endpoint would evaluate risk of relapse in the overall DRP patient population, but the percentage of patients included among the various dementia subgroups would be

targeted to be representative of the epidemiological norm and labeling would describe the dementia subgroup representation (some of these dementia subgroups being relatively rare in occurrence). The study was not designed nor powered to show statistical significance in individual dementia subgroups.

FDA subsequently designated pimavanserin as a Breakthrough Therapy Drug for the treatment of DRP.

Upon a positive prespecified interim efficacy analysis (IA) in Study 045, Acadia reviewed the results with FDA at a pre-sNDA meeting and then submitted an sNDA for the proposed indication for the treatment of DRP.

In April 2021 FDA issued a Complete Response Letter (CRL) indicating that, due to concerns regarding a potential differential pimavanserin treatment effect among the dementia subgroups in Study 045, the FDA considered that the broad indication for the treatment of DRP was not supported. Although Study 045 was not designed nor powered to evaluate the risk of relapse in individual dementia subgroups, some of which were composed of small numbers of patients, a lack of statistical separation in the other dementia subgroups and a particularly robust treatment effect in the PDD subgroup was noted. Concerns regarding the design and conduct of Study 019 were also raised.

As part of recent, successive post-CRL meetings with the FDA, Acadia presented sensitivity analyses for Study 019 that confirmed the primary endpoint conclusions. Acadia also conducted new analyses for Study 045 and presented data that both supported a consistent and clinically meaningful pimavanserin treatment effect across the dementia subgroups, including in patients with ADP, as well as explained potential confounding factors leading to enhanced results observed in the PDD subgroup. Accordingly, the FDA expressed a readiness to review a resubmission in support of a proposed indication for pimavanserin for the treatment of ADP.

This resubmission provides a complete response to the deficiencies outlined in the FDA's CRL to Acadia's efficacy supplements of the new drug applications (sNDA) 210793 (NUPLAZID capsules) and 207318 (NUPLAZID tablets) that were originally intended to support a proposed treatment of DRP indication.

In regard to safety and tolerability, the clinical study program evaluating pimavanserin treatment in frail, elderly patients with neurodegenerative disease (NDD) (1683 patients with NDD exposed to pimavanserin as of 08 September 2021), including patients with ADP, has expanded significantly since the original approval for the treatment of PDP.

The safety profile in NDD patients is well-characterized and favorable, and consistent with patients with ADP and PDP. Importantly, the pimavanserin clinical study safety data demonstrate a lack of negative effect on cognition and motor function. Postmarketing experience of NUPLAZID treatment over the 6 years since its approval includes >40,000 patients. Due to PDP diagnosis eligibility requirements and payer restrictions, postmarketing experience with NUPLAZID consists almost exclusively of PDP patients. This experience further supports a favorable safety profile in a frail, elderly, patient population. This profile is differentiated from available antipsychotics currently used off-label which have not demonstrated efficacy for reduction of symptoms *or* risk of relapse *and* are associated with the risk of serious potential safety issues, including negative impacts on cognition and motor function.

The totality of efficacy and safety data supports a positive benefit-risk profile of pimavanserin 34 mg QD for the proposed indication for the treatment of hallucinations and delusions associated with ADP, the same dose and regimen as that which was FDA-approved for the closely-related indication for the treatment of PDP.

Product Description

Pimavanserin was approved in the US in 2016 under the tradename NUPLAZID for the treatment of hallucinations and delusions associated with PDP.

The recommended dose of NUPLAZID for the treatment of PDP is 34 mg QD, given orally.

NUPLAZID is currently available as a 34 mg capsule and a 10 mg tablet (for coadministration with strong cytochrome P450 3A4 enzyme [CYP3A4] inhibitors).

Proposed Indication

The proposed new indication for pimavanserin is for the treatment of hallucinations and delusions associated with ADP.

The recommended dose and regimen for the treatment of ADP is identical to that which is approved for NUPLAZID for the treatment of PDP: 34 mg QD.

Mechanism of Action

Pimavanserin is a selective serotonin receptor inverse agonist and antagonist at the 5-hydroxytryptamine (serotonin) receptor subtype 2A (5-HT_{2A}) receptors, and to a lesser extent, at 5-HT_{2C} receptors. Pimavanserin had no appreciable binding at over 70 other receptor targets (Hacksell et al. 2014; data on file). Specifically, in contrast to multi-receptor acting antipsychotics, pimavanserin does not exhibit measurable in vitro binding to dopaminergic, histaminergic, adrenergic, or muscarinic receptors.

1.2 Brief Overview of Regulatory History

In 2016, NUPLAZID (pimavanserin) 34 mg QD was approved on a priority basis in the US as a Breakthrough Therapy for the treatment of hallucinations and delusions associated with PDP. NUPLAZID 34 mg QD treatment demonstrated a statistically significant and clinically meaningful reduction in the severity and frequency of psychosis symptoms compared to placebo, without negatively impacting motor function (Mathis et al. 2017). The demonstrated reduction of psychosis symptoms in PDP patients in the absence of any negative impact on motor function is considered to be related to pimavanserin's selective serotonergic 5-HT_{2A} receptor inverse agonist/antagonist activity, unlike other multi-receptor acting antipsychotic drugs that primarily block dopaminergic receptors.

Upon approval, there were multiple postmarketing commitments (PMCs), including commitments to conduct a randomized withdrawal study to evaluate maintenance of efficacy and a randomized, placebo-controlled study or studies with predominantly frail and elderly patients to assess safety that would involve exposure of at least 500 patients to pimavanserin 34 mg QD for a minimum of 8 weeks.

The commitment for a randomized withdrawal study was deemed fulfilled by FDA with the completion of Study 045. Acadia recently completed enrollment in a large, placebo-controlled study in elderly, frail patients with NDD (including AD), ACP-103-046 (Study 046), that in combination with two other studies that included patients with AD (Study 019 and Study ACP-103-032), is intended to fulfill the above-described PMC to assess safety.

At an End of Phase 2 meeting in May 2017, agreement was reached with the FDA on the design of Study 045, including the relapse criteria and a prespecified efficacy IA, and that the study would be acceptable as a single, adequate and well-controlled study to support the indication of DRP if the results from the study were clinically meaningful and statistically persuasive on the primary endpoint of relapse prevention in the broad DRP population studied. This was agreed upon in the context of efficacy and safety data from Study 019 (ADP) and Study 020 (PDP). A broad DRP study population was targeted consistent with scientific consensus that psychotic symptoms in dementia were being treated as a single, unified clinical and diagnostic entity across clinical dementia diagnoses subgroups (Brenowitz et al. 2017a; Brenowitz et al. 2017b; Beach and Malek-Ahmadi 2021). As agreed with the FDA, the study was powered to detect differences between pimavanserin and placebo across the broad DRP patient population, and thus the prespecified efficacy IA was triggered after 40 relapse events occurred; the study was not powered to detect differences for the different DRP dementia subgroups.

The design of Study 045 was intended to establish the maintenance of pimavanserin efficacy, as both Studies 019 and 020 had primary efficacy endpoints following 6 weeks of treatment duration, and also address the PMC for a randomized withdrawal study.

In October 2017, the FDA granted Breakthrough Therapy Designation to pimavanserin for the treatment of hallucinations and delusions associated with DRP, based on clinical evidence of substantial improvement with pimavanserin treatment as observed in two clinical studies that could be considered to evaluate important subgroups within the overall DRP patient population: Study 019 (ADP) and Study 020 (PDP). It should be noted that in Study 020, a cohort of 25% of the patients with PDP were mildly cognitively impaired (i.e., Mini-Mental State Examination [MMSE] score of 21-24).

Upon a robustly positive IA efficacy result on the primary endpoint in Study 045 in September 2019 and a subsequent March 2020 pre-sNDA meeting, in June 2020 Acadia submitted an sNDA to support pimavanserin for the treatment of DRP based upon efficacy data derived from Study 045 (DRP), Study 019 (ADP), and Study 020 (PDP). The safety dataset had expanded considerably from the original approval, including data from >3500 patients exposed to pimavanserin in clinical studies (>1500 patients with NDD), as well as NUPLAZID postmarketing safety data at that time from >30,000 patients with PDP.

In April 2021, the FDA issued a CRL to the sNDA for pimavanserin for the treatment of DRP. In the CRL, while acknowledging that the study was not designed nor statistically powered to evaluate efficacy within individual dementia subgroups, FDA pointed out that no statistical separation was observed from placebo in any dementia subgroup other than the PDD subgroup. This led FDA to question whether the effect of pimavanserin on the time to relapse in the PDD subgroup in Study 045 was driving the overall study result in patients with DRP, and further question if there was a differential response to pimavanserin across dementia subgroups. The FDA has stated that the results from Study 045 question whether the broad indication in DRP is a useful construct for pimavanserin. In the CRL, the FDA also raised concerns as to whether Study 019 in patients with ADP could be considered adequate and well-controlled because of certain study design features and observed protocol deviations.

Following a series of meetings with Acadia to align on a strategy to address the issues in the CRL, the FDA advised that they were prepared to review a resubmission based on new analyses from the both the positive study in patients with ADP (Study 019) and the positive study in patients with DRP (Study 045), based on data from the ADP subgroup, the largest dementia subgroup in the study.

On 4 February 2022, Acadia resubmitted the sNDA for pimavanserin for a new proposed indication for the treatment of the hallucinations and delusions associated with ADP.

FDA acknowledged the resubmission as a complete response on 4 March 2022 and assigned a targeted action date of 4 August 2022.

1.3 ADP Is a Serious, Unmet Need and Off-Label Treatment With Antipsychotics Has Serious Safety Risks

Approximately 5.5 million people in the US are diagnosed with AD, of whom approximately 1.7 million (30%) also experience symptoms of psychosis. The prevalence of dementia, including AD, is expected to grow as the population ages and diagnostic capabilities advance.

Serious consequences have been associated with persistent or severe psychosis in patients with dementia. Epidemiological studies have revealed that, on average, 41% of AD patient admissions reported psychosis, including delusions in 36% and hallucinations in 18% of patients (Ropacki and Jeste 2005). Neuropsychiatric symptoms are associated with a worse prognosis in dementia (Lyketsos et al. 2006), and clinically significant neuropsychiatric symptoms have been found to be predictive of earlier progression to nursing home care, severe dementia, and death (Peters et al. 2015; Rashid et al. 2020; Stern et al. 1997). The risk for outcomes like nursing home admission, progression to severe dementia, and death is approximately 1.5–2.0 times higher in dementia patients with psychosis than in those without psychosis (Peters et al. 2015; Rashid et al. 2020; Scarmeas et al. 2005).

Despite the severity of disease, there are no FDA-approved treatments indicated for the treatment of patients with ADP. In the absence of approved treatments and reflecting dire medical need, atypical and even some typical antipsychotics are used off-label to treat patients, despite clinical studies showing marginal or no clinical benefit in this condition accompanied by serious safety risks, including accelerating cognitive decline and new onset or worsening of extrapyramidal symptoms (EPS) (Schneider et al. 2006b). A study among elderly nursing home residents with dementia found that antipsychotic medications were taken by 32.9% of elderly patients with dementia (Kamble et al. 2009). Available antipsychotic drugs used off-label are multi-receptor acting (e.g., dopaminergic, muscarinic, histaminergic, and adrenergic) with predominant dopamine blocking properties. Such multi-receptor pharmacology carries significant “off-target” liabilities for this vulnerable patient population.

Vigen et al. (2011) reported the cognitive effects of treatment with an atypical antipsychotic in the National Institute of Mental Health CATIE-AD study. In this study, patients on any atypical antipsychotic had significantly greater rates of decline in cognitive function than patients receiving placebo, as measured by the MMSE (patients receiving any antipsychotic had an average decline 2.46 points greater on the MMSE than placebo patients). Similarly, a meta-analysis of randomized, placebo-controlled trials of relatively short durations

(approximately 10–12 weeks) with atypical antipsychotics in dementia conducted by Schneider et al. (2006a) showed a significant acceleration of cognitive decline in patients taking antipsychotics compared with patients taking placebo (weighted mean difference of 0.73 in favor of placebo). In a study of elderly patients with possible or probable AD dementia residing in United Kingdom care homes, agitation treated with quetiapine was associated with significant cognitive decline. Patients who received quetiapine experienced, on average, an estimated mean difference in change in severe impairment battery score from Baseline of -14.6 points compared with the placebo-treated group at six weeks (95% confidence interval [CI]: -25.3, -4.0; p=0.009), indicating a significantly greater deterioration in the quetiapine group (Ballard et al. 2005). This pronounced negative impact of currently used antipsychotics on cognitive function has been equated to approximately a doubling in the rate of cognitive decline associated with the natural history of the disease (Coupland et al. 2019; Gray et al. 2015; Nevalainen et al. 2015) (Papenberg et al. 2017). The dopamine blocking activity of antipsychotics has also been linked to the emergence or worsening of EPS, including tremors, dystonia, tardive dyskinesia, and parkinsonism (Kales et al. 2015). Additional adverse effects with these drugs include orthostatic hypotension, hematologic abnormalities, and metabolic, gastrointestinal, thromboembolic, and sedative effects. These toxicities contribute to an increased risk for falls (and associated fractures), infection, aspiration pneumonia, and other serious complications in this vulnerable population (Reynolds 2011; Ballard and Howard 2006; Mintzer et al. 2007). The majority of these risks are serious and are communicated to prescribers and patients as Warnings and Precautions in their approved labeling.

Particular concern related to off-label use of antipsychotics is related to increase in mortality risk. A large meta-analysis conducted by the FDA revealed that antipsychotic drugs carry a risk of increased mortality in elderly patients with DRP. This analysis included 17 placebo-controlled studies and found that, compared with patients treated with placebo, the risk of death was 1.6- to 1.7-times greater in patients with DRP treated with antipsychotics (FDA 2005). This meta-analysis resulted in a Boxed Warning in labeling for the antipsychotic drug class for increased risk of mortality in elderly patients with DRP. Similar findings were published in the meta-analysis by Schneider et al. (2005).

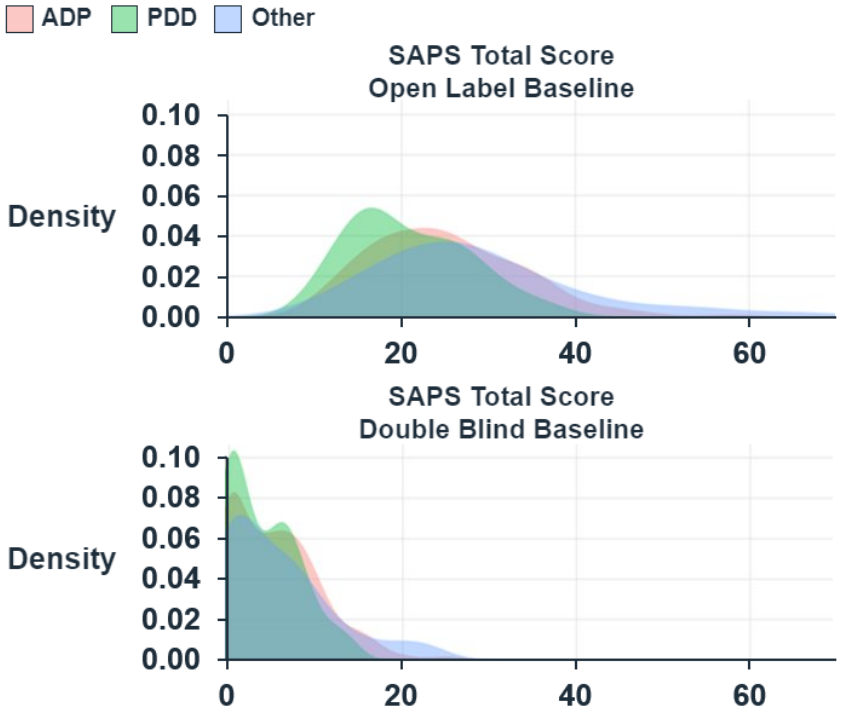
Given the serious consequences of ADP and lack of approved, effective, and safe treatment options, there is a significant unmet need for a therapeutic option with a positive benefit-risk profile. Patients need an effective treatment for their ADP that does not exacerbate the underlying condition or introduce significant safety liabilities.

1.4 Overview of Efficacy

The efficacy of pimavanserin for the treatment of patients with ADP was demonstrated in a positive, randomized, placebo-controlled study in patients with ADP, Study 019, with confirmatory evidence from a positive study (Study 020) in closely-related approved indication, PDP, and supportive evidence from an overall positive randomized withdrawal study in patients with DRP, Study 045.

Data from Studies 019 and 020 support common clinical presentations of psychosis and consistent treatment response across dementia subgroups supporting the closely related nature of the ADP and PDP conditions. Likewise, analyses of symptom distribution in Study 045 showed a similar pattern of psychotic symptoms across dementia subgroups, qualitatively and quantitatively, both pre- and post-treatment (open-label [OL] and double-blind [DB] Baselines, respectively), which is consistent with the consensus view that psychosis symptoms of dementia stem from common pathology across dementia subgroups (Figure 1–1).

Figure 1–1 Distribution of Total SAPS-H+D at OL and DB Baseline (ITT Analysis Set at IA) – Study 045



Source: Study 045 CSR Addendum Figure AH14.SAPS.Density

Abbreviations: ADP=Alzheimer's disease psychosis; CSR=clinical study report; DB=double-blind; DLB=dementia with Lewy bodies; FTD=frontotemporal dementia; IA=interim analysis; ITT=Intention-to-treat; OL=open-label; PDD=Parkinson's disease dementia; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations+Delusions; VaD=vascular dementia

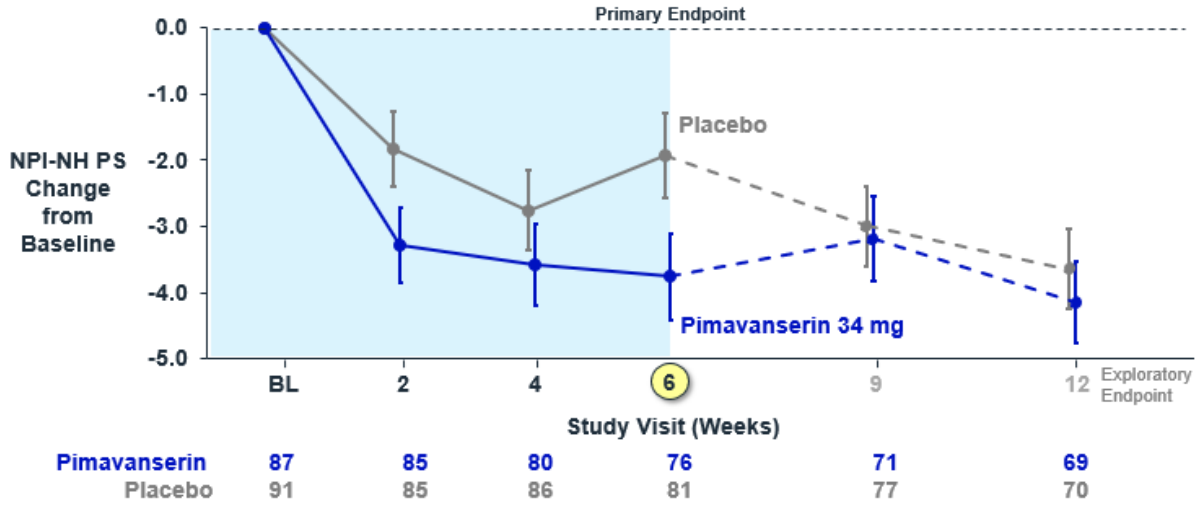
Note: Other included patients with a subgroup of VaD, DLB, or FTD.

Study 019 was a randomized, DB, placebo-controlled, parallel-group study in patients with possible or probable AD (N=181) conducted across 133 nursing care homes in the United Kingdom (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria). Patients had persistent psychotic symptoms despite receiving psychosocial therapy for psychosis and symptoms severe enough to warrant treatment with an antipsychotic agent. Patients were randomized 1:1 to pimavanserin 34 mg QD or placebo stratified by baseline MMSE total score (<6 and ≥6) and Neuropsychiatric Inventory–Nursing Home Version Psychosis Score (NPI-NH PS) (<12 and ≥12), and entered into a 12-week DB treatment period. The primary endpoint was change from Baseline to Week 6 (Day 43) in the NPI-NH PS. The final 6 weeks (Weeks 6-12) were included principally to assess the potential for adverse cognitive effects of pimavanserin treatment. Efficacy was assessed during that

6-12 week treatment period on an exploratory basis. Efficacy results could be summarized as follows:

- The primary endpoint of change from Baseline to NPI-NH PS at Week 6 showed statistically significantly greater reduction with the pimavanserin 34 mg treatment group versus placebo (p=0.045, effect size=0.32) (Figure 1–2). These results compare favorably to the off-label use of atypical antipsychotics where the efficacy has been observed to be marginal (effect size ≤0.2) (Ma et al. 2014; Tampi et al. 2016; Maher et al. 2011).

Figure 1–2 Change from Baseline Through Week 12 in NPI-NH PS (MMRM, OC, Full Analysis Set) – Study 019



Source: Study 019 CSR Figure 1.1

Abbreviations: CSR=clinical study report; MMRM=mixed-effect model repeated measures; NPI NH PS=Neuropsychiatric Inventory-Nursing Home Version Psychosis Score; OC=observed cases

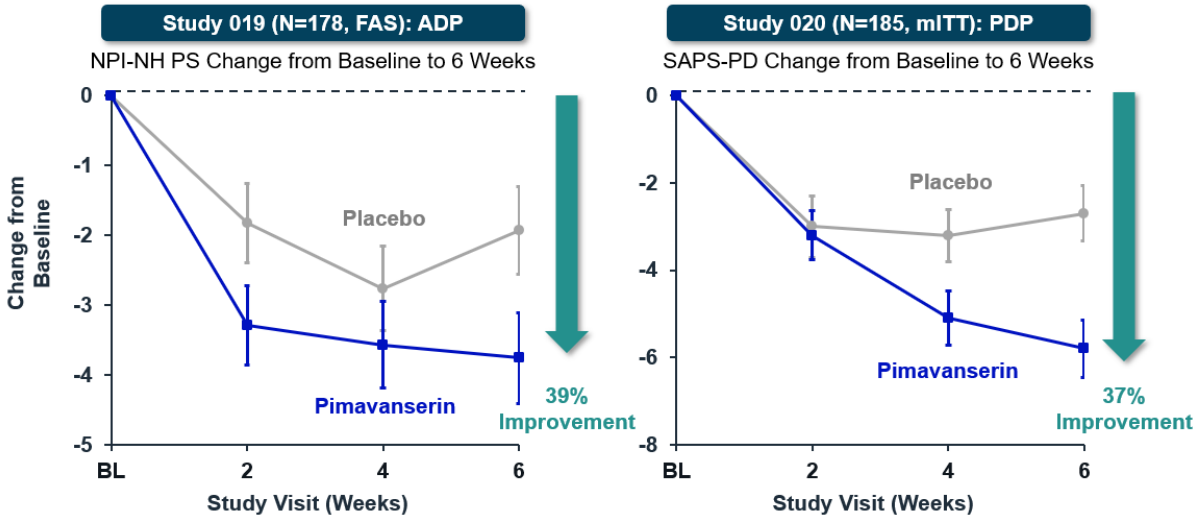
- In the prespecified subgroup of patients with more severe psychosis (i.e., NPI-NH PS ≥12 at Baseline), the magnitude of efficacy was larger (p=0.011, effect size=0.73), suggesting that a principle benefit in the study was seen in more severely psychotic patients in greatest need for pharmacologic therapy.
- In addition to the primary efficacy endpoint at Week 6, efficacy was assessed through 12 weeks as an exploratory endpoint. Small nominal differences and lack of statistical separation between pimavanserin and placebo at the Week 9 and Week 12 timepoints raised the question about durability of effect of pimavanserin. This observation suggested the need to properly evaluate the maintenance of efficacy with pimavanserin, which was affirmatively addressed in Study 045.

- A greater proportion of patients responded to pimavanserin versus placebo at Week 6 and achieved nominal statistical significance
    - 55.2% versus 37.4%, p=0.016; number needed to treat (NNT) (CI)=6 (4, 30) when response is defined as a ≥30% reduction, and
    - 50.6% versus 34.1%, p=0.024; NNT (CI)=7 (4, 46), when response is defined as a ≥50% reduction.
- More robust results were observed in the subgroup with more severe psychosis at Baseline (88.9% vs. 43.3%, p=<0.001; NNT [CI]=3 [2, 5] when response is defined as a ≥30% reduction and 77.8% vs. 43.3%, p=0.008; NNT [CI]=3 [2, 10], when response is defined as a ≥50% reduction).
- No statistical separation from placebo was observed on other secondary efficacy endpoints.

Study 020 was a randomized, DB, placebo-controlled, parallel group outpatient study in patients with PDP (N=199) and was the pivotal study leading to pimavanserin approval in the US for the treatment of PDP. Study 020 demonstrated the following:

- Statistically significant and clinically meaningful improvement was observed in the pimavanserin treatment group relative to placebo on the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD) primary endpoint at Week 6, with a least squares mean (LSM) difference (pimavanserin-placebo) of -3.06 (p=0.001, effect size=0.50)
- In the prespecified analysis of the subgroup of patients with mild cognitive impairment (MMSE score 21-24; ~25% of patients), the observed LSM difference was higher: -5.71 (p=0.002, effect size=0.99)
- Responder analyses also demonstrated a clinically meaningful response in a majority of patients.
- Studies 019 in ADP patients and Study 020 in PDP patients showed remarkably similar response to pimavanserin treatment on the studies' primary endpoints evaluating reduction in psychosis symptoms, both quantitatively and qualitatively (Figure 1–3).

Figure 1–3 Consistent and Similar Response to Pimavanserin Treatment: Study 019 in ADP (Left Panel) and Study 020 in PDP (Right Panel)



Sources: Study 020 CSR Table 14.2.1.1.1, Figure 1.1; Study 019 CSR Table 14.2.1.1.1; Study 019 CSR Addendum Figure AH.NPIb.fas

Abbreviations: ADP=Alzheimer's disease psychosis; CSR=clinical study report; FAS=Full Analysis Set; LSM=least square means; mITT=modified Intention-to-treat; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version Psychosis Score; PDP=Parkinson's disease psychosis; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson's disease; SE=standard error

Note: Data presented as LSM±SE.

For Studies 019 and 020, the FAS and mITT were defined as randomized subjects with Baseline and at least one post-baseline value of the primary efficacy variable.

Study 045 was a multi-center, placebo-controlled, randomized withdrawal (relapse prevention) study in patients (N=391) with all-cause dementia (National Institute on Aging-Alzheimer's Association [NIA-AA] 2011 guidelines; MMSE range between 6 and 24) and met clinical criteria for one (or more) of the following disorders: possible or probable AD, PDD, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), or vascular dementia (VaD), based on Investigator's designation of most likely clinical diagnosis of dementia (Tariot et al. 2021). The study evaluated this population of DRP as a unitary construct and was informed by the scientific consensus that psychotic symptoms in dementia could be studied as a single unified entity given co-occurrence of various dementia pathologies (Cummings et al. 2020; Beach and Malek-Ahmadi 2021). It should be noted that, while Study 045 enrolled PD patients with dementia, psychosis, and MMSE score between 6-24, Study 020 had enrolled PD patients with psychosis and normal cognitive function or mildly cognitively impaired [i.e., MMSE range 21-30]).

A randomized withdrawal design was chosen as it is well accepted as the optimal design for assessing maintenance of efficacy, particularly for neuropharmacologic drugs. The primary

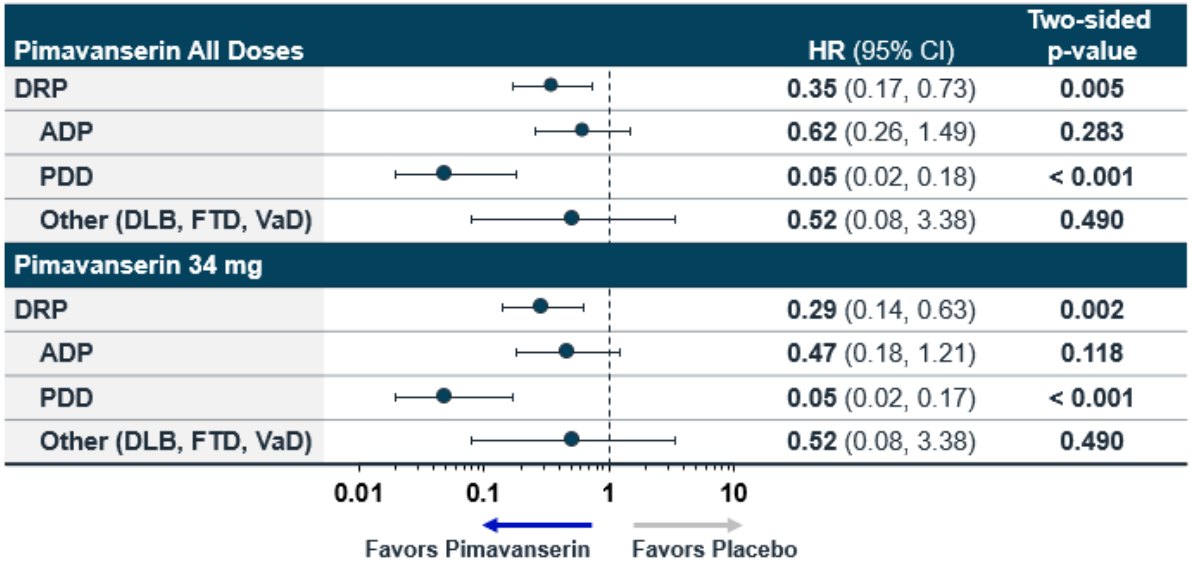
efficacy endpoint was time from randomization to relapse in the DB period. The key secondary endpoint was time from randomization to discontinuation from the DB period for any reason. Exploratory endpoints in the OL and DB period included change and percent change from OL and DB Baseline in Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (20-item) (SAPS-H+D), SAPS-H, and SAPS-D to assess hallucinations and delusions, as well as Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I) scores, which provided the clinician's view of severity and improvement of hallucinations and delusions.

As standard for randomized withdrawal studies, and as was prespecified in the study protocol and statistical analysis plan, an efficacy IA was conducted after 40 adjudicated relapse events had accrued. The prespecified stopping criterion was defined as a one-sided p-value less than the O'Brien-Fleming stopping boundary of 0.0033. All analyses were prespecified for the overall DRP patient population targeted in the study. Accordingly, as contemplated in the design presented at the End of Phase 2 meeting and throughout the study, the prespecified stopping criterion at the IA was focused on the overall DRP study population and did not incorporate separate analyses by dementia subgroups within the overall DRP study population. The study was terminated based on recommendations of the data and safety monitoring board (DSMB) following positive results at IA. The study met the primary endpoint O'Brien-Fleming stopping rule at the IA (hazard ratio [HR]=0.35, 95% confidence interval [CI]: 0.17, 0.73; one-sided p=0.0023, O'Brien-Fleming stopping rule one-sided p<0.0033). Pimavanserin also significantly reduced the risk of all-cause discontinuation (key secondary endpoint) by 2.2-fold compared with placebo based on the prespecified hierarchical algorithm to control overall type I error, tested also at the one-sided 0.0033 O'Brien-Fleming significance level (HR=0.45, 95% CI: 0.26, 0.79; one sided p=0.0024).

Exploratory subgroup analysis by dementia subgroup revealed that the PDD subgroup (~18%) demonstrated a very large treatment difference compared to placebo (HR=0.05, 95% CI: 0.02, 0.18, one-sided p<0.0001). However, the largest subgroup evaluated, ADP (66.3%), also contributed meaningfully to the overall significant and clinically meaningful efficacy of pimavanserin in this study with a reduction in hazard of relapse of 38% (Figure 1–4).

The pimavanserin 34 mg subgroup (i.e., patients who were stabilized at the 34 mg dose during the OL period and then randomized to 34 mg or placebo in the DB period) was also analyzed, as 34 mg is the approved pimavanserin dose for the treatment of PDP and the dose proposed for the treatment of ADP. Further, of the 123 patients with ADP in Study 045 at the time of the IA, 116 (~94%) patients were taking pimavanserin 34 mg. Studies 019 and 020 only evaluated a pimavanserin dose of 34 mg.

Figure 1–4 Hazard Ratios in the Overall DRP Patient Population and Dementia Subgroups (ITT Analysis Set at IA) – Study 045



Sources: 045 CSR Addendum Figures AH14.1.4.DEMPCAUS.GROUP.ITT, AH14.1.4.DEMPCAUS.GROUP.ITT34

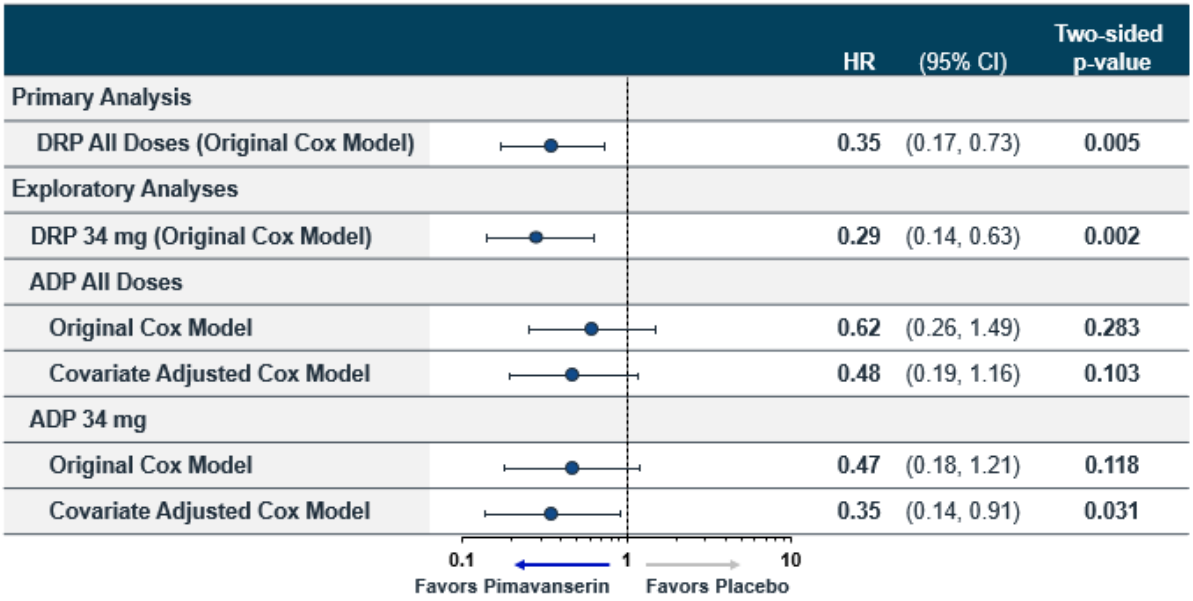
Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; CSR=clinical study report; DLB=dementia with Lewy bodies; DRP=dementia-related psychosis; FTD=frontotemporal dementia; HR=hazard ratio; IA=interim analysis; ITT=Intention-to-treat; PDD=Parkinson's disease dementia; VaD=vascular dementia

Examination of the data from the ADP dementia subgroup during the DB period showed the following:

- Clinically meaningful reductions in hazard of relapse (38% [all doses] to 53% [34 mg dose)]) versus placebo.
- Symptom severity analyses evaluating severity of hallucinations and delusions over time following randomization into the DB period consistently show maintenance of benefit of pimavanserin over placebo.
- Responder analyses evaluating categorical worsening of symptoms showed pimavanserin was consistently better than placebo, with single digit NNTs.
- The consistency of efficacy favoring pimavanserin over placebo across various efficacy measurements further supports a true pharmacologic benefit in ADP.
- A strong exposure-response relationship was observed, with higher pimavanserin exposure associated with a lower risk of relapse.
- The proposed therapeutic dose of pimavanserin (i.e., 34 mg) consistently showed greater efficacy on all endpoints.
- In an additional post-hoc analysis, a more precise, covariate adjusted Cox regression model correcting for confounding effects of baseline

disease severity variables between pimavanserin and placebo in the ADP dementia subgroup also yielded a consistent, clinically meaningful benefit seen with the primary analysis model (HR=0.48, 95% CI: 0.19, 1.16, two-sided p=0.103), with a slightly stronger effect when patients receiving pimavanserin 34 mg were examined (HR=0.35, 95% CI: 0.14, 0.91, two-sided p=0.031) (Figure 1-5).

Figure 1–5 Time to Relapse Analyses for ADP (Baseline Covariate Adjusted Cox Model) (ITT Analysis Set at IA) – Study 045



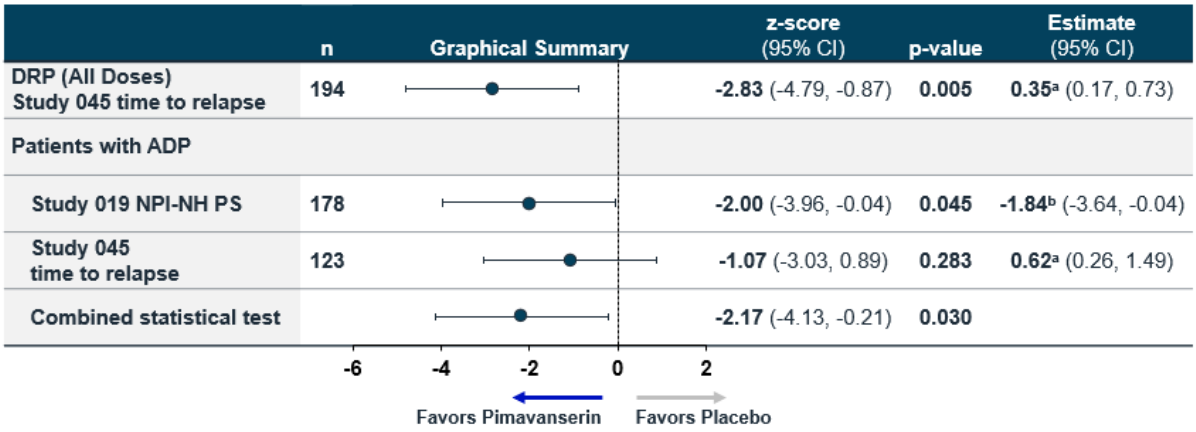
Sources: Study 045 CSR Addendum Tables 14.2.1.5.1, AH14.2.1.5.1.OL34, 14.2.1.10.3, AH14.2.1.5.1.OL34.AD, AH14.2.1.5.1.MODEL5drp, AH14.2.1.5.1.MODEL5adAIC; post resubmission Table AH14.2.1.5.1.MODEL5drp34AIC

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; CSR=clinical study report; HR=hazard ratio; IA=interim analysis; ITT=Intention-to-treat; PBO=placebo; PIM=pimavanserin; SAPS-H+D=Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions; Y/N=yes/no

Note: The original Cox regression model includes effects for treatment, dementia subgroup (randomization strata) and region; the covariate adjusted Cox regression model includes effects for treatment, antipsychotic use within 14 days of screening (Y/N), OL baseline SAPS-H+D, OL baseline dementia severity (mild versus not mild), and OL baseline antidementia medication use (Y/N).

As shown in the below forest plot of a common metric of z-score, representing the level of statistical evidence across studies and endpoints, results for the primary efficacy endpoints from Study 019 (ADP) and Study 045 (ADP subgroup) evidence a benefit of pimavanserin treatment of patients with ADP across endpoints and studies. Furthermore, the combined statistical test assessing the total statistical evidence across these two studies supports a clinically meaningful benefit of pimavanserin for the treatment of patients with ADP (Figure 1–6).

Figure 1–6 Overall Statistical Evidence for Pimavanserin Treatment Effect in Patients With Psychosis Across Two Studies



Source: Post-submission Figure ForestD-forest-slim-no046
Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; DRP=dementia-related psychosis; LSM=least square means; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version psychosis score
Notes: Estimates with 95% CI and 2-sided p-values are from the primary analysis models in each study; z-scores correspond to the p-values based on the standard normal distribution; 95% CI of z-scores are z-scores +/- 1.96 standard error units. Combined Statistical Test z-scores are derived from a bivariate standard normal distribution with correlation of zero and calculated as (sum of z-scores across 2 studies)/sqrt(2).
[a] Hazard ratio (pimavanserin/placebo)
[b] LSM difference in change from Baseline values (pimavanserin – placebo)

In summary, a range of analyses of pimavanserin efficacy data across multiple clinical studies and endpoints shows consistent and meaningful improvement of psychosis symptoms and prevention of relapse of psychosis in patients with ADP. This aggregated evidence of benefit is a true treatment effect (not likely a chance finding) and is consistent with the FDA's guidance pertaining to demonstrating substantial evidence of effectiveness for drugs (Guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* [lines 419-430; Dec 2019]).

1.5 Overview of Safety

As of 08 September 2021, Acadia has significantly expanded the clinical study safety database in 1683 frail, elderly patients with NDD exposed to pimavanserin since the original FDA-approval in April 2016 (Table 1–1). Specifically, data are available from 14 clinical studies, of which 721 patients had a clinical diagnosis of AD, 572 of whom had psychosis. The integrated safety database (16 June 2020 data cutoff) included 1502 frail, elderly patients with NDD who were exposed to pimavanserin.

Table 1–1 Duration of Pimavanserin Exposure in Patients With NDD (including AD) From Completed Studies and Unblinded Interim Analyses

Patient Population	<3 months	≥3 months	≥6 months	≥12 months	Total pimavanserin at data cutoff
Total NDD population[a]	766	917	740	394	1683
Subset of patients with AD[b]	260	461	288	160	721
Subset of patients with ADP[b]	226	346	180	97	572

Sources: sNDA Section 2.7.4.1.2.1; Section 5.3.5.3 Tables RADPIMEXT.1.6 and RADPPIMEXT.1.6

Abbreviations: AD=Alzheimer's disease; ADP=Alzheimer's disease psychosis; IA2=second interim analysis; NDD=neurodegenerative disease; sNDA=supplemental new drug application

Note: For ongoing Studies 046 and 047, exposure is calculated only for the subset of subjects unblinded in IA2 for Study 046. For Study 047, exposure is calculated to 08Sep2021.

[a] Clinical studies contributing patients: 005, 006, 010, 012, 014, 015, 020, 048, 019, 032, 033, 045, 046 (IA2), 047 (IA2)

[b] Clinical studies contributing patients: 019, 032, 033, 045, 046 (IA2), 047 (IA2)

Overall, the clinical safety and tolerability profile for pimavanserin continues to support the positive benefit-risk of treatment of hallucinations and delusions in patients with ADP.

Frequencies of treatment-emergent adverse events (TEAEs), TEAEs leading to study drug discontinuation or study termination, and deaths within 30 days of last dose were generally similar between pimavanserin 34 mg and placebo for the patients with NDD in DB, placebo-controlled, parallel-group studies and for patients with AD in DB, placebo-controlled, parallel-group studies. Serious TEAEs occurred at slightly higher frequency in pimavanserin treated patients with NDD in DB, placebo-controlled, parallel-group studies (NDD pool) and pimavanserin treated patients with AD in DB, placebo-controlled, parallel-group studies (AD pool) (Table 1–2).

Table 1–2 Overall Summary of TEAEs in Patients With NDD and AD in the Pimavanserin Clinical Study Safety Database (Safety Analysis Sets) – Study-Adjusted

TEAE	NDD		AD	
	PIM 34 mg (N=580) %	PBO (N=575) %	PIM 34 mg (N=292) %	PBO (N=282) %
Any TEAE	53.9	54.5	55.5	56.3
Any serious TEAE	7.1	4.2	8.0	5.6
Any TEAE leading to study drug discontinuation or study termination	5.8	4.7	5.2	7.0
Death within 30 days of last dose	1.2	1.2	1.4	1.8

Sources: Tables RADPG.2.13; RADPG.2.14; RADPG.2.15; RADPG.2.16; NPG.2.13; NPG.2.14; NPG.2.15; NPG.2.16

Abbreviations: AD=Alzheimer's disease; AE=adverse event; IA2=second interim analysis; NDD=neurodegenerative disease; PBO=placebo; PIM=pimavanserin; TEAE=treatment-emergent adverse event

Notes: A TEAE was an AE with an onset date on or after the first study dose date and no later than the last study dose date plus 30 days. The NDD pool included Studies 005, 006, 012, 014, 019, 020, 032, and 046IA2. The AD pool included Studies 019, 032, and 046IA2. Study adjusted % is a weighted average of the study specific percentages for the dose group. The weight for a study is the number of subjects included in the analysis from the study divided by the number of subjects across all studies that are included in the analysis.

Mortality has been analyzed using two different timeframes to allow comparison with published data, including the Schneider et al. (2005) and FDA's 17-study meta-analyses of mortality and atypical antipsychotics (which is reflected in class labeling for antipsychotic drugs):

- deaths occurring within 30 days of the last dose
- deaths occurring within the intended treatment period plus 30 days thereafter.

The incident rate ratios and odds ratios of deaths occurring within 30 days of last dose and of deaths occurring within the intended treatment period plus 30 days thereafter are presented for patients with NDD treated with pimavanserin 34 mg or placebo in the NDD parallel group, placebo-controlled pool (NDD pool) in Table 1–3. Mortality rates associated with pimavanserin treatment (pimavanserin 34 mg vs. placebo) in the overall NDD patient population were relatively balanced versus placebo; the incidence rate ratio (IRR) (95% CI) of deaths was 1.02 (0.36, 2.90) for deaths occurring within 30 days of the last dose and 1.28 (0.48, 3.43) for deaths occurring within the intended treatment period plus 30 days thereafter. Similar results were observed in the NDD pool for patients who received placebo or pimavanserin (all doses).

Table 1–3 Comparison of Pimavanserin Mortality Rate in NDD With Published Meta-Analyses

	Deaths Within 30 Days of the Last Dose	Deaths Occurring Within the Intended Period of Treatment plus 30 Days Thereafter
Pimavanserin 34 mg (N=580), n (%)	7 (1.2)	9 (1.6)
Pimavanserin all doses (N=833), n (%)	8 (1.0)	10 (1.2)
Placebo (N=649), n (%)	7 (1.1)	8 (1.2)
IRR (pimavanserin 34 mg/placebo) (95% CI)	1.02 (0.36, 2.90)	1.28 (0.48, 3.43)
IRR (pimavanserin all doses/placebo) (95% CI)	1.01 (0.37, 2.80)	1.22 (0.46, 3.23)
OR (pimavanserin 34 mg/placebo) (95% CI)	0.99 (0.34, 2.85)	1.28 (0.47, 3.47)
OR (pimavanserin all doses/placebo) (95% CI)	1.00 (0.36, 2.81)	1.24 (0.47, 3.31)
FDA Meta-Analysis: All drugs: IRR (95% CI)		1.71 (1.38, 2.11)
FDA Meta-Analysis: Atypical: IRR (95% CI)		1.65 (1.29, 2.09)
Meta-Analysis, Schneider et al. 2005: Antipsychotics OR (95% CI)	1.54 (1.06, 2.23)	

Sources: Section 5.3.5.3 Tables NPG.3.4.2, AH.NPG.3.4.1.INTRTDUR

Abbreviations: CI=confidence interval; FDA=Food and Drug Administration; IRR=incidence rate ratio; OR=odds ratio; NDD=neurodegenerative disease

Note: The pimavanserin mortality rate is based on data from the NDD pool, which included pimavanserin treated patients with neurodegenerative disease in double-blind, placebo-controlled, parallel-group studies.

The IRR (CI) of 1.28 (0.48, 3.43) for pimavanserin 34 mg versus placebo for deaths in the NDD pool occurring within the intended treatment period plus 30 days thereafter is nominally lower than the value FDA calculated for antipsychotic drugs in their 17-study meta-analysis, IRR (CI) 1.71 (1.38, 2.11), but the confidence intervals overlap (Table 1–3, FDA Email Correspondence).

Similarly, the odds ratio (OR) (CI) of 0.99 (0.34, 2.85) for pimavanserin 34 mg versus placebo for deaths in the NDD pool occurring within 30 days of the last dose is nominally lower than the value Schneider et al. (2005) calculated for antipsychotic drugs in their meta-analysis, OR (CI) 1.54 (1.06, 2.23), but the confidence intervals overlap (Table 1–3).

When the data from AD patients are examined, a similar low number of deaths was observed on pimavanserin 34 mg treatment versus placebo (the IRR [95% CI] of deaths was 0.82 [0.22, 3.05] for deaths occurring within 30 days of the last dose and 0.99 [0.29, 3.41] for deaths occurring within the intended treatment period plus 30 days thereafter).

As of 28 October 2021, at least 44,765 patients (representing 35,038 person-years [PY]) have been exposed to NUPLAZID (pimavanserin) in the postmarketing setting since its launch for the treatment of PDP in the US. Extensive and periodic evaluation of postmarketing deaths and reported adverse events (AEs) during this time showed no patterns or trends suggesting a common underlying pathology. Indeed, the reported AEs are reflective of the comorbidities in

an elderly population with PDP. In addition, a Medicare study of PD patients presented by academic and government scientists, including FDA authors, reviewed all-cause mortality with pimavanserin use versus atypical antipsychotics and determined that pimavanserin use was associated with significantly lower mortality compared with atypical antipsychotics (HR=0.78, 95% CI: 0.65, 0.94). However, the reduced mortality was restricted to patients not in nursing homes (Mosholder et al. 2020).

Also, an Acadia-sponsored Medicare safety study by RTI (Health Solutions), an independent epidemiology group, reviewed mortality risk associated with pimavanserin use compared with atypical antipsychotics in patients with PDP and showed similar results. The matched HR for mortality for pimavanserin versus comparator was 0.78 (95% CI: 0.67, 0.91). Moreover, in long-term care/skilled nursing facility (LTC/SNF) residents the HR was 0.78 (95% CI: 0.60, 1.01). Estimated HRs were similar across all sensitivity analyses (including patients without a psychosis diagnosis) and subgroups (sex, age, dementia diagnosis, and LTC residence) (Layton 2022).

In spite of these encouraging reports, Acadia proposes to keep, but modify, the existing Boxed Warning for NUPLAZID (pimavanserin) in a manner consistent with the approach taken by the FDA as part of the original approval of NUPLAZID for the treatment of PDP to now also accommodate the proposed indication for the treatment of ADP.

No new safety signals were observed in the additional integrated analyses of patients with AD as compared to patients with NDD.

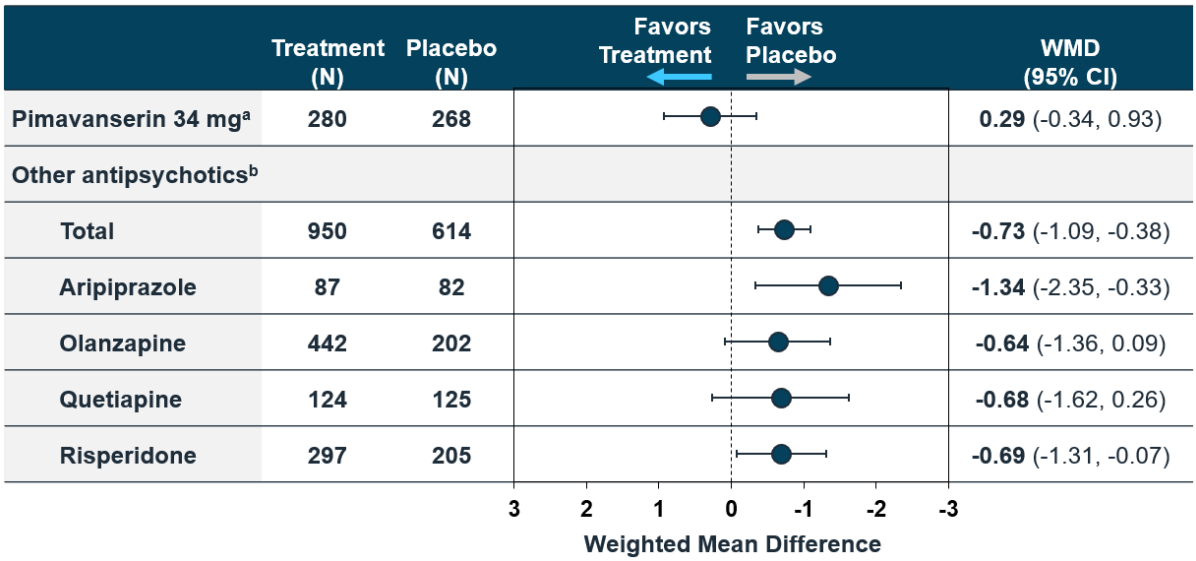
Analyses are also provided to support the lack of effect on cognition and motor function in patients with ADP to help inform the overall benefit-risk for use of pimavanserin in the indication for treatment of ADP.

Safety data support the conclusion that pimavanserin is not associated with the numerous adverse effects observed with off-label use of available multi-receptor acting antipsychotic drugs, including no evidence for cognitive decline or motor dysfunction with chronic use.

Acceleration of cognitive decline is of clear clinical detriment to the dementia patient population, in which cognitive impairment is a core symptom of the disease, and treatment with approved antipsychotics used off-label has been shown to be associated with worsening cognitive function. Measurement of MMSE was included in three DB, placebo-controlled, parallel group studies with pimavanserin for a treatment duration of up to 12 weeks to assess the potential effects of pimavanserin on cognition in these frail, elderly patients, most of whom were suffering from dementia.

Data from an integrated analysis of these studies showed no evidence of a decline in cognition, as measured by MMSE score, with pimavanserin treatment compared with placebo (Figure 1–7). Based on a meta-analysis, pimavanserin 34 mg has shown a numerical improvement on MMSE compared with placebo, with a difference of 0.29; however, other antipsychotics significantly worsened the MMSE scores as compared with placebo with a difference of -0.73.

Figure 1–7 Meta-Analysis of Cognitive Function Measured by Changes in MMSE Scores by Drug



Source: Section 5.3.5.3 Figure RADPG.1.1.1

Abbreviations: CI=confidence interval; MMSE=Mini-Mental State Examination; WMD=weighted mean difference

[a] This meta-analysis compares pimavanserin 34 mg to placebo for Alzheimer's disease patients in Studies 019, 032 and 046 (AD pool).

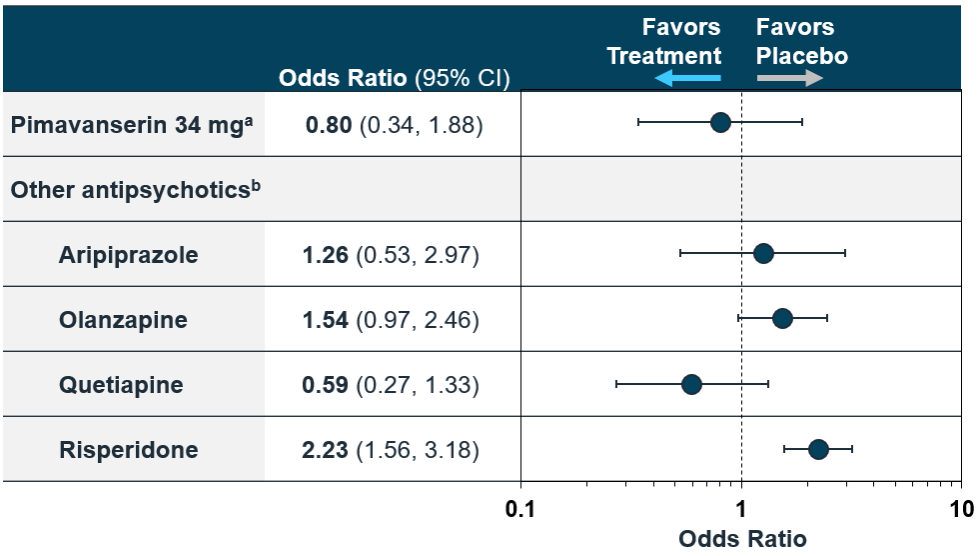
[b] Adapted from Schneider et al. 2006a

A similar safety profile evidencing lack of adverse effect on cognition, as measured by MMSE, was observed over the long-term (38 weeks) in the randomized withdrawal Study 045.

Approved multi-receptor acting antipsychotics, that primarily act via dopamine blocking activity, are also associated with the emergence of EPS. As with the assessment of cognitive function, multiple DB, placebo-controlled, parallel-group studies of pimavanserin treatment of DRP (including ADP) and PDP patients have evaluated the potential for the adverse effect of motor function using the Extrapyramidal Symptoms Rating Scale–Abbreviated (ESRS-A) and the Unified Parkinson's Disease Rating Scale (UPDRS) scales. Overall, no negative impact of pimavanserin treatment on motor function was observed in any study. Similarly, no negative impact of pimavanserin on motor function was observed with long-term

pimavanserin treatment in Study 045. This is supported by the meta-analysis of EPS AEs comparing to other antipsychotics (Figure 1-8).

Figure 1–8 Meta-analysis of Motor Function Measured by Adverse Events of EPS by Drug



Source: Section 5.3.5.3 Figure RADPG.1.2.1.

Abbreviations: CI=confidence interval; EPS=extrapyramidal symptoms

Note: The odds ratio is calculated using a logistic regression model which includes the binary outcome of Extrapyramidal syndrome events (Yes, No), with the factor of treatment group.

[a] This meta-analysis compares pimavanserin 34 mg to placebo for Alzheimer's disease patients in Studies 019, 032 and 046 (AD pool). In Study 032, subjects who were in the pimavanserin 20 mg group were excluded from this analysis.

[b] From Yunusa et al. 2019.

In summary, pimavanserin safety data from a large clinical study database in patients with NDD, including patients with ADP, supports a favorable safety profile, including a differentiated safety profile from currently available antipsychotics used off-label, particularly with regards to two important aspects:

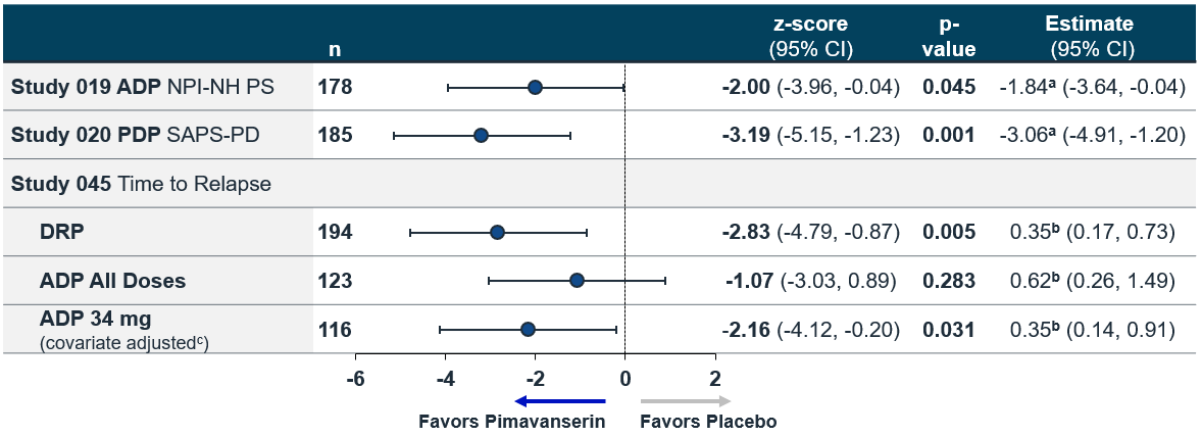
- lack of negative impact on cognition and
- no adverse effects on motor function

Overall, pimavanserin safety and tolerability is supportive of a positive benefit-risk in ADP patients. Furthermore, NUPLAZID postmarketing data from >40,000 patients with PDP over 6 years since FDA-approval continue to support a positive benefit-risk. Additional real world observational data evaluating mortality rates and falls in PD and PDP patients receiving pimavanserin versus atypical antipsychotics have also supported the favorable safety profile of NUPLAZID (Layton et al. 2022; Mosholder et al. 2020).

1.6 Substantial Evidence of Effectiveness and Positive Benefit-Risk for Pimavanserin for the Treatment of ADP

Pimavanserin consistently demonstrated clinically meaningful reduction in psychosis symptoms and prevention of relapse of psychosis in patients with ADP across multiple clinical studies and endpoints. These data consist of a positive study in patients with ADP, coupled with an FDA-approval for pimavanserin for the closely-related indication for the treatment of PDP, which is independent confirmatory evidence of pimavanserin's effectiveness consistent with FDA's (draft) Guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (lines 419-430; Dec 2019). In addition, supportive evidence is provided from an overall positive study in patients with DRP in which ADP, the largest dementia subgroup, showed clinically meaningful improvement in a manner consistent with the overall DRP patient population (Figure 1–9).

Figure 1–9 Substantial Evidence of Effectiveness for ADP



Sources: Study 019 CSR Table 14.2.1.1.1; Study 020 CSR Table 14.2.1.1.1; Study 045 CSR Addendum Tables 14.2.1.5.1, 14.2.1.10.3, AH14.2.1.5.1.MODELadAIC

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; DRP=dementia-related psychosis; LSM=least square means; N=no; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version psychosis score; OL=open-label; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson's Disease; Y=yes

Notes: Estimates with 95% CI and 2-sided p-values are from the primary analysis models in each study; z-scores correspond to the p-values based on the standard normal distribution; 95% CI of z-scores are z scores +/- 1.96 standard error units. For Study 045, the original Cox regression model includes effects for treatment, dementia subgroup (randomization strata) and region; the covariate adjusted Cox regression model includes effects for treatment group, antipsychotic use within 14 days of screening (Y/N), OL baseline SAPS-H+D, OL baseline dementia severity (mild versus not mild), and OL baseline antidementia medication use (Y/N).

[a] LSM difference in change from Baseline values (pimavanserin – placebo)
[b] Hazard ratio (pimavanserin/placebo)
[c] post-hoc analysis

Alzheimer's disease psychosis is a serious condition for which there are no FDA-approved drugs. Pimavanserin has shown consistent and clinically meaningful efficacy without negatively impacting cognition or motor function. This is in contrast to currently available

antipsychotic drugs used off-label to treat patients with ADP, clinical studies of which have shown marginal or no clinical benefit while being associated with serious safety risks, including acceleration of cognitive decline and EPS.

Overall, the totality of available clinical study and postmarketing data support a positive benefit-risk profile for pimavanserin as a treatment for hallucinations and delusions associated with ADP, an area of great unmet need.

2 BACKGROUND ON ALZHEIMER'S DISEASE AND ALZHEIMER'S DISEASE PSYCHOSIS

SUMMARY

- There are approximately 8 million people with dementia in the US, including 70% (5.5 million) with AD, of which 30% (1.7 million) experience psychosis.
- ADP persists and its severity and frequency increase over time, with dire consequences.
    - ADP symptomatic consequences are life-altering, leading to loss of independence as well as increased distress and burden for the patient, family, and caregivers.
- There are currently no FDA-approved treatments for patients with ADP and current off-label options are inadequate and often cause harm rather than benefit:
    - Non-pharmacological interventions commonly fail.
    - Antipsychotics are frequently used if symptoms are frequent, severe, dangerous, and cause distress; however, efficacy is equivocal at best and toxicities are significant.
    - Multireceptor acting antipsychotics are associated with cognitive decline, increased mortality, and parkinsonism.
- **What do patients and caregivers want and need in treatment?**
    - Patients with ADP deserve more than current off-label options.
    - Patients and their families, and the healthcare system at large need an effective therapy that is not associated with significant toxicities, especially on core symptoms of the disease.
    - Patients, physicians, and payers need a therapy that is recognized by health authorities as appropriate for clinical use.

2.1 Overview of Alzheimer's Disease and Alzheimer's Disease Psychosis

Dementia is a devastating syndrome that is neurodegenerative in nature. The core feature of dementia is declining cognitive function resulting in functional impairment. The most common neurodegenerative dementing illnesses are AD, DLB, PDD, VaD, and FTD (Gale et al. 2018; Goodman et al. 2017).

Although cognitive decline is the core feature of dementia, behavioral and neuropsychiatric manifestations of neurodegenerative dementias, including AD, are almost universally present over the disease course and include hallucinations and delusions (Jellinger 2012; Fischer et al. 2016; Reus et al. 2016). Alzheimer's disease psychosis refers specifically to hallucinations or delusions that are secondary to the underlying AD and not to an unrelated medical cause (e.g., delirium).

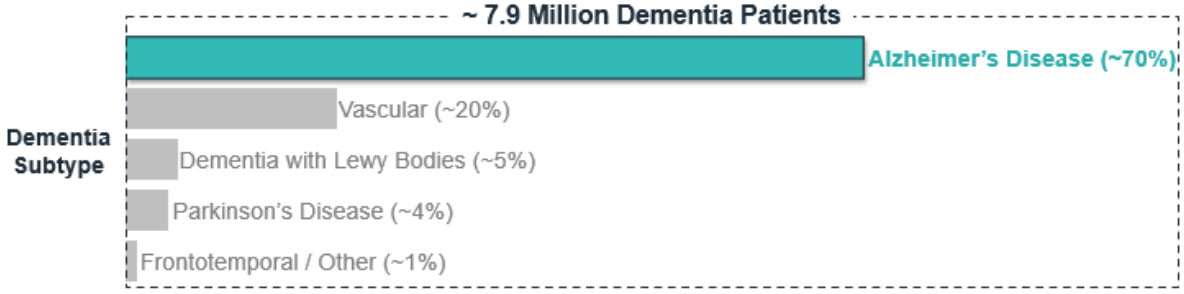
Alzheimer's disease psychosis can be frequent, severe, and persistent and can occur with increasing severity and frequency as dementia progresses, leading to loss of independence as well as causing distress to the patient, family, and caregivers (Alva et al. 2019; Lyketsos et al. 2002; Ropacki and Jeste 2005; Hongisto et al. 2018; Peters et al. 2015; Kasper et al. 2015). Psychosis' core feature of distortion of reality can compound the disorientation a patient experiences as cognition declines, leading to additional distress (RTI Health Solutions 2020; RTI Health Solutions 2021). The presence of neuropsychiatric signs and symptoms in AD is predictive of increased caregiver burden, decreased quality of life, poor caregiver-care recipient relationship, and earlier progression to nursing home care, severe dementia, and death (Lyketsos et al. 2006; Peters et al. 2015; Stern et al. 1997; Kales et al. 2007; Vernon et al. 2019). Thus, there is a close relationship between the clinical manifestations of ADP and morbidity/mortality (Jellinger 2012).

There is a clear unmet medical need for a therapeutic option with a positive benefit-risk profile that decreases the severity and frequency of psychotic symptoms and prevents the re-emergence of symptoms in frail, elderly patients with ADP. It is crucial that effective therapy addresses psychosis without negatively affecting cognition and demonstrates a favorable safety and tolerability profile with chronic administration.

2.1.1 Epidemiology

There are approximately 8 million people with dementia in the US, including approximately 5.5 million people with AD (70%), of which approximately 1.7 million (30%) have psychosis (Figure 2–1). The prevalence of dementia, including AD, is expected to grow as the population ages and diagnostic capabilities advance (Plassman et al. 2007; Alzheimer's Association 2017; Chi et al. 2019).

Figure 2–1 Estimated Number of People With Dementia and AD in the US

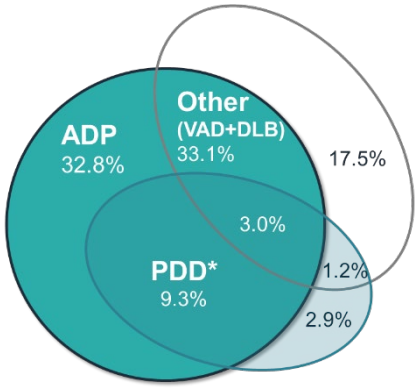


Sources: Goodman et al. 2017; Plassman et al. 2007; Hebert et al. 2013; Alzheimer's Association 2017; Vann Jones and O'Brien 2014; Hogan et al. 2016; Aarsland et al. 2005

Abbreviations: AD=Alzheimer's disease; US=United States

It is known, based on literature and clinical experience, that dementias have great overlap in symptomatology and pathology (Figure 2-2). The results of the Brenowitz et al. (2017b) autopsy study show that the majority of patients with established dementia and psychosis have overlapping underlying proteinopathies and neuropathology. Reflected in the large circular area in Figure 2-2, ADP pathology is shared with all dementias, including the majority of patients with PDD pathology. This pathological overlap indicates that patients with ADP, are in fact, very similar to those experiencing PDD.

Figure 2-2 Overlapping Clinical Symptomatology of Dementias Aligns With Known Pathological Overlap



Sources: Brenowitz et al. 2017a; Brenowitz et al. 2017b
Abbreviations: ADP=Alzheimer's disease psychosis; DLB=dementia with Lewy bodies; PDD=Parkinson's disease dementia; VaD=vascular dementia

Hallucinations and delusions are prevalent across all types of dementia, although prevalence rates and specific clinical presentations differ (Table 2–1) (Ballard et al. 1997; Cummings et al. 2018; Fischer et al. 2016; Johnson et al. 2011). At any given time, approximately 30% of dementia patients experience psychosis (point prevalence).

Table 2–1 Delusions and Hallucinations in Patients With Various Dementias

Disease	Hallucinations (%)	Delusions (%)
Alzheimer's disease	11-17	10-39
Vascular dementia	5-14	14-27
Dementia with Lewy bodies	55-78	40-57
Parkinson's disease dementia	32-63	28-50
Frontotemporal dementia	1.2-13	2.3-6

Sources: Table 2.7.3.1-1; Cummings et al. 2018

2.1.2 Prognosis

Serious consequences have been associated with persistent or severe psychosis in patients with dementia. Epidemiological studies have revealed that, on average, 41% of AD patient admissions reported psychosis, including delusions in 36% and hallucinations in 18% of patients (Ropacki and Jeste 2005). Neuropsychiatric symptoms are associated with a worse prognosis in dementia (Lyketsos et al. 2006), and clinically significant neuropsychiatric symptoms have been found to be predictive of earlier progression to nursing home care, severe dementia, and death (Peters et al. 2015; Rashid et al. 2020; Stern et al. 1997). The risk for outcomes like nursing home admission, progression to severe dementia, and death is approximately 1.5–2.0 times higher in dementia patients with psychosis than in those without psychosis (Peters et al. 2015; Rashid et al. 2020; Scarmeas et al. 2005).

Consistent with the natural history outlined above, analysis of Medicare and commercial private insurance claims has shown that healthcare utilization of patients with dementia increases after diagnosis of psychotic symptoms and persists for years afterwards, driven by increased use of acute services, such as inpatient stays (Frazer et al. 2020). These data also show increased use of long-term care resources associated with psychosis in dementia. On average, patients entered long-term nursing homes within a year (347 days) after psychotic symptoms were identified (compared to 610 days for matched dementia patients without psychotic symptoms observed over the same time period) and stayed in this living situation for longer than patients without psychosis (605 vs. 548 days, respectively). As with hospitalizations, increased costs associated with long-term care persist for years after psychotic symptoms are identified.

2.2 Current Treatment Options

2.2.1 Standard of Care

Despite the high impact of ADP on morbidity and mortality in patients with AD, there are currently no approved drugs in the US for the treatment of patients with ADP. In clinical practice, antipsychotic medications are commonly used off-label to treat psychotic symptoms

in patients with dementia when nonpharmacologic interventions are no longer effective. A study among elderly nursing home residents with dementia found that antipsychotic medications were taken by 32.9% of elderly patients with dementia (Kamble et al. 2009). Further, in a study based on claims data from 2008-2016, approximately 66% of 49,509 patients with DRP were prescribed an antipsychotic (Rashid et al. 2022).

2.2.2 Benefit-Risk of Available Antipsychotics

The American Psychiatric Association practice guidelines recommend that after an evaluation of the potential benefit and harm of therapy to the patient, antipsychotic medication should only be used for the treatment of psychosis when symptoms are severe, dangerous, and/or cause significant distress to the patient, and patients who do not respond should be taken off the treatments, minimizing exposure to ineffective treatment (Reus et al. 2016). This recommendation is based on data from multiple randomized clinical trials, including those in dementia patients with AD, showing modest and often equivocal efficacy, as well as results of meta-analyses demonstrating an increased risk of mortality in elderly patients with psychosis (Reus et al. 2016; Ralph and Espinet 2018; Ma et al. 2014; Tampi et al. 2016; Schneider et al. 2006a; Schneider et al. 2006b; Maher et al. 2011; Ballard and Howard 2006; Zhai et al. 2016).

Despite the wide off-label use in clinical practice, new drug applications (NDAs) for antipsychotic drugs have been submitted for indications involving psychosis in frail and elderly populations, but not approved based primarily on evidence of serious adverse events (SAEs) and death (Mathis et al. 2017) and an overall negative benefit-risk ratio. It is relevant to note that the Boxed Warning for these products includes a statement that they are not approved for the treatment of patients with DRP. As such, from a regulatory standpoint, the FDA has not determined that there is evidence of a favorable benefit-risk profile of currently approved antipsychotics for the treatment of DRP, including ADP. Approved antipsychotic drugs have been commonly categorized into two classes: conventional antipsychotics (also known as first generation or typical antipsychotics) and “atypical” antipsychotics (also known as second generation antipsychotics). Drugs in either class are multi-receptor acting, but target principally, to variable degrees, dopamine receptors to block the action of naturally occurring dopamine in the brain. Dopamine receptor antagonist activity is a significant concern because AD is linked to decreased levels of dopaminergic neurotransmitters (Pan et al. 2019).

In current treatment guidelines, first generation antipsychotics are generally not recommended for use in first line treatment of ADP, due to the particularly severe unfavorable side effect profile of these drugs. Importantly, studies using administrative

databases that have examined a wide range of antipsychotics found the risk of mortality with first-generation antipsychotics was generally greater than the risk with second generation antipsychotics (Reus et al. 2016). In particular, data from multiple studies in dementia support that haloperidol may have the highest risk for all-cause mortality among antipsychotic agents (Ralph and Espinet 2018). Practice guidelines recognize that haloperidol may be appropriate for emergency management of severe psychosis due to the availability of an intravenous and short-acting intramuscular formulation (Reus et al. 2016).

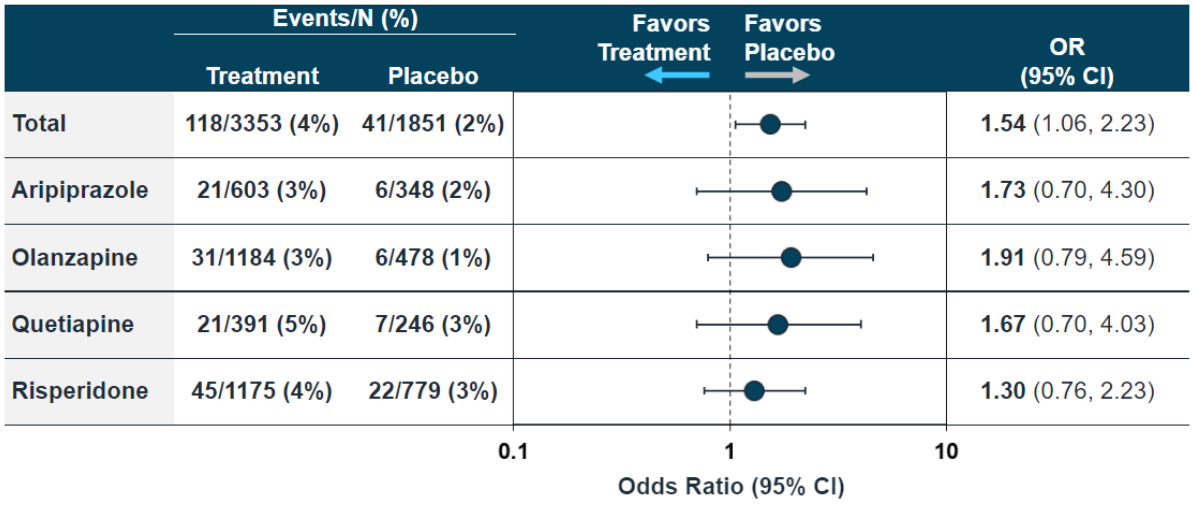
Second generation atypical antipsychotics are more commonly utilized off-label for the treatment of ADP. However, atypical antipsychotics are also associated with a significant acceleration in cognitive decline in patients with dementia, including AD, as well as a number of other toxicities due in part to their dopaminergic and anticholinergic activity (Section 2.2.2.2).

Several other central-nervous system-acting medications are used off-label for the treatment of the symptoms and/or consequences of psychosis in dementia, including AD. None have demonstrated reliable efficacy, and all are associated with significant risks in elderly, frail patients.

2.2.2.1 Mortality Risks Associated With Antipsychotic Drugs

A large meta-analysis conducted by the FDA revealed that antipsychotic drugs carry a risk of increased mortality in elderly patients with DRP. This analysis included 17 placebo-controlled trials and found that compared with patients treated with placebo, the risk of death was 1.6- to 1.7-times greater in patients treated with antipsychotics (FDA 2005). Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group (FDA 2005). The deaths were mostly cardiovascular or infectious (e.g., pneumonia) in nature. This meta-analysis resulted in a Boxed Warning in labeling for the antipsychotic drug class for increased risk of mortality in elderly patients with DRP. Similar findings were published in the meta-analysis by Schneider et al. (2005), shown in Figure 2–3.

Figure 2–3 Mortality Risks Associated With Approved Antipsychotics



Abbreviations: CI=confidence interval; OR=odds ratio
Source: Schneider et al. 2005

2.2.2.2 Decline in Cognitive and Motor Function

Multi-receptor acting atypical antipsychotics are also associated with a significant acceleration in cognitive decline in patients with dementia, as well as a number of other toxicities due in part to their dopaminergic and anticholinergic activity. Vigen et al. (2011) reported the cognitive effects of treatment with an atypical antipsychotic in the National Institute of Mental Health CATIE-AD study. In this study, patients on any atypical antipsychotic had significantly greater rates of decline in cognitive function than patients receiving placebo, as measured by the MMSE (an average decline in MMSE that was 2.46 points greater than placebo over the 36 weeks, p=0.004). In a study of elderly patients with possible or probable AD dementia residing in United Kingdom care homes, agitation treated with quetiapine was associated with significantly greater cognitive decline than placebo. Patients who received quetiapine experienced, on average, an estimated mean difference in change in severe impairment battery score from Baseline of -14.6 points compared with the placebo-treated group at 6 weeks (95% CI: -25.3, -4.0; p=0.009), indicating a significantly greater deterioration in the quetiapine group (Ballard et al. 2005).

Similarly, a meta-analysis of randomized, placebo-controlled trials of relatively short durations (approximately 10–12 weeks) with atypical antipsychotics in dementia conducted by Schneider et al. (2006a) showed a significant acceleration of cognitive decline in patients taking antipsychotics compared with patients taking placebo (the weighted mean difference in the size of the decline on MMSE score was 0.73 points, p <0.0001). This pronounced negative impact of currently used multi-receptor acting antipsychotics on cognitive function,

equates to approximately a doubling in the rate of cognitive decline associated with the natural history of the disease, is believed to be associated with the common pharmacologic properties of these drugs, namely blocking of dopamine receptors (Coupland et al. 2019; Gray et al. 2015; Nevalainen et al. 2015) and anticholinergic activity (Papenberg et al. 2017).

The dopamine blocking activity of antipsychotics has also been linked to the emergence or worsening of extrapyramidal symptoms, including tremors, dystonia, tardive dyskinesia, and parkinsonism (Kales et al. 2015).

2.2.2.3 Key Adverse Events Associated With Antipsychotics

The lack of selectivity of multi-receptor acting antipsychotics with respect to receptor activity also results in a number of dose-limiting side effects, including EPS, orthostatic hypotension, hematologic abnormalities, and metabolic, gastrointestinal, thromboembolic, and sedative effects. These toxicities contribute to an increased risk for falls (and associated fractures), infection, aspiration pneumonia, and other serious complications in this vulnerable population (Reynolds 2011; Ballard and Howard 2006; Mintzer et al. 2007). The majority of these risks are serious and are communicated to prescribers and patients as Warnings and Precautions in the antipsychotics' FDA approved labeling. The American Geriatrics Society has placed antipsychotics on their often quoted Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults (American Geriatrics Society 2019).

3 CLINICAL EFFICACY OF PIMAVANSERIN FOR THE TREATMENT OF ADP

SUMMARY

- The substantial evidence of efficacy of pimavanserin for the treatment of patients with ADP is demonstrated in a positive study in patients with ADP, Study 019, with confirmatory evidence based upon a positive study in PDP (Study 020), a closely-related FDA-approved indication. Further supportive evidence of pimavanserin's benefit for the treatment of ADP is observed in the positive randomized withdrawal study in patients with DRP, Study 045, in which the largest dementia subgroup, ADP, showed consistent and clinically meaningful benefit of pimavanserin treatment.
    - Data from Studies 019, 020, and 045 support a common clinical presentation of psychosis and consistent antipsychotic treatment response across dementia subgroups confirming the concept of ADP and PDP being closely-related conditions.

- Study 019 was a randomized, DB, placebo-controlled study that enrolled patients with ADP with severe dementia in long-term care (MMSE score [mean±standard error {SE}]=10±0.40) and demonstrated the following:
  - The primary endpoint of change from Baseline to NPI-NH PS at Week 6 showed a statistically significantly greater reduction with the pimavanserin 34 mg treatment group versus placebo (p=0.045, effect size=0.32). These results compare favorably to the off-label use of atypical antipsychotics where the efficacy is marginal (effect size ≤0.2).
  - In the prespecified subgroup of patients with more severe psychosis (i.e., NPI-NH PS ≥12 at Baseline), the magnitude of efficacy was larger (p=0.011, effect size=0.73) suggesting that a principle benefit in the study was seen in more severely psychotic patients in greatest need for pharmacologic therapy.
  - A greater proportion of patients responded to pimavanserin versus placebo and achieved nominal statistical significance (55.2% vs. 37.4%, p=0.016, when response is defined as a ≥30% reduction and 50.6% vs. 34.1%, p=0.024, when response is defined as a ≥50% reduction). Even better results were observed in the subgroup with more severe psychosis at Baseline (88.9% vs. 43.3%, p=<0.001, when response is defined as a ≥30% reduction and 77.8% vs. 43.3%, p=0.008, when response is defined as a ≥50% reduction).
- Study 020 was a randomized, DB, placebo-controlled, outpatient study in patients with PDP and was the pivotal study leading to pimavanserin approval in the PDP indication. Study 020 demonstrated the following:
  - Statistically significant and clinically meaningful improvement was observed in the pimavanserin group relative to placebo in the SAPS-PD primary endpoint at Week 6 with an LSM difference (pimavanserin-placebo) of -3.06 (p=0.001, effect size=0.50).
  - In the prespecified analysis of the subgroup of PDP patients with mild cognitive impairment (MMSE score 21-24; ~25% of patients), the observed LSM difference was higher: -5.71 (p=0.002, effect size=0.99).
  - Responder analyses also demonstrated a clinically meaningful response in a majority of patients.
- Study 045 was a randomized withdrawal study that enrolled patients with DRP and met the primary endpoint O'Brien-Fleming stopping rule at the IA (HR=0.35, 95%

CI: 0.17, 0.73; one-sided p=0.0023, O'Brien-Fleming stopping rule one-sided p<0.0033). DRP patients included PDD patients (~18%), who demonstrated very large treatment difference compared to placebo (HR=0.05, 95% CI: 0.02, 0.18, one-sided p<0.0001). However, these results in the PDD patient group are primarily driven by differences in the rates of relapse of PDD patients on placebo in the randomized period (an effect we believe is associated with their use of dopaminergic motor therapies which are known to exacerbate psychotic symptoms). As evident from the tipping point simulation based analyses, other dementia subgroups, specifically ADP, also contributed meaningfully to the overall significant efficacy of pimavanserin in this study. Examination of the data from the ADP subgroup, the largest subgroup in the study, comprising 66.3% of patients, showed the following:

- Clinically meaningful reductions in hazard of relapse (38% [all doses] to 53% [34 mg dose]) versus placebo.
- Symptom severity analyses evaluating severity of hallucinations and delusions over time following randomization into the DB period show maintenance of benefit of pimavanserin over placebo.
- Responder analyses evaluating categorical worsening of symptoms showed pimavanserin was consistently better than placebo (van Elteren test, p=0.04), with single digit NNTs.
- The consistency of efficacy favoring pimavanserin over placebo across various efficacy measures further supports pimavanserin benefit in ADP.
- A strong exposure-response relationship was observed, with higher exposure associated with a lower risk of relapse.
- The proposed therapeutic dose of pimavanserin 34 mg consistently showed greater efficacy than overall on all endpoints.
- An additional, post-hoc analysis, covariate adjusted Cox regression model correcting for confounding effects of baseline disease severity variables between pimavanserin and placebo was conducted in the ADP subgroup. This showed consistent, clinically meaningful benefit seen with the primary analysis model (HR=0.48, 95% CI: 0.19, 1.16) with slightly stronger effect observed when patients receiving pimavanserin 34 mg were examined (HR=0.35, 95% CI: 0.14, 0.91).

3.1 Study 019

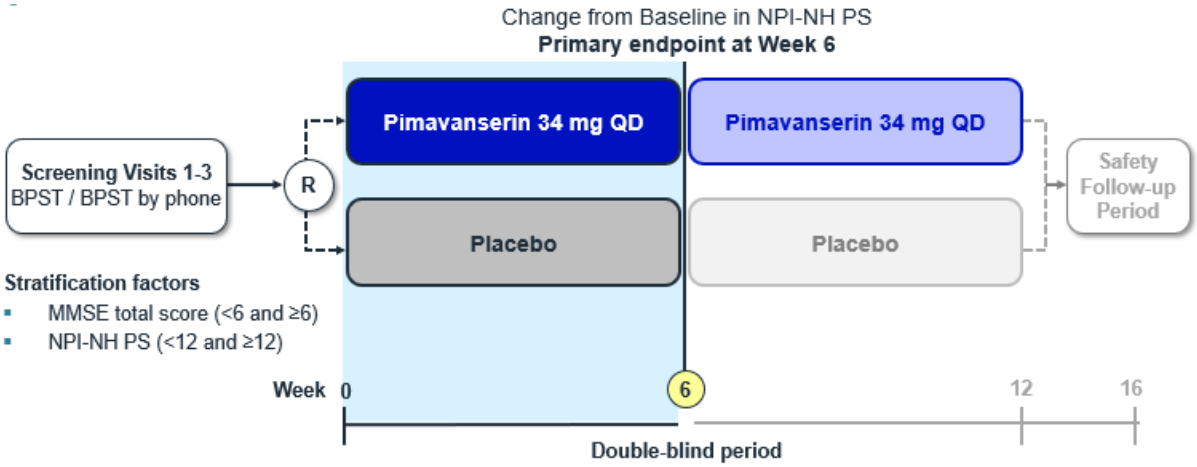
3.1.1 Study Design

Study 019 was a randomized, DB, placebo-controlled, parallel-group study in patients (mean age: 85.9 years) with possible or probable AD conducted across 133 nursing care homes in the United Kingdom (NINCDS-ADRDA criteria). Patients had persistent psychotic symptoms despite receiving psychosocial therapy for psychosis and symptoms severe enough to warrant treatment with an antipsychotic agent (NPI-NH score of ≥4 on either the Hallucinations or Delusions scale, or a combined score of ≥6).

Patients were randomized 1:1 to pimavanserin 34 mg QD or placebo stratified by baseline MMSE total score (<6 and ≥6) and NPI-NH PS (<12 and ≥12) and entered into a 12-week DB treatment period. The primary endpoint in Study 019 was change from Baseline to Week 6 (Day 43) in the NPI-NH PS.

The second 6 weeks of Study 019 (Weeks 6-12) were included principally for an assessment of safety requiring longer duration of treatment, specifically to assess the potential for adverse cognitive effects of pimavanserin treatment. During this period, efficacy was also evaluated on an exploratory basis. Following the completion of the DB period or early termination, patients entered into the 4-week safety follow-up period (Figure 3–1).

Figure 3–1 Study Design – Study 019



Abbreviations: BPST= brief structured psychosocial therapy; MMSE=Mini-Mental State Examination; NPI-NH=Neuropsychiatric Inventory–Nursing Home Version psychosis score; QD=once daily; R=randomized

3.1.1.1 Enrollment Criteria

Key inclusion criteria (IC) included:

- Male or female, ≥50 years of age, and a nursing home resident for ≥4 weeks
- Diagnosis of possible or probable AD as defined by the NINCDS-ADRDA criteria
- At least a 1-month history of psychotic symptoms (hallucinations and/or delusions) that developed after the diagnosis of AD was established
- Symptoms severe enough at Screening and Baseline to warrant treatment with an antipsychotic agent as documented by Domains A and B of the NPI-NH, and defined as a score of 4 or greater on either the hallucinations (frequency×severity) or delusions (frequency×severity) scales or a total combined score of 6 or greater

Key exclusion criteria (EC) included:

- Have psychotic symptoms (hallucinations and/or delusions) which are likely a part of a toxic, metabolic or infection-induced delirium/encephalopathy, psychosis due to substance abuse, psychosis associated with schizophrenia, bipolar disorder, or psychotic depression
- Patients with an MMSE score of <1 or >22
- Use of any medications prohibited or in a manner otherwise restricted as per protocol

3.1.1.2 Primary Endpoint

The primary efficacy endpoint was change from Baseline to Week 6 (Day 43) in NPI-NH PS, a validated scale (Wood et al. 2000). The primary endpoint was evaluated at 6 weeks given the regulatory precedent for antipsychotic drug development (Khin et al. 2012; EMA guidance 2012). Additionally, natural history studies have shown that transient, spontaneous improvement can occur without treatment in subsequent weeks with relapse over subsequent months (Vik-Mo et al. 2018). This natural history supports the Week 6 endpoint in a clinical trial.

The NPI-NH scale is described further in Appendix Section 7.3.

3.1.1.3 Statistical Analysis Methods

The Full Analysis Set (FAS), defined as all randomized patients who received at least one dose of study drug and had both a Baseline and at least one post-baseline NPI-NH PS evaluation, was used for the analyses of all efficacy endpoints.

The primary efficacy endpoint was analyzed using mixed-effect model repeated measures (MMRM). The model included the fixed-effect categorical factors of baseline MMSE category (<6 and ≥6), baseline NPI-NH PS (as a continuous value), treatment arm (pimavanserin 34 mg and placebo), visit (Days 15, 29, 43, 64, and 85), and treatment-by-visit interactions. An unstructured covariance pattern was used to estimate the variance covariance matrix of the within-patient repeated measures.

3.1.2 Study Participants

3.1.2.1 Patient Disposition

A total of 181 patients (90 pimavanserin 34 mg and 91 placebo) were randomized, and 178 patients (87 pimavanserin 34 mg and 91 placebo) were included in the FAS. Three patients were excluded from the FAS because they did not have a post-baseline NPI-NH PS. A total of 140 patients (77%) completed the study: 67 patients (74%) in the pimavanserin group and 73 patients (80%) in the placebo group. In the Safety Analysis Set, the most common reasons for discontinuation were AEs (7% in pimavanserin group, 11% in the placebo group) and withdrawal by patient (8% in the pimavanserin group, 4% in placebo group).

3.1.2.2 Patient Demographics and Baseline Characteristics

The two treatment groups were well balanced for demographics or other characteristics at Baseline (Table 3–1). The mean age of randomized patients was approximately 86 years, and most of the patients were female and White. The mean MMSE score of patients was 10, and the mean duration of psychotic symptoms was approximately 24 months.

Table 3–1 Demographics and Baseline Disease Characteristics (Safety Analysis Set) – Study 019

Parameter Statistic	Pimavanserin 34 mg (N=90)	Placebo (N=91)
Age (years), Mean (minimum, maximum)	85.7 (68, 99)	86.1 (64, 99)
Age ≤85 years, n (%)	41 (45.6)	41 (45.1)
Age >85 years, n (%)	49 (54.4)	50 (54.9)
Sex, n (%)		
Male	17 (18.9)	18 (19.8)
Female	73 (81.1)	73 (80.2)
Race, n (%)		
White	84 (93.3)	89 (97.8)
Non-White	6 (6.7)	2 (2.2)
Duration of ADP months, Mean (minimum, maximum)	25.60 (1.7, 182.0)	22.70 (1.7, 76.9)
Duration of AD months, Mean (minimum, maximum)	68.03 (8.4, 232.9)	55.52 (9.0, 128.5)
NPI-NH psychosis score,[a] Mean (minimum, maximum)	9.5 (4, 24)	10.0 (4, 24)
NPI-NH psychosis score ≥12[a], n (%)	28 (31.1)	30 (33.0)
MMSE,[a] Mean (minimum, maximum)	10.2 (1, 21)	9.8 (1, 22)

Source: sNDA Table 2.7.3.2-21

Abbreviations: AD=Alzheimer's disease; ADP=Alzheimer's disease psychosis; MMSE=Mini-Mental State Examination; NPI-NH=Neuropsychiatric Inventory–Nursing Home Version; sNDA=supplemental new drug application

[a] Scores were obtained from continuous values in the database.

3.1.3 Efficacy Results

3.1.3.1 Primary Endpoint

Study 019 met its primary endpoint, demonstrating a statistically significant greater mean reduction from Baseline to Week 6 (Day 43) in the NPI-NH PS in the pimavanserin 34 mg group versus placebo in the FAS (p=0.045, effect size=0.32; Table 3–2, Figure 3–2). These results compare favorably to the off-label use of atypical antipsychotics where the efficacy is marginal (effect size ≤0.2) (Ma et al. 2014; Tampi et al. 2016; Maher et al. 2011). On average, patients in the pimavanserin group doubled the reduction from Baseline in their NPI–NH PS at Week 6 compared to the placebo group (40% vs. 19%). Of note, the magnitude of symptom reduction observed at Week 6 with pimavanserin in Study 019 is similar to that observed in PDP patients after 6 weeks of pimavanserin treatment in Study 020 (Section 3.4).

Importantly, in the prespecified subgroup of patients with more severe psychosis (i.e., NPI-NH PS ≥12 at Baseline), the magnitude of efficacy was more than double the overall ADP population (p=0.011, effect size=0.73) suggesting that a principal benefit in the study was seen in more severely psychotic patients in greatest need for pharmacologic therapy (Ballard et al. 2019) (Table 3–2).

Table 3–2 Primary Efficacy: Change From Baseline to Week 6 (Day 43) in NPI-NH PS (MMRM, OC, Full Analysis Set) – Study 019

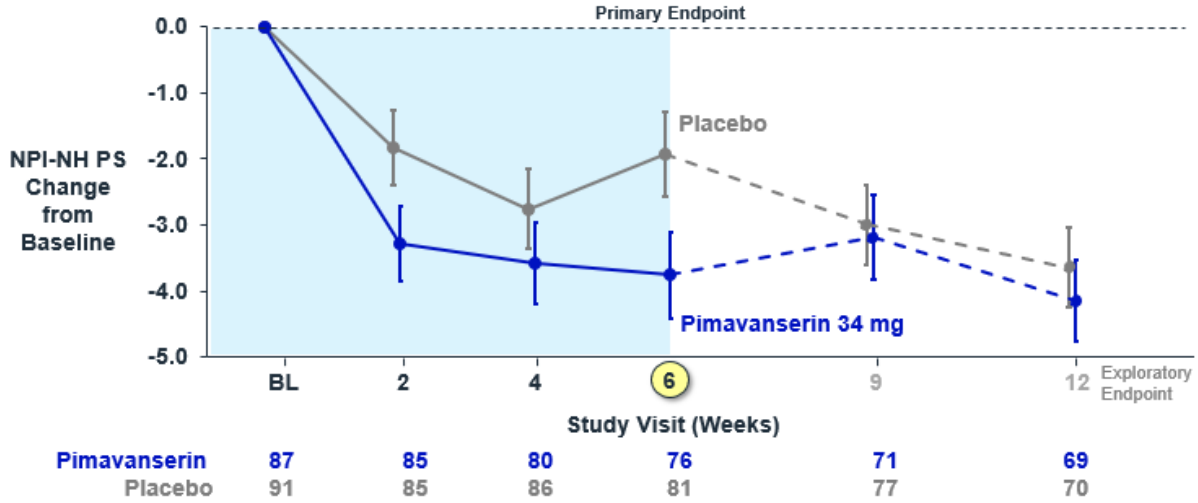
Timepoint Statistic	All Patients (Primary Analysis)		Patients with Severe ADP (Baseline NPI-NH PS ≥12)	
	Pimavanserin 34 mg (N=87)	Placebo (N=91)	Pimavanserin 34 mg (N=27)	Placebo (N=30)
Baseline (Day 1)				
Mean (SE)	9.52 (0.52)	10.00 (0.59)	15.30 (0.82)	16.67 (0.82)
Change from Baseline to Week 6 (Day 43)				
N	76	81	27	25
Mean (SE)	-3.82 (0.83)	-2.00 (0.75)	-9.63 (1.05)	-6.36 (1.31)
MMRM LSM (SE)	-3.76 (0.65)	-1.93 (0.63)	-10.15 (1.17)	-5.72 (1.21)
Difference in MMRM LSM (SE)	-1.84 (0.91)		-4.43 (1.68)	
95% of CI of difference	-3.64, -0.04		-7.81, -1.04	
MMRM p-value	0.045		0.011	
Effect size (Cohen's *d*)	0.32		0.73	

Source: sNDA Table 2.7.3.2-22

Abbreviations: CI=confidence interval; LSM=least squares mean; MMRM=mixed-effect model repeated measures; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version Psychosis Score; OC=observed cases; SE=standard error; sNDA=supplemental new drug application

Note: Across studies within this document, a positive effect size indicates a treatment effect in favor of pimavanserin.

Figure 3–2 Change from Baseline Through Week 12 in NPI-NH PS (MMRM, OC, Full Analysis Set) – Study 019



Source: Study 019 CSR Figure 1.1

Abbreviations: CSR=clinical study report; MMRM=mixed-effect model repeated measures; NPI-NH PS=Neuropsychiatric Inventory-Nursing Home Version Psychosis Score; OC=observed cases

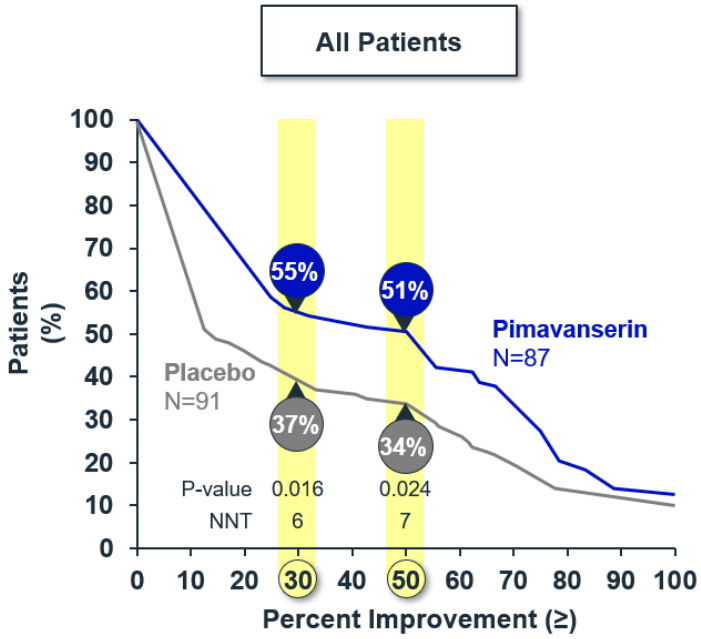
Although the primary efficacy endpoint was assessed at Week 6, the patients were followed in a DB fashion through 12 weeks. This duration was chosen principally to enable the assessment of potential adverse impact on cognition (as measured by MMSE). Efficacy was assessed from 6-12 weeks on an exploratory basis. Nevertheless, small nominal differences and lack of statistical separation between pimavanserin and placebo observed at the Week 9 and 12 timepoints raised concern about durability of effect seen at the Week 6 primary endpoint. This observation suggested the need to properly evaluate the maintenance of efficacy with pimavanserin. To address this, and with FDA agreement, a randomized withdrawal (relapse-prevention) study was proposed and initiated. Study 045, DRP study, was conducted and confirms maintenance of pimavanserin efficacy.

3.1.3.2 Responder Analysis

An NPI-NH PS responder analysis was conducted, which supported the significant and clinically relevant treatment effect of pimavanserin. The cumulative response curves looking at all possible responder cutoffs (0%-100% improvement) consistently showed that the pimavanserin group had a higher proportion of patients responding, as compared to the placebo group (Figure 3–3). The subgroup of patients with more severe psychosis at OL Baseline (NPI-NH PS ≥12) demonstrated more robust efficacy. The nominal p-values from the non-parametric (van Elteren) test of the two curves for all patients and the subgroup with more severe psychosis are 0.052 and 0.004, respectively.

Response on scales evaluating psychosis severity is generally defined as a 30% reduction from the Baseline score, or, in some cases, as a 50% reduction from the Baseline score (EMA guidance 2012; Durgam et al. 2015; Leucht 2014). By both of these definitions, a greater proportion of patients responded to pimavanserin versus placebo at Week 6 and achieved nominal statistical significance (55.2% vs. 37.4%, p=0.016; number needed to treat [NNT] [CI]=6 [4, 30] when response is defined as a ≥30% reduction and 50.6% vs. 34.1%, p=0.024; NNT [CI]=7 [4, 46], when response is defined as a ≥50% reduction). (Citrome et al. 2013).

Figure 3–3 Cumulative Response Curves Based on Percent Improvement in NPI-NH PS at Week 6 (Full Analysis Set) - Study 019



Sources: Study 019 CSR Addendum Figures AH.CDFResponder.M, AH.CDFResponder.M.baseGE12; Tables AH.NNT.fas; AH.NNT.npi

Abbreviations: CSR=clinical study report; NNT=number needed to treat; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version Psychosis Score

Note: A patient is considered as meeting the response cutoff if the improvement in NPH-NH PS at Week 6 is ≥ the response cutoff. Subjects whose NPI-NH PS score at Week 6 worsened from Baseline were considered as having 0% improvement.

NNT is calculated as 1/(incidence on placebo – incidence on pimavanserin) and rounded up to the next integer. The denominator is the number of randomized subjects with at least one post-DB-baseline SAPS-H+D score.

3.1.4 Efficacy Conclusions - Study 019

In conclusion, Study 019 was a parallel-group, DB, placebo-controlled study that independently demonstrated statistically significant efficacy of pimavanserin 34 mg QD in the treatment of patients with ADP. Moreover, the efficacy was clinically meaningful as demonstrated by the effect size, responder analyses, and NNTs, which were ≤10. Additional exploratory efficacy analyses (e.g., responder analyses, patients with more severe psychosis) confirmed the primary efficacy results and supported the clinical meaningfulness of the primary efficacy endpoint results. The apparent decrease in magnitude of effect after the 6-week primary endpoint led to an agreement between Acadia and the FDA to a methodologically accepted randomized withdrawal study design (Study 045) to assess and establish maintenance of pimavanserin efficacy.

3.2 Study 019: Study Design and Conduct Review Issues Raised in the CRL

The design of Study 019 is consistent with the expectations for an adequate and well-controlled study as stipulated in relevant FDA regulations. Additional analyses conducted to understand the potential impact of the observed protocol deviations on study results consistently supported the primary efficacy conclusion.

3.2.1 Study Design

Acadia considers the design of Study 019 consistent with the applicable FDA regulations that define the requisite characteristics for an adequate and well-controlled study, as set forth in 21 CFR 314.126(b). Notable features of the study included:

- Principal Investigator was Dr. Clive Ballard, a recognized expert in the dementia field, including clinical research (Ballard et al. 2018).
- Randomized, double-blind, and placebo-controlled design
- Patients recruited from 133 care homes in wider London, United Kingdom area
- Twenty Sub-Investigators were trained and employed as raters for assessment of the primary endpoint
- Treatment-group randomization was stratified by Baseline psychosis severity and cognitive status categories

3.2.2 Study Conduct

Acadia acknowledges the noteworthy nature and quantity of identified protocol deviations, which were fully disclosed and evaluated in the original CSR and subsequent documents. To assess the potential impact of these deviations on the study results and conclusions, qualitative and quantitative aspects of reported protocol deviations are discussed below, including a number of sensitivity analyses.

Various analyses of the Per Protocol Analysis Set were conducted. Analyses of the primary endpoint conducted on both the FAS and Per Protocol Analysis Set confirmed the lack of impact of the protocol deviations on the overall efficacy conclusion of the study (Table 3–3; Figure 3–4, per protocol analysis). In fact, these analyses suggest that once protocol deviations are accounted for, study results appear even stronger in favor of pimavanserin. Importantly, while Per Protocol analyses can be susceptible to bias because the treatment groups may not be comparable, this may not be the case for Study 019 because only one subject was excluded based on a postrandomization deviation.

Table 3–3 Primary Endpoint: NPI-NH PS Change From Baseline to Week 6 (Day 43): Full Analysis Set vs. Per Protocol Analysis Set (MMRM) – Study 019

Full Analysis Set	**PIM 34 mg (N=87)**	**Placebo (N=91)**	**Delta**	**Effect size**	**P-value**
	-3.76	-1.93	-1.84	0.32	0.045
Per Protocol Analysis Set	**PIM 34 mg (N=45)**	**Placebo (N=50)**	**Delta**	**Effect size**	**P-value**
	-5.57	-2.27	-3.31	0.61	0.006

Sources: Study 019 CSR Tables 14.2.1.1.1 (FAS) and 14.2.1.1.2 (PP)

Abbreviations: CSR=clinical study report; MMRM=mixed-effect model repeated measures; NPI-NH=Neuropsychiatric Inventory–Nursing Home Version;

Note: the MMRM model included treatment groups, baseline MMSE strata (<6 and ≥6), baseline NPI-NH PS score as continuous variable, visit and treatment by visit interactions.

Protocol Deviations Related to Timing of Psychotic Symptom Documentation Versus AD Diagnosis

Inclusion criterion #3 required that psychotic symptoms developed only after the diagnosis of AD was established. The purpose of this criterion was to confirm that the psychosis was observed in the context of AD and not due to another primary psychiatric or medical condition. It is noteworthy that:

- Due to difficulties establishing the date of AD diagnosis, the date of onset of psychosis was sometimes reported as "UNK" (or unknown) or reported as the same date as AD onset for these patients resulting in protocol deviations.
- Investigator had confirmed and documented that the study participants had an AD diagnosis and had psychosis which was not attributed to other medical conditions (i.e., delirium, substance abuse, schizophrenia, or other underlying psychiatric illness). To this end, presence of psychotic disorders not associated with AD were excluded by psychiatric assessment, medical history and medical records, in addition to robust assessment of ADP symptoms to confirm robustness of primary diagnosis.
- These deviations were balanced at study entry between the two treatment arms (20 patients in the pimavanserin group and 19 patients in the placebo group).
- The lack of treatment interaction with Per Protocol covariate status on inclusion criterion #3 (Figure 3–4, unable to confirm date of ADP diagnosis) suggested no significant impact of these protocol deviations on the efficacy conclusion.

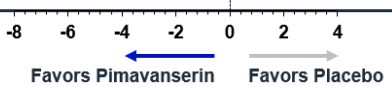
Protocol Deviations Related to Restricted and Prohibited Concomitant Medications

Although some study patients used prohibited concomitant medications during the study, there were a number of mitigating factors:

- There were no deviations related to prohibited use of concomitant antipsychotics between Baseline and the assessment of the primary endpoint at Week 6.
- Almost half (44%) of the concomitant medication protocol deviations were related to the use of citalopram or escitalopram at Baseline (exclusion criterion #7; ≤20 mg QD), which were originally restricted because of their potential to increase corrected QT interval on electrocardiogram (QTc interval). The protocol was amended to allow the use of limited doses (20 mg QD) of citalopram or escitalopram if corrected QT interval using Fridericia's correction method (QTcF) values were below 425 ms.
- A full safety evaluation indicated that no increased risk of QTc prolongation or cardiovascular events was observed as a result of concomitant medication use.
- The number of protocol deviations related to the use of exclusionary medication at the time of randomization was balanced between the two treatment arms (23 patients in the pimavanserin group and 19 patients in the placebo group).
- The lack of treatment interaction with per protocol covariate status on exclusion criterion #7 (Figure 3–4; use of prohibited/restricted concomitant medications) suggested no significant impact of these protocol deviations on the efficacy conclusions.

Figure 3–4 Exploratory Analyses Evaluating the Impact of Protocol Deviations on Primary Efficacy Endpoint – Study 019

	Pimavanserin Week 6	Placebo Week 6	LSM Difference (95% CI)	MMRM p-value	Covariate*trt p-value
Primary analysis	76/87	81/91	**-1.84** (-3.64, -0.04)	**0.045**	
Per-protocol covariate	76/87	81/91	**-1.88** (-3.67, -0.09)	**0.040**	**0.989**
Per-protocol	38/45	46/50	**-3.31** (-5.66, -0.96)	**0.006**	
Not per-protocol	38/45	35/41	**-0.65** (-3.46, 2.17)	**0.648**	
Unable to confirm date of ADP diagnosis	76/87	81/91	**-1.84** (-3.64, -0.04)	**0.046**	**0.977**
Meet	56/67	63/72	**-2.32** (-4.27, -0.37)	**0.200**	
Did not meet	20/20	18/19	**-0.87** (-5.24, 3.51)	**0.691**	
Use of prohibited / restricted conmeds	76/87	81/91	**-1.87** (-3.67, -0.06)	**0.043**	**0.428**
Meet	56/64	65/72	**-1.77** (-3.85, 0.32)	**0.096**	
Did not meet	20/23	16/19	**-2.42** (-6.26, 1.43)	**0.210**	



Source: Study 019 CSR Addendum Figure AH1.4.PP

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; conmeds=concomitant medication; CSR=clinical study report; LSM=least squares mean; MMRM=mixed-effect model repeated measures; trt=treatment

Informed Consent

It is important to note that while procedural errors in informed consent documentation occurred, the spirit of the informed consent process was achieved:

- Informed consent forms were obtained and signed by the LARs prior to randomization for all patients in Study 019.
- A thorough review of study documentation has led to a conclusion that the protection of rights, safety, and welfare of patients participating in this clinical research study were preserved.

In summary, the study design of Study 019 is consistent with the expectations for an adequate and well-controlled study as stipulated in relevant FDA regulations, and additional analyses conducted to understand the potential impact of the observed protocol deviations consistently supported the primary efficacy conclusion.

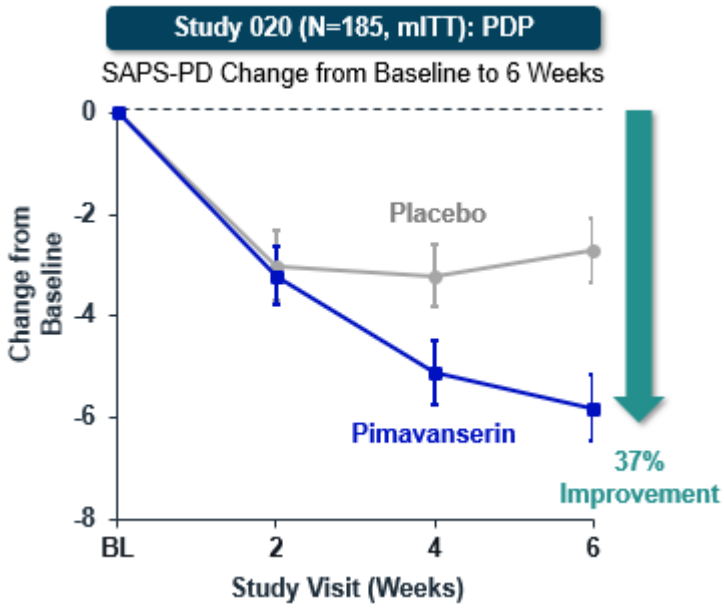
3.3 Study 020

Study 020 was a randomized, DB, placebo-controlled, outpatient study in patients with PDP (N=199; mean age ~72 years) and was the pivotal study leading to pimavanserin FDA-approval for the treatment of PDP. The study included a subset of patients with an MMSE score <25 at Baseline comprised approximately 25% of patients from Study 020.

The study included a 2-week screening period, 6 weeks of DB treatment, and 4 weeks of safety follow-up. Patients meeting eligibility criteria at the end of the screening period were randomized in a 1:1 ratio to either placebo or pimavanserin 34 mg QD for the duration of the DB treatment period.

The primary efficacy endpoint was the mean change in the SAPS-PD score from Baseline to Day 43 (Week 6). The treatment difference based on all randomized PD patients (with or without dementia) was -3.06 (p=0.001, effect size=0.50) (Figure 3–5). Analyses of the subset with an MMSE score <25 at Baseline showed a robust effect in the pimavanserin 34 mg group compared with the placebo group (treatment difference of 5.71, p=0.002, effect size=0.99). Responder analyses also demonstrated a clinically meaningful response in a majority of patients.

Figure 3–5 SAPS-PD Score Change From Baseline (LSM±SE) Through Week 6 (MMRM; OC) (mITT Analysis Set) – Study 020

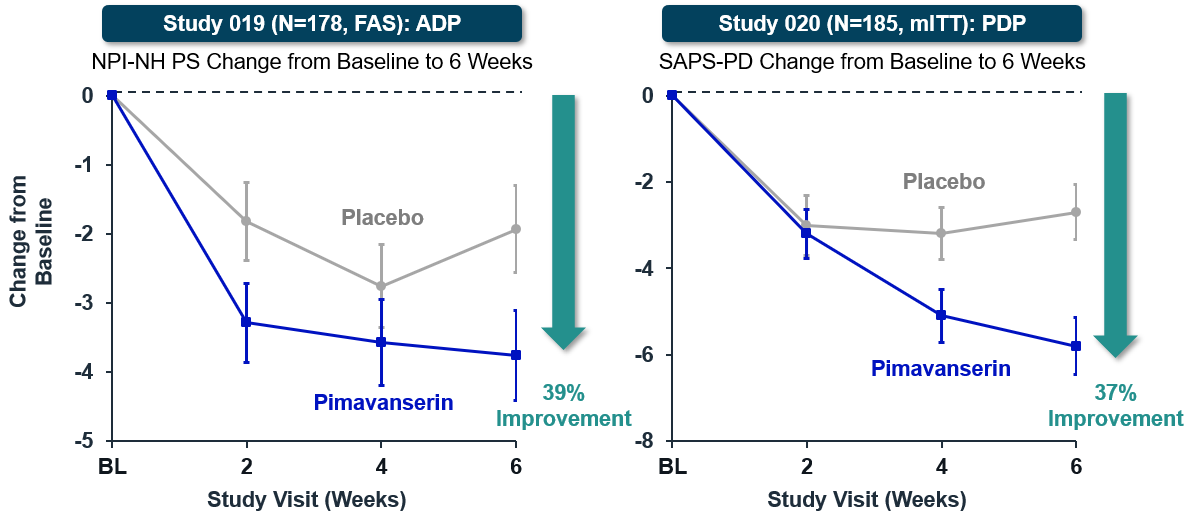


Sources: Study 020 CSR Table 14.2.1.1.1, Figure 1.1
Abbreviations: CSR=clinical study report; LSM=least square means; mITT=modified Intention-to-treat; MMRM=mixed-effects model repeated measures; OC=observed cases; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson's disease; SE=standard error
Note: Data presented as LSM±SE.
The mITT was defined as randomized subjects with Baseline and at least one post-baseline value of the primary efficacy variable.
The SAPS-PD scale is described in Appendix Section 7.3.

3.4 Consistent Efficacy of Pimavanserin in Studies 019 (ADP) and 020 (PDP)

The treatment effect in patients with ADP is consistent not only across studies; it is also consistent with the treatment effect observed in patients with PDP, which was considered clinically meaningful by the FDA (Mathis et al. 2017) and resulted in the original approval of NUPLAZID for the treatment of PDP. Comparing the results of the two studies in the acute treatment paradigm, Study 019 in patients with ADP and Study 020 in patients with PDP, both reached statistical significance on their primary endpoints at Week 6 ($p<0.05$) and their primary endpoints measuring change from Baseline in severity of psychotic symptoms were remarkably similar (Study 019 NPI-NH PS change, 39%; Study 020 SAPS-PD change, 37%) (Figure 3–6) and greater than twice the change from Baseline observed in the placebo groups.

Figure 3–6 Consistent and Similar Response to Pimavanserin Treatment in Parallel Placebo-Controlled Studies: Study 019 in ADP (Left Panel) and Study 020 in PDP (Right Panel)



Sources: Study 020 CSR Table 14.2.1.1.1, Figure 1.1; Study 019 CSR Table 14.2.1.1.1; Study 019 CSR Addendum Figure AH.NPIb.fas

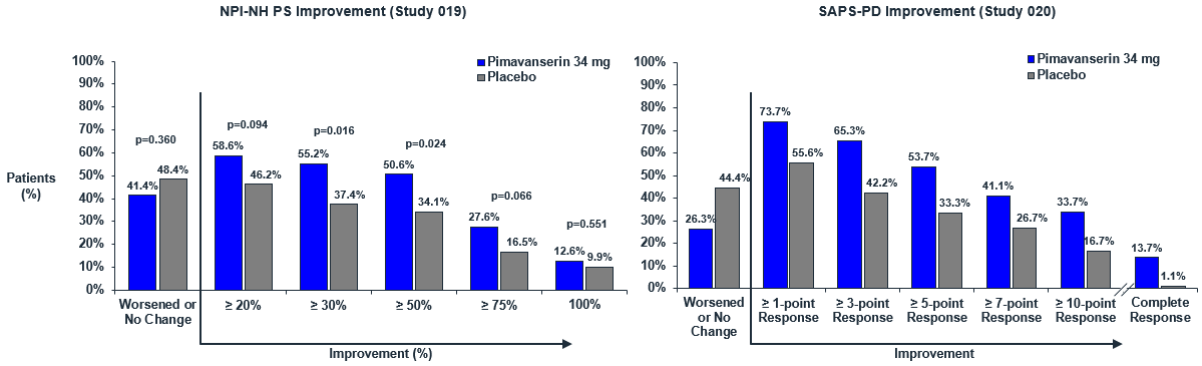
Abbreviations: ADP=Alzheimer's disease psychosis; CSR=clinical study report; FAS=Full Analysis Set; LSM=least square means; mITT=modified Intention-to-treat; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version Psychosis Score; PDP=Parkinson's disease psychosis; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson's disease; SE=standard error

Note: Data presented as LSM±SE.

For Studies 019 and 020, the FAS and mITT were defined as randomized subjects with Baseline and at least one post-baseline value of the primary efficacy variable.

Furthermore, multiple responder analyses in Study 019 and Study 020 consistently showed a clinically meaningful response in a majority of patients (Figure 3-7; Table 3–4) (the analyses conducted for Study 020 leading to a novel presentation of efficacy in the NUPLAZID FDA-approved labeling) (Mathis et al. 2017).

Figure 3–7 Responder Analyses for Study 019 in ADP (Left Panel) and Study 020 in PDP (Right Panel)



Source: Study 019 CSR Figures 11-3; Study 020 Figure adapted from NUPLAZID US Prescribing Information Figure 4 (Acadia Pharmaceuticals Inc. 2020, Appendix Section 7.1)
Abbreviations: CSR=clinical study report; ITT=Intention-to-treat; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version Psychosis Score; SAPS-PD=Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions (9 items specific to Parkinson's disease); US=United States
Note: For Study 020, complete response=SAPS-PD score reduced to 0 from Baseline. Subjects with missing values were counted as non-responders.
For Study 019, missing values imputed as nonresponders. P-values from Cochran-Maentel-Haenszel (CMH) test, stratified by baseline MMSE category (<6 and ≥6; 2 levels) and NPI-NH PS category (<12 and ≥12; 2 levels)

Table 3–4 Responder Analyses and NNT's for Study 019 (ADP) and Study 020 (PDP)

Study Primary Endpoint Scales	≥30% Symptom Reduction				≥50% Symptom Reduction			
	PIM	PBO	Adjusted Difference	NNT (95% CI)	PIM	PBO	Adjusted Difference	NNT (95% CI)
Study 019 NPI-NH PS[a]	55%	37%	17% (p=0.02*)	6 (4, 30)	51%	34%	16% (p=0.02*)	7 (4, 46)
Study 020 SAPS-PD[b]	49%	36%	12% (p=0.09)	8 (ns)	37%	28%	8% (p=0.24)	11 (ns)

Sources: Study 019 CSR Table 14.2.1.4.1; Study 019 CSR Addendum Table AH.NNT.fas; Study 020 CSR Tables 14.2.3.20.3 and 14.2.3.20.4
Abbreviations: CI=confidence interval; CSR=clinical study report; PIM=pimavanserin 34 mg QD; PBO=placebo; NNT=number needed to treat; NPI-NH PS= Neuropsychiatric Inventory–Nursing Home Version Psychosis Score; ns=not statistically significant; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson's disease
[a] The primary endpoint for Study 019 was change from Baseline to Day 43 (Week 6) in NPI-NH PS. Subjects missing NPI-NH PS scores at Week 6 are considered as non-responders. Adjusted difference and p-values were calculated using weighting scheme of Cochran-Mantel-Haenszel test, stratified by baseline NPI-NH PS category (<12 and ≥12) and baseline MMSE category (<6 and ≥6).
[b] The primary endpoint for Study 020 was change from Baseline to Day 43 (Week 6) in SAPS-PD. Subjects missing SAPS-PD scores at Week 6 are considered as non-responders. Adjusted difference and p-values were calculated using weighting scheme of Cochran-Mantel-Haenszel test, stratified by baseline SAPS-PD severity.
* nominally statistically significant; ns=not statistically significant and therefore CI could not be calculated.
Note: NNT is calculated as 1/(response rate in PIM – response rate in PBO) and rounded up to the next integer

3.5 Study 045

Study 045 was a multi-center, placebo-controlled, randomized withdrawal (relapse prevention) study in patients with all-cause dementia (NIA-AA 2011 guidelines; MMSE range between 6 and 24) and met clinical criteria for one (or more) of the following disorders: possible or probable AD, PDD, DLB, FTD, or VaD, based on Investigator's designation of most likely clinical diagnosis of dementia (Tariot et al. 2021). The study evaluated this population of DRP as a unitary construct and was informed by the scientific consensus that psychotic symptoms in dementia could be studied as a single unified entity given co-occurrence of various dementia pathologies (Cummings et al. 2020; Beach and Malek-Ahmadi 2021). Note: PDD patients enrolled in Study 045 differed from PDP patients enrolled in Study 020. While Study 045 enrolled PD patients with dementia, psychosis, and MMSE score between 6-24 (mean:19.4), Study 020 enrolled PD patients with psychosis and normal cognitive function or mildly cognitively impaired (i.e., MMSE range 21-30; mean: 26.3).

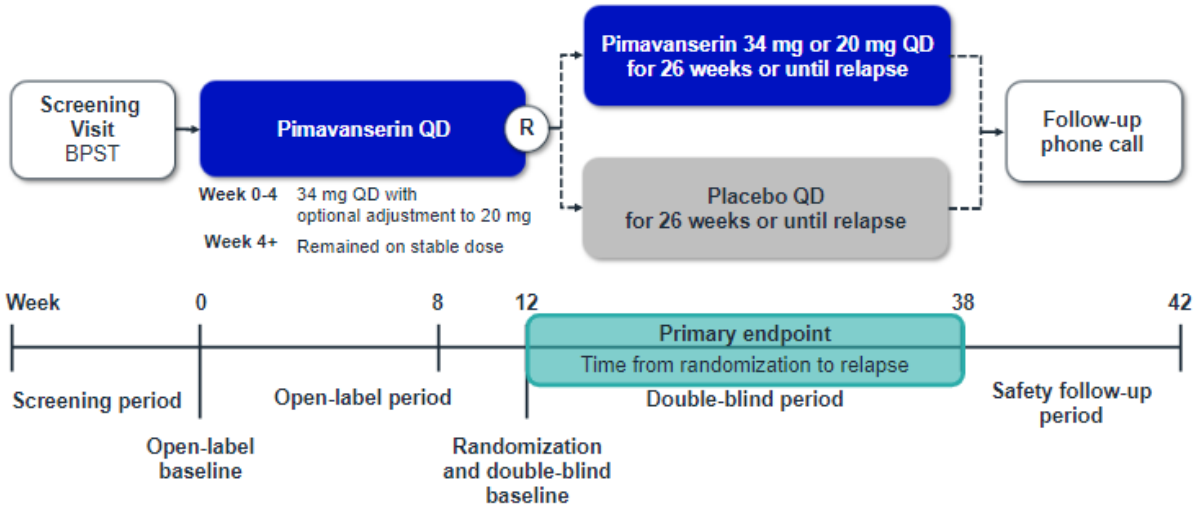
A randomized withdrawal design was agreed with the FDA as it is an optimal design to evaluate maintenance of effect without long-term placebo exposure, and is well accepted as the standard for maintenance trials in psychosis.

3.5.1 Study Design

3.5.1.1 Overview

Study 045 consisted of a Screening period of up to 5 weeks, an OL treatment stabilization period of 12 weeks, a DB treatment period of up to 26 weeks, and a safety follow-up period of approximately 4 weeks (Figure 3–8).

Figure 3–8 Study Design – Study 045



Abbreviations: BPST=brief psychosocial therapy; OL=open-label; QD=once daily; R=randomization
Note: Those patients who were stabilized at 34 mg during the OL period and then randomized to stay on pimavanserin 34 mg or placebo (randomized from 34 mg pimavanserin in the OL period) comprise the 34 mg analysis set.

During the Screening Period, the designated study partner/caregiver received instruction by trained site personnel for engaging in brief structured psychosocial therapy (BPST) with the patient with a frequency of 5 times per week (minimum of 3 times per week). The BPST was intended to aid the patient and caregiver in managing the patient's neuropsychiatric symptoms and, thus, to prevent patients whose psychosis was manageable with non-pharmacologic therapies from being enrolled (consistent with practice guidelines).

Patients meeting the eligibility criteria (Section 3.5.1.2) were enrolled in the OL period and received pimavanserin 34 mg QD beginning at Week 0 (OL Baseline). Dose adjustments to 20 mg QD were permitted between Weeks 1 and 4 based on tolerability. After Week 4, the patient's dose remained fixed at either 34 or 20 mg QD. Patients meeting the response criteria at Weeks 8 and 12 were randomly assigned 1:1 to continue their pimavanserin dose or matching placebo in the DB period. The response criteria, defined as ≥30% reduction from Week 0 on SAPS-H+D total score and a CGI-I score of ≤2 relative to Week 0, were designed to capture clinically relevant changes in hallucinations and delusions in combination with an improvement of "very much improved" or "much improved." The SAPS-H+D and CGI-I are further described in Appendix Section 7.3. Randomization was stratified by designated dementia subgroup (AD or FTD-spectrum disorders, VaD, and PDD or DLB) and region. Patients not meeting response criteria at Weeks 8 and 12 were withdrawn from study drug and entered into the safety follow-up period of the study.

During the DB period, relapse criteria were assessed by Investigators weekly for the first 2 weeks after randomization (Weeks 13 and 14), every 2 weeks until Week 26, every 4 weeks through Week 38, and at unscheduled visits. An independent adjudication committee (IAC) determined whether the criteria for protocol-defined relapse were met by adjudicating all double-blind early termination and relapse events that occurred before the study discontinuation date (the date when the Sponsor notified the study sites that the study was ending).

The protocol-defined relapse criteria for DRP included the following:

- Patient experienced a ≥30% increase (worsening) from Week 12 (DB Baseline) on the SAPS-H+D total score AND had a CGI-I score of 6 or 7 (much worse or very much worse) relative to the DB Baseline; or
- Patient was treated with an antipsychotic (other than pimavanserin) for dementia-related delusions and/or hallucinations; or
- Patient stopped study drug or withdrew from study for lack of efficacy (as reported by the patient or study partner/caregiver), or the Investigator discontinued study drug due to lack of efficacy; or
- Patient was hospitalized for worsening DRP.

Any patient who met any of the relapse criteria after randomization was withdrawn from the study and entered into the safety follow-up period of the study.

3.5.1.2 Enrollment Criteria

Key inclusion criteria included:

- Male or female ≥50 and ≤90 years of age
- All-cause dementia according to National Institute on Aging Alzheimer's Association guidelines, 2011
- MMSE score ≥6 and ≤24
- Met the clinical criteria for one of the following disorders, with or without cerebrovascular disease: dementia associated with PD, dementia with Lewy bodies, possible or probable AD, frontotemporal dementia-spectrum disorders, or vascular dementia
- Had psychotic symptoms for at least 2 months
- Had all of the following scores at Visit 1 (Screening) and Visit 2 (OL Baseline):
    - SAPS-H+D total score ≥10; AND
    - CGI-S ≥4 (moderately ill); AND

- SAPS-H+D global item (H7 or D13) score ≥4 (marked)

- If the patient was taking an antipsychotic medication at the time of Screening, the antipsychotic must have been discontinued 2 weeks or 5 half-lives (whichever was longer) prior to Visit 2.).

Key exclusion criteria included:

- Had psychotic symptoms that were primarily attributable to delirium, substance abuse, or a medical or psychiatric condition (e.g., schizophrenia, bipolar disorder, delusional disorder) other than dementia
- Had a current major depressive episode (within 3 months of Screening), according to the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition

3.5.1.3 Efficacy Endpoints

The primary efficacy endpoint was time from randomization to relapse (Section 3.5.1.1) in the DB period.

The key secondary endpoint was time from randomization to discontinuation from the DB period for any reason (other than termination of the study by the Sponsor). Exploratory endpoints in the OL and DB period included change and percent change from Baseline in SAPS-H+D, SAPS-H, and SAPS-D to assess hallucinations and delusions, as well as Clinical Global Impression–Severity (CGI-S) and CGI-I scores, which provided the clinician's view of severity and improvement of hallucinations and delusions. Additional information on the respective efficacy measures is provided in Appendix Section 7.3.

3.5.1.4 Statistical Analysis Methods

Determination of Sample Size

Study 045 planned to enroll approximately 356 patients to randomize approximately 178 patients with DRP who met the response criteria at Weeks 8 and 12 of the OL period.

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 (HR=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 IA 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 treatment groups (giving a total estimate of 178 patients).

Interim Efficacy Analysis

As prespecified in the study protocol and statistical analysis plan, an efficacy IA was conducted after 40 adjudicated relapse events had accrued. The prespecified stopping criterion was defined as a one-sided p-value less than the O'Brien-Fleming stopping boundary of 0.0033.

All analyses were prespecified for the overall DRP patient population targeted in the study. In accordance with the alignment with FDA at the End of Phase 2 meeting, the prespecified stopping criterion at the IA were focused on the overall DRP study population and did not entail expectation for the separate analyses by dementia subgroups within the overall DRP study population.

The study was terminated based on recommendations of the data and safety monitoring board (DSMB) following positive results at IA, which met the prespecified stopping criteria for efficacy.

Primary Efficacy Analysis for DRP Population

The analysis of the primary efficacy endpoint (time from randomization to relapse) in the DB period was based on independent adjudication committee adjudicated relapse events for patients in the Intention-to-treat (ITT) Analysis Set, which included all randomized patients. Patients who discontinued early or completed the study without having experienced a relapse event were censored at the date of their last SAPS-H+D assessment. Patients ongoing in the DB period as of the database cutoff date for the IA were censored at the date of their last SAPS-H+D assessment on or prior to the IA database cutoff. The treatment effect was represented by the HR. The time from randomization to relapse in the DB period was compared between treatment groups using a Cox regression model with covariates for designated dementia subgroup (AD or FTD-spectrum disorders, VaD, or PDD or DLB), and region (North America, Western Europe, Eastern Europe, and Latin America), and a robust sandwich-type variance estimator.

A hierarchical testing procedure was used to control the overall type I error rate for the primary and key secondary efficacy endpoints with both endpoints being tested at the one-sided 0.0033 significance level. Hypothesis testing occurred for the primary endpoint followed by the key secondary endpoint.

Key Secondary Efficacy Analysis for DRP Population

The key secondary efficacy endpoint (time from randomization to discontinuation) was analyzed using the same Cox regression model described for the primary efficacy endpoint. Patients who did not experience a relapse event and who completed the 26 week DB period

were censored at the date of their last dose. Patients ongoing in the DB period as of the IA database cutoff date were censored at that date. For patients who experienced a relapse event, the time to discontinuation was calculated as date of relapse minus date of randomization plus 1. For patients who did not experience a relapse event and who discontinued early from the DB period for any reason other than termination of the study by Sponsor, the time to discontinuation was calculated as date of last dose minus date of randomization plus 1.

Open-Label Exploratory Endpoints

Observed values and change from OL Baseline in SAPS-H+D scores, as well as OL responder rates were summarized for all patients combined, by randomization status, and by final dose level of OL pimavanserin (34 mg or 20 mg) for the Open-Label Safety Analysis Set and by protocol designated dementia subgroup (AD or FTD spectrum disorders, VaD, PDD or DLB), as well as by post-hoc defined dementia subgroup (AD, PDD, or Other). For the post-hoc analysis, complete response was defined as having SAPS-H+D score of 0 (100% reduction) and CGI-I score of 1 or 2 at OL Week 12.

Additional Analyses

To further evaluate the efficacy of pimavanserin observed in Study 045, a series of additional analyses were performed and are described as follows:

- Additional analyses of the *overall DRP dataset* and *dementia subgroups* in Study 045 to evaluate:
    - Pattern of psychotic symptoms across dementia subgroups, qualitatively and quantitatively, at OL and DB Baseline
    - Consistency and similarity of efficacy observed across dementia subgroups
    - Reasons for differential effect of PDD subgroup following withdrawal of pimavanserin treatment and possible impact of concomitant dopaminergic therapy
    - Extent of contribution to the overall positive results of Study 045 by PDD subgroup versus other dementia subgroups, principally ADP subgroup.

The above additional analyses demonstrated a consistent pimavanserin treatment effect across the dementia subgroups and the meaningful contribution of the ADP subgroup in the context of robustly positive DRP study.

- Additional analyses of efficacy were performed in the ADP subgroup of Study 045 to evaluate:

- Relapse rate
- Change in SAPS-H+D from Baseline in DB period
- Responder analysis in the DB period
- Consistency of efficacy across endpoints
- Exposure-response (E-R)
- 34 mg subgroup efficacy
- Covariate adjusted analysis on time from randomization to relapse and time to discontinuation

The above additional analyses provide supportive evidence for efficacy of pimavanserin in the ADP subgroup in the context of an overall robustly positive DRP study.

3.5.2 Study Participants

3.5.2.1 Patient Disposition

A total of 794 patients were screened during approximately 24 months of study enrollment, and 392 patients were enrolled in the OL period and initiated pimavanserin 34 mg.

Of the 392 patients enrolled and treated in the OL period, 41 were ongoing in the OL period at the time of the study discontinuation date. Of the remaining 351 patients, 217 (61.8%) met sustained response criteria and were randomized into the DB period. The most common reason for early termination during the OL period was lack of response (19.9%), which is concordant with the study design in which patients not meeting formal response criteria were required to terminate from the study. A total of 27 patients (7.7%) discontinued due to AEs and 17 patients (4.8%) withdrew consent. No definite pattern or characteristics were noted in patients who were terminated early from the study.

Of the 217 randomized patients, 66 patients (31 patients in the placebo group and 35 patients in the pimavanserin group) were ongoing at the time of the study discontinuation date and were not summarized further. The most common reasons for early termination during the DB period prior to the study discontinuation date were relapse of hallucinations and delusions associated with DRP and withdrawal of consent. All terminations due to withdrawal of consent were reviewed by the Investigator, IAC, and Study Medical Monitor to ensure that none were due to unreported lack of efficacy.

3.5.2.2 Patient Demographics and Baseline Characteristics

In the OL period, the mean age was 74.5 years, 58.4% of patients were female, 96.6% were White, and 53.3% were from Eastern Europe (Table 3–5). The majority of patients lived at

home (95.2%), and the most common caregiver relationship was either the patient's child (40.8%) or the spouse/partner (35.5%). Baseline demographics were generally balanced between patients randomized to the placebo and pimavanserin groups in the DB period.

At OL Baseline, the most likely primary cause of dementia in the enrolled patients was identified by Investigators as one of the following subgroup: AD (66.3%), PDD (15.1%), and "other" (18.6%), which included VaD (9.7%), DLB (7.1%), and FTD disorders (1.8%), each of which included a relatively small number of patients.

Table 3–5 Baseline Demographics and Disease Characteristics in the OL and DB Periods (OL Safety Analysis Set and DB Safety Analysis Set) – Study 045

	OL Period	DB Period	
Parameter	**Overall (N=392)**	**Pimavanserin (N=105)**	**Placebo (N=112)**
Age (years), mean (SE)	74.5 (0.42)	73.8 (0.82)	74.9 (0.81)
Sex, female, n (%)	229 (58.4)	62 (59.0)	69 (61.6)
Race, White, n (%)	371 (96.6)	103 (98.1)	107 (98.2)
Region, n (%)			
North America	118 (30.1)	28 (26.7)	29 (25.9)
Eastern Europe	209 (53.3)	65 (61.9)	67 (59.8)
Western Europe	38 (9.7)	5 (4.8)	7 (6.3)
Latin America	27 (6.9)	7 (6.7)	9 (8.0)
Most likely primary dementia subgroup, n (%)			
Alzheimer's disease	260 (66.3)	67 (63.8)	70 (62.5)
Parkinson's disease dementia	59 (15.1)	19 (18.1)	23 (20.5)
Other	73 (18.6)	19 (18.1)	19 (17.0)
Frontotemporal dementia spectrum disorder	7 (1.8)	1 (1.0)	2 (1.8)
Vascular dementia	38 (9.7)	12 (11.4)	13 (11.6)
Dementia with Lewy bodies	28 (7.1)	6 (5.7)	4 (3.6)
MMSE total score, mean (SE)	16.7 (0.24)	18.3 (0.53)	17.9 (0.55)
SAPS-H+D, mean (SE)	24.4 (0.47)	5.0 (0.51)	5.2 (0.51)
CGI-S, mean (SE)	4.7 (0.03)	2.3 (0.10)	2.3 (0.10)

Source: sNDA Table 2.7.3.2-4; Study 045 CSR Tables 11-2, 11-3, 11-5, 11-6

Abbreviations: OL=open-label; DB=double-blind; CGI-S=Clinical Global Impression–Severity CSR=clinical study report; MMSE=Mini-Mental State Examination; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions (20-item); SE=standard error; sNDA=supplemental new drug application

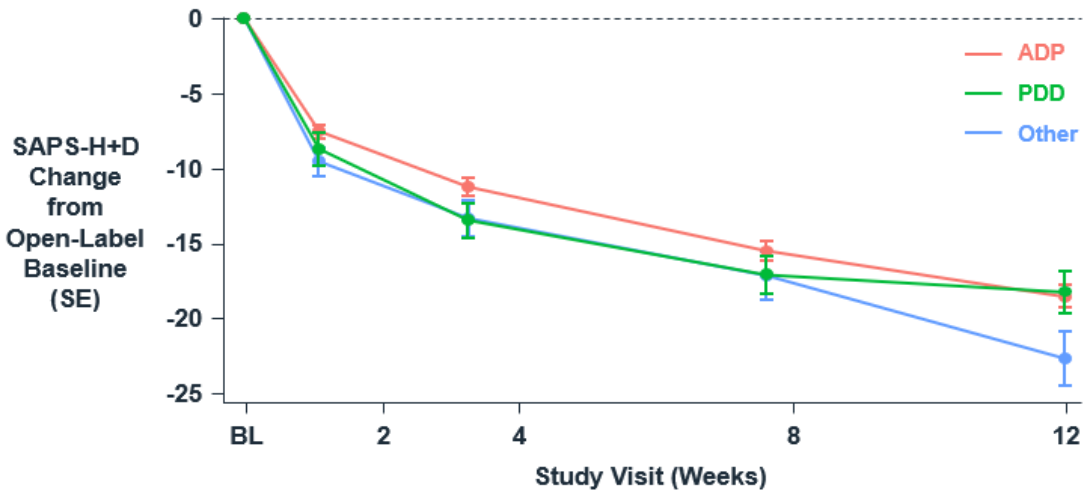
Note: Data in OL period column are baseline at entry to OL period; data in DB period columns are baseline at entry to DB period.

3.5.3 Efficacy Results

3.5.3.1 Open-Label Period Results

Over the course of the OL period, pimavanserin treatment resulted in substantial reduction in SAPS-H+D score across dementia subgroups (Figure 3–9). A total of 41 patients were ongoing in the OL period at the time of study discontinuation following the interim analysis and were withdrawn for administrative reasons. Of 351 remaining eligible patients, 217 (61.8%) had a sustained response (≥30% SAPS-H+D improvement and CGI-I very much or much improved at both Weeks 8 and 12) and were randomly assigned to continue receiving pimavanserin or to receive placebo in the DB period. The proportion of patients experiencing sustained response at the end of the OL period was generally similar across dementia subgroups (Table 3–6). Additionally, among the 351 eligible patients, a meaningful proportion of patients (20.8%) achieved complete response (defined as complete resolution of symptoms in SAPS-H+D and CGI-I of 1 or 2) at the end of the OL period.

Figure 3–9 SAPS-H+D Change from OL Baseline by Dementia Subgroup in the OL Period – Study 045



Source: Study 045 CSR Addendum Figure AH14.2.3.1.1.DEMC.GROUP

Abbreviations: ADP=Alzheimer's disease psychosis; CSR=clinical study report; DLB=dementia with Lewy bodies; FTD=frontotemporal dementia; OL=open-label; PDD=Parkinson's disease dementia; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales; SE=standard error; VaD=vascular dementia

Note: "Other" includes patients with a subgroup of VaD, DLB, or FTD.

Table 3–6 Study 045: Sustained and Complete Symptom Responses at OL Week 12

	Sustained Response[a] Rate	100% Symptom Reduction [b]
	% (n/N)[c]	% (n/N)[c]
Overall	61.8 (217/351)	20.8 (73/351)
ADP	59.8 (137/229)	19.2 (44/229)
PDD	71.2 (42/59)	27.1 (16/59)
Other[d]	60.3 (38/63)	20.6 (13/63)

Source: Study 045 CSR Addendum Table OLphase

Abbreviations: ADP=Alzheimer's disease Psychosis; CGI-I=Clinical Global Impression–Improvement; CSR=clinical study report; OL=open-label; PDD=Parkinson's disease dementia; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales.

a 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.

b This number reflects the percentage who had complete symptom reduction in SAPS-H+D (score=0) and a CGI-I score of 1 or 2 at Week 12; includes subjects in the OL phase who were randomized into the DB phase.

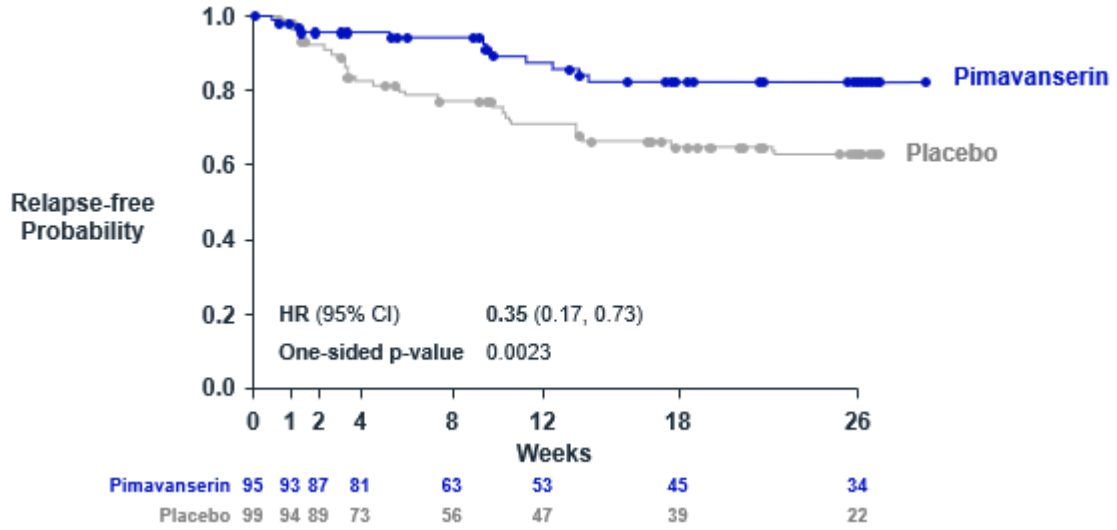
c Excluded 41 subjects who were ongoing at the time of study discontinuation.

d Other included patients with a subgroup of dementia with Lewy bodies, vascular dementia, or frontotemporal dementia.

3.5.3.2 Primary Efficacy Results

The primary analysis was based on the 194 patients randomized on or before the database cutoff date for the efficacy IA. The overall primary and key secondary endpoint results were highly statistically significant in favor of pimavanserin treatment. The primary efficacy endpoint was time to relapse in the DB period. Pimavanserin demonstrated a >2.8-fold reduction in hazard of relapse of psychosis compared with placebo (HR=0.35, 95% CI: 0.17, 0.73; one-sided p=0.0023) (Figure 3–10) and the DSMB advised stopping the study early for efficacy (O'Brien-Fleming stopping boundary of 0.0033). The proportion of patients who relapsed was more than double in the placebo treatment arm (28/99=28.3%) compared with the pimavanserin treatment arm (12/95=12.6%) (Tariot et al. 2021); 37 out of 40 relapsed patients met the relapse criteria of SAPS-H+D and CGI-I.

Figure 3–10 Study 045: Time from Randomization to Relapse in DB Period (ITT Analysis Set) – Overall DRP Population



Sources: Study 045 CSR Figure 14.1.1, Table 14.2.1.5.1
Abbreviations: CI=confidence interval; CSR=clinical study report; DRP=dementia-related psychosis; HR=hazard ratio; ITT=Intention-to-treat

3.5.3.3 Key Secondary Efficacy Results

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 Sponsor). During the DB period, 38 patients (38.4%) in the placebo group and 21 patients (22.1%) in the pimavanserin group were discontinued from the study for any reason. Pimavanserin significantly reduced the risk of all-cause discontinuation by 2.2-fold compared with placebo based on the prespecified hierarchical algorithm to control overall type I error, tested at the one-sided 0.0033 O'Brien-Fleming significance level (HR=0.45, 95% CI: 0.26, 0.79; one-sided p=0.0024).

3.5.4 Evaluation of Efficacy Across Dementia Subgroups

Study 045 statistical analysis plan defined exploratory analyses to be conducted across dementia subgroups (i.e., AD, PDD, DLB, VaD, and FTD) to evaluate general directional consistency with the study primary analysis. Hence, dementia subgroups were only evaluated for directional consistency in efficacy outcomes as the study was not powered for statistical significance by individual subgroups. Clinically meaningful and directionally positive reductions in the risk of psychosis relapse were observed across dementia subgroups, demonstrating a directionally consistent response across dementia subgroups (Figure 3–11). A particularly robust effect for reduction in risk of relapse was observed in the PDD subgroup, which represented approximately 18% of the overall population. The largest

subgroup (63%) comprised of patients with ADP demonstrated clinically meaningful reductions in hazard of relapse (38% [all doses] to 53% [34 mg dose]). The HR observed in ADP was consistent with that observed with approved drugs including antipsychotics approved for treatment of psychiatric disorders such as schizophrenia or bipolar disorder.

Figure 3–11 Time From Randomization to Relapse in DB Period: DRP Overall and by Dementia Subgroups for All Doses (ITT Analysis Set at IA)- Study 045

	Relapse Events, n/N (%)		HR (95% CI)	Two-sided p-value
	Pimavanserin	Placebo		
Pimavanserin All Doses				
DRP	12/95 (12.6%)	28/99 (28.3%)	**0.35** (0.17, 0.73)	**0.005**
ADP	8/61 (13.1%)	14/62 (22.6%)	**0.62** (0.26, 1.49)	**0.283**
PDD	1/15 (6.7%)	10/20 (50%)	**0.05** (0.02, 0.18)	**< 0.001**
Other (DLB, FTD, VaD)	3/19 (15.8%)	4/17 (23.5%)	**0.52** (0.08, 3.38)	**0.490**

Sources: Study 045 CSR Addendum Figures AH14.1.4.DEMPCAUS.GROUP.ITT

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; CSR=clinical study report; DB=double-blind; DLB=dementia with Lewy bodies; DRP=dementia-related psychosis; FTD=frontotemporal dementia; HR=hazard ratio; IA=interim analysis; ITT=Intention-to-treat; PDD=Parkinson's disease dementia; VaD=vascular dementia

To further understand the robust effect observed in PDD and the impact on overall results, additional exploratory analyses were conducted to 1) check consistency of pimavanserin response across subgroups, and 2) further evaluate the effect in the PDD subgroup.

3.5.4.1 Analysis of Potential Qualitative Interaction

A Gail-Simon (or crossover) test (Gail and Simon 1985) was performed on the risk difference in an attempt to understand whether the differences are directionally different (i.e., qualitative interaction). The test was performed on the risk difference of relapse in two ways:
1) stratified by region (levels: North America, Western Europe, Eastern Europe, Asia Pacific, Latin America), and designated dementia subgroup randomization strata (AD or FTD, VaD, PDD or DLB); 2) stratified by dementia subgroups (AD, PDD, and other) on DRP overall population. The results showed no evidence of a crossover interaction on the risk difference directions (i.e., the difference between the two treatment groups is positive or negative) across randomization strata (interaction p-value >0.9) or across individual dementia subgroups (p=0.75). These results support the conclusion that the treatment effect observed across different dementia subgroups in Study 045 are directionally consistent.

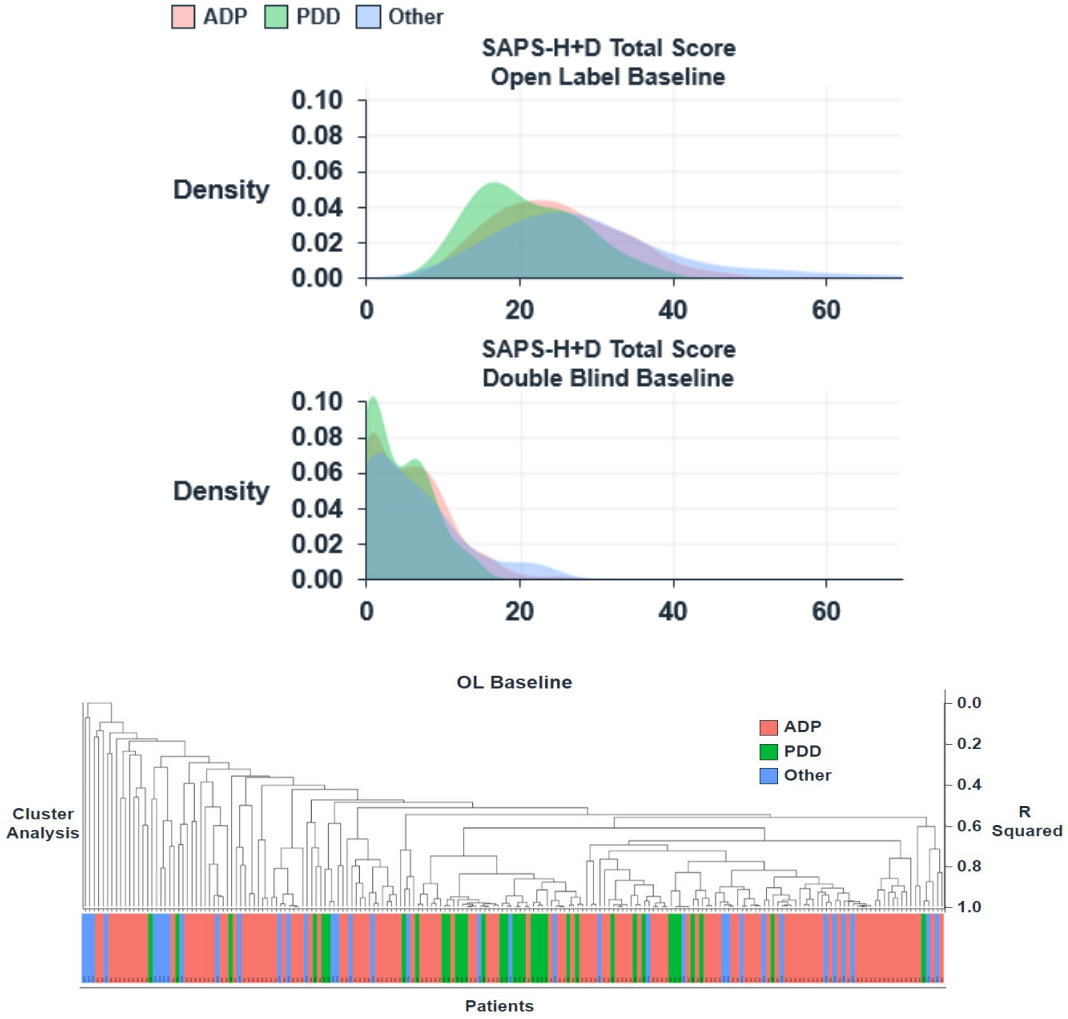
3.5.4.2 Consistent Symptoms of Psychosis Across Dementia Subgroups – Analysis of OL and DB Phases of the Study 045

Symptom presentation and neurobiology of psychosis is overlapping across dementia subgroups (Brenowitz et al. 2017a; Cummings et al. 2020). Study 045 provided a unique opportunity to further confirm this concept.

An exploration of total SAPS-H+D scores at OL Baseline in ADP, PDD, and the other subgroups (grouped as "Other") indicated that the distribution of SAPS-H+D total scores is similar across dementia subgroups at the entry into OL period and after 12 weeks of OL pimavanserin treatment (Figure 3–12, top panel). Further exploratory analyses that grouped patients based on SAPS-H+D item score profiles showed that patients with ADP, PDD and Other dementias were all intermixed (colored vertical bars next to different colored bars) rather than showing item patterns with subgroups grouped near each other (shown as blocks of the same color, Figure 3–12, bottom panel). This demonstrates the similarity of psychosis symptoms across ADP, PDD, and other dementia subgroups. Post-OL treatment symptoms at the DB Baseline also showed no clustering, consistent with the OL Baseline results.

These analyses confirm that the ADP and PDD subgroups have similar constellations of psychotic symptoms which are similarly amenable to treatment with pimavanserin, hence supporting generalizability of primary DRP population study results to ADP.

Figure 3–12 Distribution of Total SAPS-H+D at OL and DB Baseline (Top Panel) and Hierarchical Cluster Analyses of Item Scores at OL Baseline (Bottom Panel) (ITT Analysis Set at IA) – Study 045



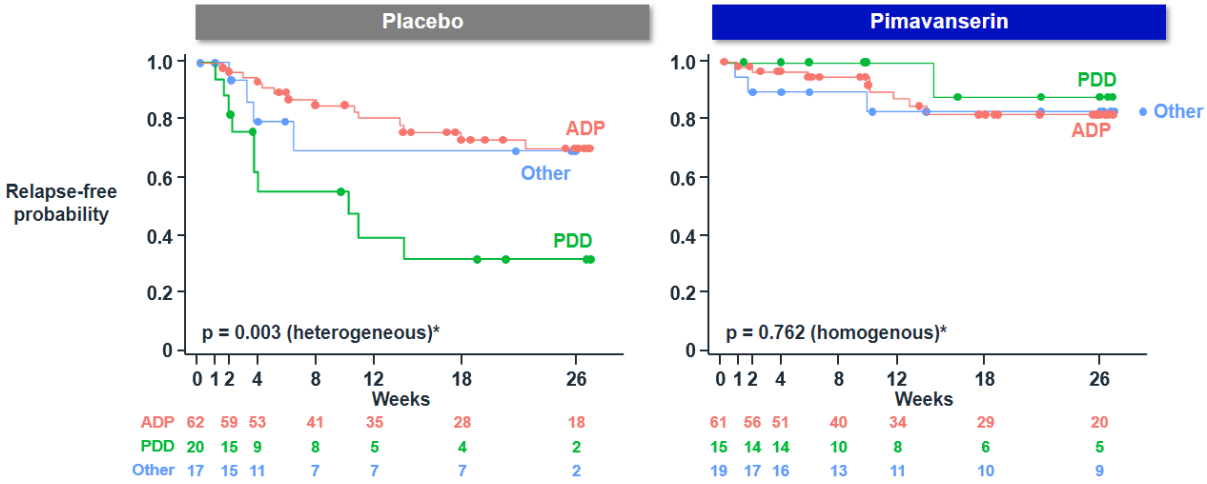
Source: Study 045 CSR Addendum Figure AH14.SAPS.Density; AH14. SAPS.Cluster
Abbreviations: ADP=Alzheimer's disease psychosis; CSR=clinical study report; DB=double-blind; DLB=dementia with Lewy bodies; FTD=frontotemporal dementia; IA=interim analysis; ITT=Intention-to-treat; OL=open-label; PDD=Parkinson's disease dementia; SAPS-H+D=Scale for the Assessment of Positive Symptoms-Hallucinations+Delusions; VaD=vascular dementia
Note: Other included patients with a subgroup of VaD, DLB, or FTD.

3.5.4.3 PDD Subgroup and Potential Impact of Dopaminergic Treatment

Patients who were randomized to pimavanserin group showed similar survival probabilities across clinically diagnosed dementia subgroups, with a notable variability in HRs being driven by the differential placebo survival probabilities in the PDD subgroup (Figure 3–13). A test of homogeneity on the survival curves indicated that the relapse patterns in the pimavanserin treatment arm were consistent across dementia subgroups (p=0.762); while for

the placebo treatment arm, the relapse patterns were heterogeneous across dementia subgroups (p=0.003).

Figure 3–13 Relapse Pattern of Patients Receiving Pimavanserin and Placebo – Study 045 Subgroups (ADP, PDD, and Other)



Sources: Study 045 CSR Addendum Figures AH14.1.1.PIM.GROUP2 and AH14.1.1.PBO.GROUP2; Tables AH14.2.1.20.1.PIM.GROUP and AH14.2.1.20.1.PBO.GROUP

Abbreviations: AD=Alzheimer's disease; CSR=clinical study report; DLB=dementia with Lewy bodies; FTD=frontotemporal dementia; PD=Parkinson's disease; PDD=Parkinson's disease dementia; VaD=vascular dementia

Note: Other included patients with a subgroup of VaD, DLB, or FTD.

*Test of homogeneity of relapse-free survival curves

Acadia evaluated possible sources of the significantly smaller HR in the PDD subgroup compared to the other dementia subgroups (e.g., ADP). One distinctive feature of the PDD subgroup is almost universal concomitant dopaminergic therapy (e.g., levodopa) (34/35 or 97% of PDD patients in Study 045 were on dopaminergic therapy). In addition to the psychotic symptoms that are often associated with PD itself, the dopaminergic medications used to manage motor symptoms of idiopathic PD can precipitate or accelerate psychotic symptoms, including hallucinations and delusions (Organon Global Inc. 2021), particularly in the context of withdrawal of a successful antipsychotic therapy.

In Study 045, withdrawal of an effective antipsychotic therapy of pimavanserin while the patients were taking dopaminergic medications (i.e., randomization to placebo group during the DB period), may have contributed to the observed more rapid return of psychosis symptoms in patients in the PDD subgroup compared with patients in other dementia subgroups who were not taking dopaminergic therapies, resulting in higher relapse rate and faster time to relapse. An examination of the time to relapse on the 40 relapsed patients indicates that for those who were on dopaminergic concomitant medication, once withdrawn from the effective antipsychotic therapy of pimavanserin (i.e., randomized to placebo), the

time to relapse is much faster than those not on dopaminergic therapy (5.0 weeks for those placebo relapsed patients on dopaminergic vs. 8.4 weeks for those placebo relapsed patients not on dopaminergic) (Table 3–7). A similar pattern was observed among PDD and non-PDD patients. Among the 21 placebo patients on dopaminergic therapy, 19 (90%) are PDD patients and none are ADP patients (Figure 3–14), which indicates that the above observed negative effect of dopaminergic therapy for placebo patients is almost unique to PDD subgroup. This may provide context for interpretation of the observed significantly smaller HR in the PDD subgroup as compared to other subgroups (e.g., ADP).

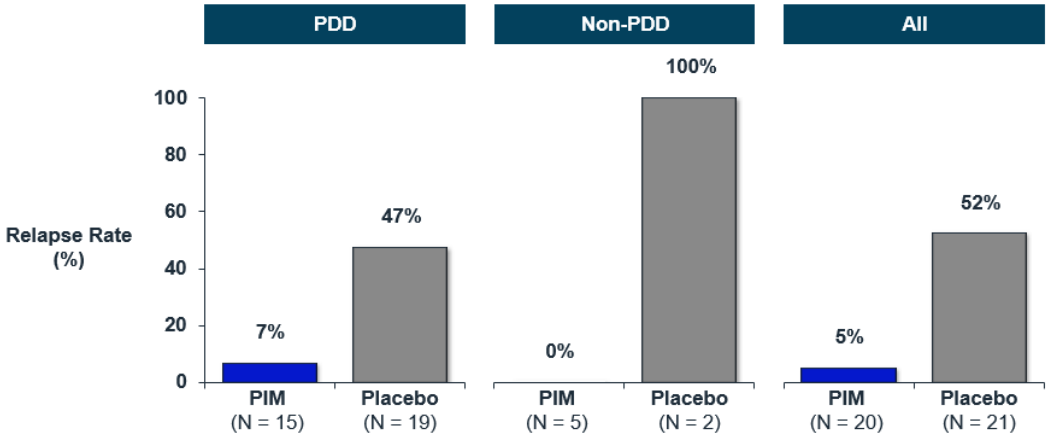
Table 3–7 Time to Relapse (Weeks) for Relapsed Patients on Placebo Treatment by Concomitant Dopaminergic Therapy and PDD Diagnosis

Parameter	*Placebo Patients Who Relapsed*		
	PDD (N=10)	***Non*-PDD (N=18)**	***All (N=28)***
On dopaminergic treatment			
n	9	2	*11*
Mean (SE)	5.0 (1.52)	5.0 (1.57)	*5.0 (1.25)*
Min, max	1, 14	3, 7	*1, 14*
Not on dopaminergic treatment			
n	1	16	*17*
Mean (SE)	10.4 (N/A)	8.3 (1.57)	*8.4 (1.48)*
Min, max	*10, 10*	*2, 23*	*2, 23*

Source: Study 045 CSR Addendum Table AH.RelapseDopa2, Table AH.RelapseDopa

Abbreviations: CSR=clinical study report; N/A=not available; PDD=Parkinson's disease dementia; SE=standard error

Figure 3–14 Relapse Rates of Patients on Dopaminergic Therapy (PDD vs. Non-PDD)



Sources: Study 045 CSR Addendum Tables AH14.2.1.5.1.DOPA and AH14.2.1.5.1.PD.DOPA

Abbreviations: AD=Alzheimer's disease; CSR=clinical study report; DLB=dementia with Lewy bodies; PBO=placebo; PDD=Parkinson's disease dementia; PIM=pimavanserin; VaD=vascular dementia

Note: Subjects in Non-PDD on dopaminergic therapies include: 4 DLB (3 PIM and 1 PBO); 1 VaD in PBO; 2 AD in PIM

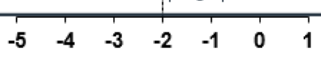
3.5.4.4 Impact of PDD Subgroup on Overall Study Outcome: A Tipping Point Simulation Based Analysis

The CRL raised the question of whether the PDD subgroup "drove" the positive outcome of Study 045 due to the low HR of relapse in PDD patients. Simulations were conducted to evaluate the probability of a positive study under conditions of attenuated efficacy in PDD. This was assessed by attenuating the PDD subgroup effect size by adding relapse events to the pimavanserin arm for the PDD subgroup. These simulations showed that the addition of 9 events resulted in an average HR of 0.59 in the PDD subgroup (expected p=0.226), and an average HR of 0.55 for overall DRP (expected p=0.041, Figure 3–15). Under this circumstance, the PDD subgroup would be consistent with the other dementia subgroups, and yet the study would still be expected to have p<0.05.

These results underscore the contributions of ADP and other non-PDD subgroups to the overall success of the study.

Figure 3–15 Simulation – Impact of PDD Subgroup on Primary Outcome – Study 045

	z-score	Expected p-value	Expected HR	Median z-score	z-score (95% CI)
Overall DRP					
1 Event added		0.006	0.38	-2.75	**-2.75** (-2.79, -2.72)
2 Events added		0.008	0.40	-2.67	**-2.67** (-2.71, -2.62)
3 Events added		0.010	0.42	-2.58	**-2.58** (-2.64, -2.52)
4 Events added		0.013	0.44	-2.50	**-2.50** (-2.56, -2.42)
5 Events added		0.016	0.47	-2.41	**-2.41** (-2.48, -2.32)
6 Events added		0.021	0.49	-2.32	**-2.32** (-2.40, -2.22)
7 Events added		0.026	0.51	-2.23	**-2.23** (-2.31, -2.12)
8 Events added		0.033	0.53	-2.14	**-2.14** (-2.23, -2.02)
9 Events added		0.041	0.55	-2.05	**-2.05** (-2.14, -1.92)
PDD					
1 Event added		< 0.001	0.11	-3.49	**-3.69** (-5.10, -2.99)
2 Events added		0.002	0.17	-3.12	**-3.16** (-3.85, -2.56)
3 Events added		0.005	0.23	-2.79	**-2.80** (-3.37, -2.26)
4 Events added		0.013	0.29	-2.49	**-2.49** (-3.02, -1.98)
5 Events added		0.028	0.35	-2.21	**-2.20** (-2.71, -1.70)
6 Events added		0.054	0.40	-1.93	**-1.93** (-2.41, -1.45)
7 Events added		0.094	0.46	-1.68	**-1.68** (-2.13, -1.21)
8 Events added		0.150	0.52	-1.44	**-1.44** (-1.88, -0.97)
9 Events added		0.226	0.59	-1.22	**-1.21** (-1.84, -0.75)



Source: Simulation Report (Study 045)
Abbreviations: CI=confidence interval; DRP=dementia-related psychosis; HR=hazard ratio; PDD=Parkinson's disease dementia

To further evaluate pimavanserin efficacy in ADP, Acadia performed a number of additional analyses focused on the ADP subgroup from Study 045.

3.5.5 Supportive Evidence for Pimavanserin for the Proposed Indication: Treatment of ADP

To further support the proposed indication for pimavanserin 34 mg QD for the treatment of ADP, additional analyses were focused on the ADP subgroup and ADP 34 mg subgroup.

3.5.5.1 Primary Endpoint Efficacy Analysis

There were a total of 123 patients with ADP randomized in the DB period at the time of IA, of which 116 patients were randomized to pimavanserin 34 mg or placebo. These 116 patients comprised the ADP 34 mg analysis population set. Importantly, the 34 mg group was comprised of those patients who were stabilized at 34 mg during OL period prior to randomization and then randomized to stay on either 34 mg or corresponding placebo during the DB period. The remaining 7 patients (6%) had titrated to 20 mg pimavanserin by Week 4 of the OL period and ultimately randomized to stay on either 20 mg or corresponding placebo during the DB period. This design feature of Study 045 allowed an unbiased evaluation of the efficacy of pimavanserin in the ADP subgroup based on dose, specifically the 34 mg proposed dose.

Prospectively planned exploratory efficacy analyses of dementia subgroups, including the largest dementia subgroup, ADP, showed that patients with ADP who remained on pimavanserin were 38% (all doses) less likely to experience a relapse of psychotic symptoms compared with those on placebo (HR=0.62, 95% CI: 0.26, 1.49) (Table 3–8). Analyses of the ADP 34 mg subgroup patients showed an enhanced effect of 53% risk reduction (HR=0.47, 95% CI: 0.18, 1.21) (Table 3–8). These results in ADP are generally consistent with the overall population in DRP, supporting that the overall positive results in Study 045 are generalizable to ADP.

The magnitude of efficacy observed in the subgroup of ADP patients with more severe psychosis at OL Baseline (SAPS-H+D >24 [median score]) was more robust, with 51% reduction in risk of relapse on pimavanserin versus placebo (HR=0.49, 95% CI: 0.10, 2.26); a similar enhanced effect was observed in the ADP 34 mg subgroup (7/31 [23%] relapsed in placebo group vs. 0/20 relapsed in pimavanserin 34 mg group).

This clinically meaningful magnitude (38% [all doses] to 53% [34 mg dose] reduction in hazard of relapse) is similar to the effects seen in numerous relapse prevention studies of comparable design that supported labeling updates for approved drugs for maintenance treatment in psychiatric indications (Leucht et al. 2012; Smith et al. 2007).

Table 3–8 Analyses of Time to Relapse in DRP and the ADP, DRP 34 mg and ADP 34 mg Subgroups (ITT Analysis Set at IA) – Study 045

	DRP (All Doses)		ADP (All Doses)	
	Pimavanserin	Placebo	Pimavanserin	Placebo
Relapse rate, n/N (%)	12/95 (12.6)	28/99 (28.3)	8/61 (13.1)	14/62 (22.6)
Hazard ratio (pimavanserin/placebo)	0.35		0.62	
95% CI of HR	(0.17, 0.73)		(0.26, 1.49)	
Two-sided p-value	0.005		0.283	
	DRP 34 mg		**ADP 34 mg**	
	Pimavanserin	Placebo	Pimavanserin	Placebo
Relapse rate, n/N (%)	10/89 (11.2)	27/93 (29.0)	6/57 (10.5)	14/59 (23.7)
Hazard ratio (pimavanserin/placebo)	0.29		0.47	
95% CI of HR	(0.14, 0.63)		(0.18, 1.21)	
Two-sided p-value	0.002		0.118	

Sources: Study 045 CSR Addendum Tables 14.2.1.5.1, 14.2.1.10.3, AH14.2.1.5.1.OL34 and AH14.2.1.5.1.OL34.AD

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; CSR=clinical study report; DRP=dementia-related psychosis; HR=hazard ratio; IA=interim analysis; ITT=Intention-to-treat

Note: Results from a Cox regression model included effects for treatment, dementia subgroup (randomization strata) and region.

3.5.5.2 Key Secondary Endpoint Efficacy Analysis

For the key secondary efficacy endpoint, time from randomization to discontinuation in the DB period for any reason, 20 patients (32.3%) in the placebo group and 13 patients (21.3%) in the pimavanserin group were discontinued from the study for any reason (other than termination of the study by the Sponsor). Cox regression analysis results in the ADP subgroup (HR=0.66, 95% CI: 0.33, 1.33), as well as the ADP 34 mg subgroup (HR=0.57, CI: 0.27, 1.18), were consistent with those in the DRP population (HR=0.45, 95% CI: 0.26, 0.79).

3.5.5.3 Analysis of Symptom Severity as Continuous Variable

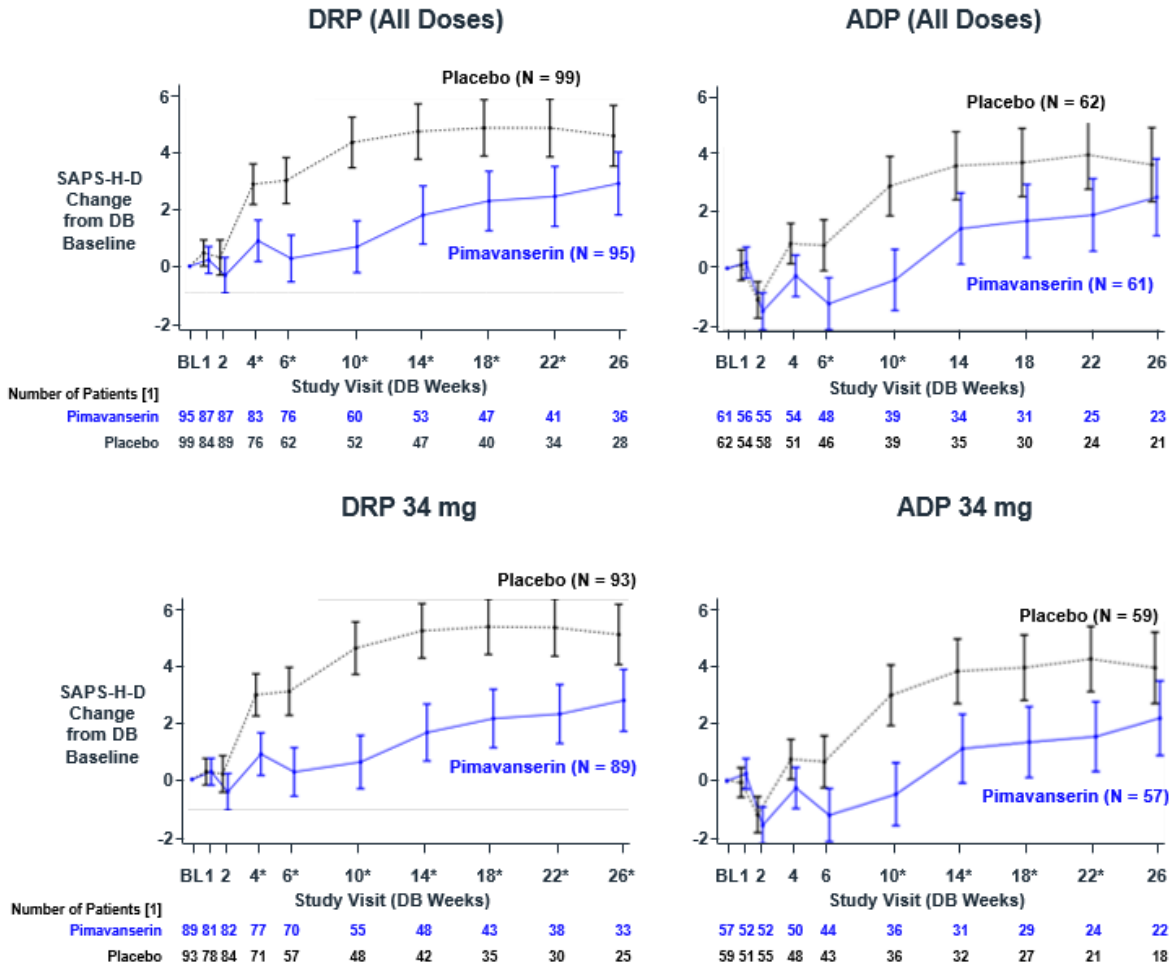
Due to the randomized withdrawal trial design, patients did not stay in the study after relapse or other events that resulted in study termination. Consequently, a simple observed case analysis of SAPS-H+D scores by visit in the DB period would not accurately reflect the true treatment effect over time due to non-random attrition bias. To avoid this, it is necessary to define certain imputation rules for subjects who discontinued treatment. Acadia conducted an analysis by imputing the missing SAPS-H+D scores in the DB period through DB Week 26 using the following approach:

- For relapsed patients: missing scores were imputed with last observation carried forward (LOCF) method.
- For censored patients: missing scores were imputed using multiple imputations (50 iterations) assuming missing at random.
- After imputation, treatment comparison was performed using an analysis of covariance (ANCOVA) model with treatment and region as factors and DB baseline SAPS-H+D score as a covariate. For DRP and DRP 34 mg populations, the randomization dementia subgroup is also included in the ANCOVA model as an additional factor.

Results in patients with DRP showed clear and sustained benefit of the continuation of pimavanserin treatment versus withdrawal of treatment with the mean SAPS-H+D scores in the pimavanserin group 1.7 to 3.7 points lower than the placebo group from DB Week 4 through Week 26. Specifically, the treatment effect achieved nominal statistical significance (p-value <0.05) from DB Week 4 through Week 22 (Figure 3–16).

Results in the ADP subgroup and ADP 34 mg subgroup (Figure 3–16) were consistent with those in DRP, with the mean SAPS-H+D scores in the pimavanserin group generally 2 to 3 points lower than the placebo group from DB Week 6 through Week 22. The treatment effect achieved nominal statistical significance from DB Week 6 through Week 10 for the ADP subgroup and from DB Week 10 through Week 22 for ADP 34 mg subgroup, respectively. In summary, in patients with DRP and ADP, pimavanserin treatment sustained clinically meaningful benefit on mean change from Baseline in SAPS-H+D across visits beyond 12 weeks of OL treatment, compared to the control group with treatment withdrawn.

Figure 3–16 Change From Baseline in SAPS-H+D (LSM+/-SE) in DRP (All Doses and 34 mg: Left Panel) and ADP (All Doses and 34 mg: Right Panel) (ITT Analysis Set at IA) – Study 045



* p-value < 0.05

Sources: Study 045 CSR Addendum Tables AH.AncovaMI.ADP, AH.AncovaMI.ADP34; Post-resubmission Figures AH.AncovaADMIIB.DRP, AH.AncovaADMIIB.DRP34, AH.AncovaADMII.ADP, AH.AncovaADMII.ADP34, Tables AH.AncovaMI.DRP, AH.AncovaMI.DRP34

Abbreviations: ADP=Alzheimer's disease psychosis; ANCOVA=analysis of covariance; BL=Baseline; CSR=clinical study report; DB=double-blind; IA=interim analysis; ITT=Intention-to-treat; LSM=least squares mean; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales; SE=standard error

[1] Number of patients by treatment group reflect the observed cases that were not imputed. LSM and SE are from an ANCOVA model incorporating imputed values for missing data.

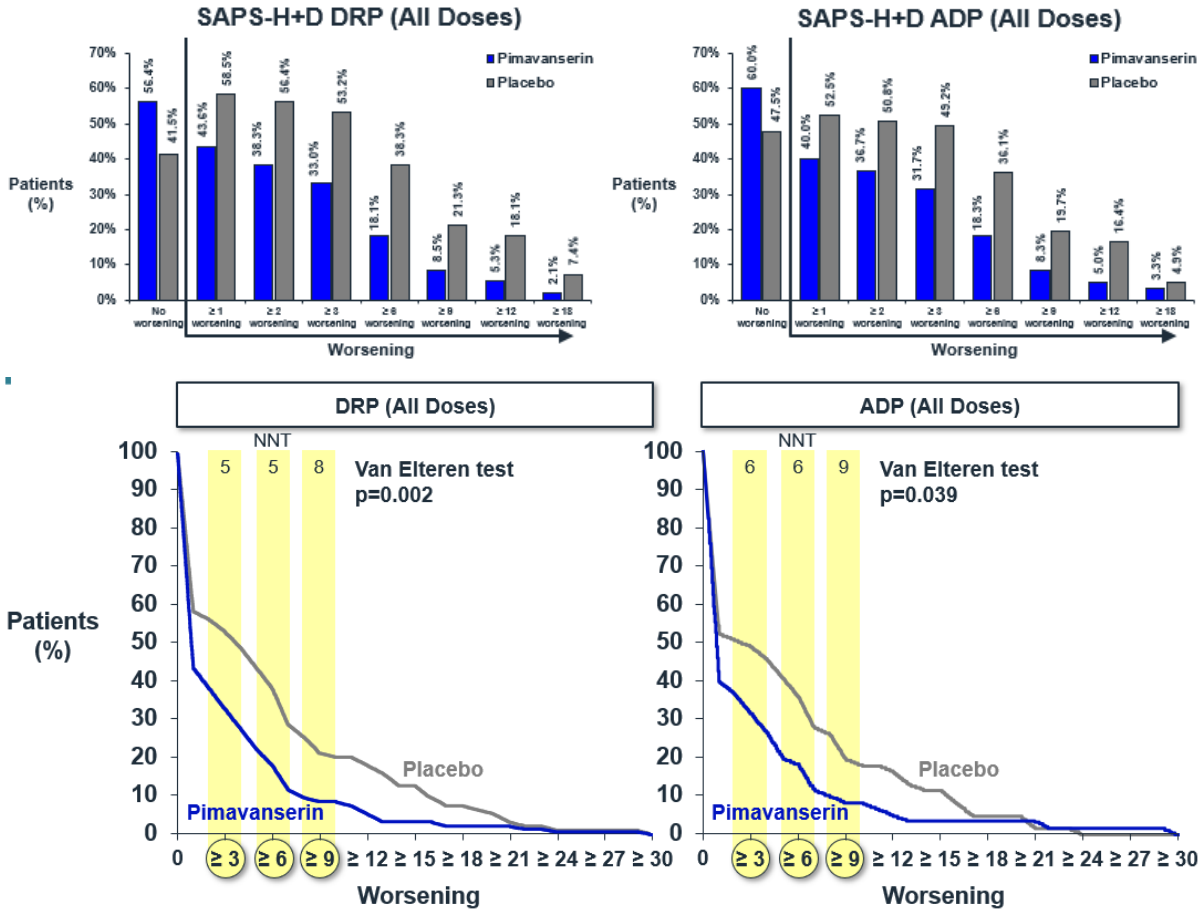
3.5.5.4 Analysis of Proportion of Patients With Worsening of Symptoms

The objective of Study 045 was to evaluate prevention of relapse of psychotic symptoms (including assessments by SAPS-H+D and CGI-I) during the DB period after 12 weeks of OL pimavanserin treatment. In addition to the prespecified by visit analysis, Acadia conducted analyses of maximum worsening from DB Baseline on the SAPS-H+D or worst

CGI-I score across all postrandomization visits to further characterize the effect of pimavanserin in preventing worsening of symptoms. The analysis in SAPS-H+D worsening demonstrated a clinically meaningful benefit in patients with DRP treated with pimavanserin versus placebo across various cutoffs (i.e., cumulative response curves with van Elteren test p=0.002) and consistent results were observed in the ADP subgroup (van Elteren test p=0.039) (Figure 3–17). The ADP 34 mg subgroup (results not shown) exhibited slightly better effect than ADP overall, as expected and observed in all other analyses. Consistent with SAPS-H+D results, the analysis of CGI-I showed clinically meaningful benefit in patients with DRP and within the ADP subgroup (Figure 3–18).

In general, efficacy outcomes for response using several different cutoffs yielded NNT values for pimavanserin versus placebo of <10 (Figure 3–17). In patients with DRP, NNT (CI) values for preventing SAPS-H+D worsening of ≥3, ≥6, and ≥9 points were 5 (3, 16), 5 (4, 13) and 8 (5, 37), respectively. In the ADP subgroup, NNT (CI) values for preventing SAPS-H+D worsening of ≥3, ≥6, and ≥9 points were 6 (3, 322), 6 (3, 46) and 9 (not significant[ns]), respectively. Of note, a single digit NNT value is commonly considered clinically meaningful and denotes an effective intervention (Citrome et al. 2013).

Figure 3–17 Maximum Worsening by SAPS-H+D Point Change: Analysis of SAPS-H+D Increase (Top Panel: DRP, Left Panel; ADP, Right Panel) and Cumulative Relapse Curves (Bottom Panel: DRP, Left Panel; ADP, Right Panel) Postrandomization (ITT Analysis Set at IA) – Study 045



Sources: Study 045 CSR Addendum Figures AH14.7D.DRP, AH14.7D.AD, AH.CDFrelapse.DRP, AH.CDFrelapse.ADP; Tables AH.SAPS.WILCOX2.DRP, AH.SAPS.WILCOX2.ADP, AH.SAPSwsnNNT.DRP, AH.SAPSwsnNNT.ADP

Abbreviations: ADP=Alzheimer's disease psychosis; CSR=clinical study report; DB=double-blind; IA=interim analysis; ITT=Intention-to-treat; NNT=number needed to treat; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales

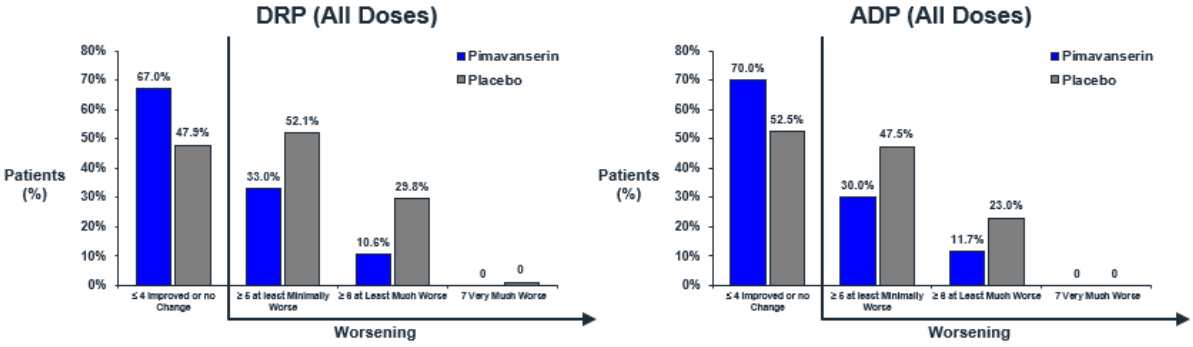
Note: Subjects who did not have post-baseline SAPS-H+D scores were excluded in this analysis.

For subjects who never worsened from Baseline (i.e., improved during the DB phase), their worst change score was set to 0 for the purpose of evaluating maximum worsening of symptoms. P-values were from a van Elteren test stratified by region (for DRP and ADP models), and randomization dementia subgroup (only for DRP model).

At each worsening cutoff (0 to 30 by increments of 1), a subject is considered as meeting the worsening cutoff if the change from Baseline of the worst post DB baseline SAPS-H+D score is ≥ worsening cutoff.

NNT is calculated as 1/(incidence on placebo – incidence on pimavanserin) and rounded up to the next integer. The denominator is the number of randomized subjects with at least one post-DB-baseline SAPS-H+D score.

Figure 3–18 Analysis of CGI-I Score (Worst post-DB baseline score) (DRP: Left Panel; ADP: Right Panel) Post-randomization (ITT Analysis Set at IA)– Study 045



Sources: Study 045 CSR Addendum Figures AH14.8D.DRP and AH14.8D.AD

Abbreviations: AD=Alzheimer's disease; ADP=Alzheimer's disease psychosis; CGI-I=Clinical Global Impression–Improvement; CSR=clinical study report; DB=double-blind

Note: Subjects who did not have post-baseline CGI-I scores were not included in the analysis.

Taken together, the above analyses confirm the benefit of pimavanserin treatment in patients with ADP not only with respect to preventing psychotic relapse, but also in control of psychotic symptoms and maintenance of achieved symptom reduction.

3.5.5.5 Consistent Benefit in ADP Across Efficacy Measures

As shown Figure 3–19, a common metric of z-scores for the different study endpoints (efficacy measures), results from Study 045 are evidencing a consistent benefit of pimavanserin treatment of patients with DRP across multiple endpoints. These endpoints provide information on efficacy from various perspectives including clinicians (SAP-H+D, CGI-I), caregivers (Zarit Burden Interview [ZBI]), and patient's quality of life (5-level version of EQ-5D [5-dimension instrument developed by EuroQol Group] [EQ-5D-5L]). The z-score represents the level of statistical evidence with 1.96 corresponding to a (nominally) significant result at a 2-sided alpha of 0.05. This benefit across multiple endpoints was also observed in the ADP subgroup and 34 mg ADP subgroup of Study 045. This consistent treatment effect further supports the efficacy of pimavanserin for the treatment of ADP.

Figure 3–19 Treatment Benefits in DRP (All Doses: top panel), ADP (All Doses: middle panel) and ADP 34 mg (bottom panel) Across Endpoints (z-scores) (ITT Analysis Set at IA) – Study 045

	N			
DRP All Doses	Pimavanserin	Placebo	z-score (95% CI)	p-value
SAPS H+D	94	94	-3.03 (-4.99, -1.07)	0.002
CGI-I	94	94	-3.15 (-5.11, -1.19)	0.002
ZBI	64	73	-0.08 (-2.04, 1.88)	0.935
EQ-5D-5L	82	82	-1.16 (-3.12, 0.80)	0.246
ADP All Doses				
SAPS H+D	60	61	-2.08 (-4.04, -0.12)	0.038
CGI-I	60	61	-2.06 (-4.02, -0.10)	0.040
ZBI	38	48	-1.25 (-3.21, 0.71)	0.211
EQ-5D-5L	52	55	-1.14 (-3.10, 0.82)	0.254
ADP 34 mg				
SAPS H+D	56	58	-2.25 (-4.21, -0.29)	0.024
CGI-I	56	58	-2.25 (-4.21, -0.29)	0.024
ZBI	35	46	-1.48 (-3.44, 0.48)	0.139
EQ-5D-5L	48	52	-1.53 (-3.49, 0.43)	0.126

Sources: Study 045 CSR Addendum Figures MetaDRP, MetaADP, MetaADP34

Abbreviations: ADP=Alzheimer's disease psychosis; CGI-I=Clinical Global Impression–Improvement; CI=confidence interval; CSR=clinical study report; EQ-5D-5L=5-level version of EQ-5D (5-dimension instrument developed by EuroQol Group); IA=interim analysis; ITT=Intention-to-treat; SAPS-H+D=Scale for the Assessment of Positive Symptoms-Hallucinations and Delusions; ZBI=Zarit Burden Interview

Note: Time-to-event endpoints used the Cox regression model which included effects for treatment, dementia subgroup (randomization strata) and region. The p-values are two-sided.

Note: Ranking for continuous endpoints: a) subjects who remained in complete symptom free (i.e., best score possible) for that endpoint post-double-blind Baseline in the double-blind period were ranked highest; b) subjects who never worsened during the double-blind period were ranked second highest; c) remaining subjects were ranked based upon the subject's maximum worsening from Baseline score. After ranking each endpoint, a van Elteren test stratified by region was used to obtain the two-sided p-values.

Note: z-scores correspond to the p-value based on standard normal distribution. 95% CI of z-scores are constructed by adding or subtracting 1.96 standard error units to the z-score.

The ZBI and EQ-5D-5L scales are described further in Appendix Section 7.3.

3.5.5.6 Pimavanserin Exposure-Response Relationship in Study 045

An exposure-response (E-R) analysis using pimavanserin exposures (daily area under the concentration-time curve [AUC]) during the DB period provided a direct approach to understanding the impact of exposure on relapse rate.

Acadia evaluated data related to E-R analyses in the DB phase of Study 045. Separate E-R analyses were performed for all DRP patients and the ADP subgroup.

In Study 045, a broad range of model-predicted daily pimavanserin exposures (AUC) were present in the ITT study population of all DRP patients postrandomization (including placebo) with pharmacokinetic information (N=185) and with ADP subgroup (N=115), thus enabling proper E-R assessments. As expected based on the study design to randomize at the start of the DB period, the patients randomized to placebo (i.e., withdrawal of pimavanserin

treatment) had declining exposure for the first ~1-2 weeks while drug concentrations of pimavanserin washed out. Exploratory graphical analyses for all DRP patients and for the ADP subgroup including extended Kaplan-Meier plots accounting for daily records were performed prior to E-R modeling, which demonstrate that patients with higher exposures are less likely to relapse in both DRP and the ADP subgroup patients.

A Cox proportional hazards E-R model was used to describe the relationship between time to relapse and daily pimavanserin AUC in the DB period. Pimavanserin daily AUC was treated as a continuous variable and was time-varying across days on study. The HR value indicates how much the risk changes per unit change in the continuous, independent variable (AUC).

The results of the Cox proportional hazards model for all DRP patients and the ADP subgroup are presented in Table 3–9. The effect of pimavanserin daily AUC was statistically significant (N=185, p-value=0.003) in the full Study 045 DRP population. The p-value for the effect of AUC on relapse rate in the smaller group of ADP patients (N=115) was 0.066. After accounting for exposure, no evaluated covariate including dementia subgroup was statistically significant. The E-R relationship in the ADP subgroup is similar to that of all DRP patients and confirms the conclusions from the exploratory assessment that higher pimavanserin exposure is associated with a higher relapse-free probability in both groups. Specifically, for each increase of 1 µg×h/mL of pimavanserin AUC, the predicted hazard for relapse was decreased by 0.48 in DRP patients and 0.57 in the ADP subgroup (Table 3–9). Based on the median exposure estimate of 1.33 µg×h/mL for a 34 mg daily dose of pimavanserin, the risk of relapse in the ADP subgroup is reduced by 53% compared with the placebo treatment (ADP subgroup with zero exposure). For ease of interpretation, the units for pimavanserin AUC used in the modeling (ng × h/mL) were translated to µg × h/mL, which were considered more convenient units for interpretation.

Table 3–9 Summary of Exposure-Response Models[a] for Time to Relapse, by Population – Study 045

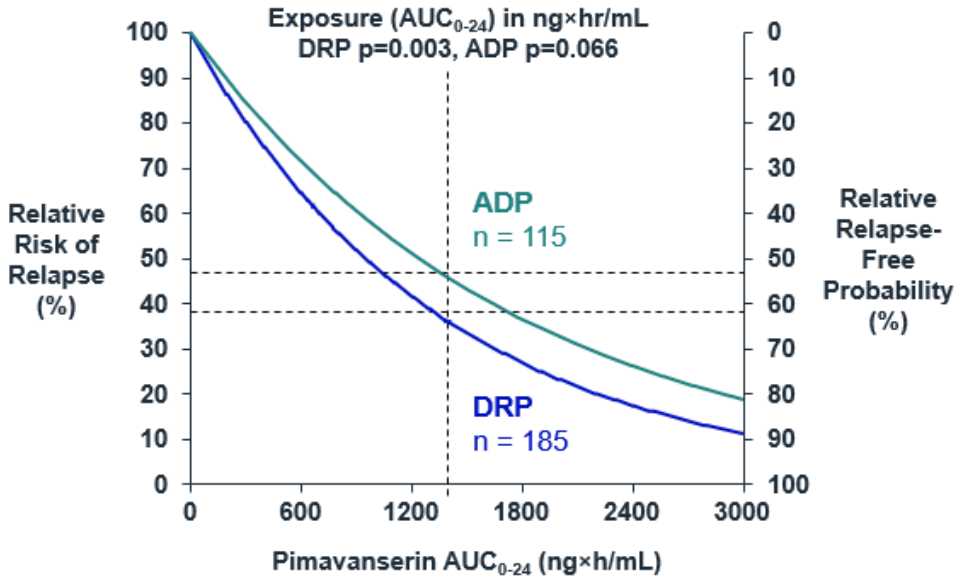
Population	Variable	Number of patients	Parameter estimate	P-value	Hazard ratio (95% CI) for 1 Unit (1 µg×h/mL) AUC_{0-24}	Hazard ratio (95% CI) at median AUC_{0-24} of 1.33 µg × h/mL	Reduction in risk at median exposure[b]
All DRP patients	Continuous AUC_{0-24}	185	-0.73	0.003	0.48[c] (0.28, 0.82)	0.38 (0.22, 0.65)	62%[d]
ADP subgroup	Continuous AUC_{0-24}	115	-0.56	0.066	0.57[e] (0.30, 1.10)	0.47 (0.25, 0.91)	53%[f]

Source: Report ACP-103-MS-018
Abbreviations: AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; CI=confidence interval
[a] Cox proportional hazards models including the effect of pimavanserin daily AUC_{0-24} as a continuous variable.
[b] Assuming the median AUC_{0-24} of 1.33 µg × h/mL from 34 mg QD pimavanserin.
[c] Hazard ratio for 1-unit increase (1 µg×h/mL) in pimavanserin daily AUC_{0-24} = exp(-0.73) = 0.48.
[d] Reduction in risk at median pimavanserin daily AUC_{0-24} = [1 - exp(-0.73 × 1.33)] × 100 = 62%.
[e] Hazard ratio for 1-unit increase (1 µg h/mL) in pimavanserin daily AUC_{0-24} = exp(-0.56) = 0.57.
[f] Reduction in risk at median pimavanserin daily AUC_{0-24} = [1 - exp(-0.56 × 1.33)] × 100 = 53%

The HR represents the relationship between relapse-free probability per 1 µg×h/mL increase in the continuous exposure measure, pimavanserin daily AUC. In contrast, the relative risk of relapse (left-hand y-axis) compared to zero exposure versus pimavanserin daily AUC, for all DRP and ADP patients, is illustrated in Figure 3–20. As pimavanserin daily AUC increases, the risk of relapse decreases (and the relapse-free probability increases; right-hand y-axis) similarly for DRP and ADP patients. The vertical reference line represents the median pimavanserin daily AUC of ng×h/mL and reflects the hazard ratios presented in Table 3–9. For context, the typical reduction in risk of relapse was calculated at the median pimavanserin daily AUC of µg×h/mL (as shown in Table 3–9). The parameter estimates and reduction in risk differ marginally between the all DRP patients and ADP subgroup despite the use of separate models in the full group and subgroups of the data.

An evaluation of the model-predicted relapse-free probability versus time, stratified by treatment and dementia subgroup, using the separate E-R models in all DRP patients and ADP subgroup, shows remarkable similarity in the trends, and the results in the ADP subgroup reflect those of the full DRP population.

Figure 3–20 Model-Predicted Relative Risk of Relapse Versus Pimavanserin AUC, in All DRP Patients and in ADP Subgroup – Study 045



Source: Report ACP-103-MS-018
Abbreviations: ADP=Alzheimer's disease psychosis; AUC=area under the concentration-time curve; AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; DRP=dementia-related psychosis

The consistency of the results and the strong E-R relationship indicate that pimavanserin benefit observed in the ADP subgroup reflects a true treatment response.

Similar results were observed in an E-R model for the SAPS-H+D. An E-R relationship was established for SAPS-H+D scores, whereby higher pimavanserin daily exposure (C_{max}) was associated with a reduction in SAPS-H+D scores, indicating improvement in symptoms. The E-R results for SAPS-H+D scores were similar for all patients with DRP and patients in the ADP subgroup (Report ACP-103-MS-018).

3.5.5.7 Post-hoc Analysis of Time to Relapse With Covariate Adjustment

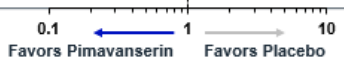
Study 045 was designed for the overall DRP population and, therefore, some important baseline covariates for the ADP subgroup were not given consideration at the design and prespecified analyses stage. To correct for potential baseline covariate imbalances and confounding effects, Acadia has refined the Cox regression model for the ADP subgroup based on the clinically informed prognostic covariates by the literature (Espay et al. 2018; Ballard et al. 2019; Ballard et al. 2018; Khin et al. 2012) and better model fitting statistics (Akaike information criterion [AIC]). Specifically, this included baseline psychosis severity as it is well established that higher baseline psychosis severity is associated with larger antipsychotic treatment effects (Khin et al. 2012). This is also supported by Study 019, where pimavanserin demonstrated greater efficacy in subgroups with higher baseline severity scores

and prior antipsychotic use (Ballard et al. 2018; Ballard et al. 2019), as well as in Study 045, in which the subgroup of ADP patients with more severe psychosis at OL Baseline (SAPS-H+D >24 [median score]) demonstrated more robust efficacy (~50% reduction in hazard of relapse) with pimavanserin treatment. The refined Cox regression model also included dementia severity at Baseline. This is informed by Study 019 where patients with lower MMSE scores at Baseline (MMSE <6) showed numerically higher magnitude of efficacy versus placebo (Ballard et al. 2018). Finally, the refined Cox model yielded better model-fitting statistics as compared with the prespecified Cox model for the ADP subgroup (AIC: 191.785 [prespecified] vs. 191.368 [refined]), further supporting the selection of this model.

The refined Cox model included the following five factors: treatment, baseline severity of psychosis, baseline dementia severity, prior antipsychotic treatment, and concomitant antidementia medications. When this refined Cox model was applied to the ADP subgroup, the resulting HRs continued to reflect a clinically meaningful effect and supported the results of the prespecified Cox model, both for the overall ADP subgroup (HR=0.48, 95% CI: 0.19, 1.16, two-sided p=0.103) and for the ADP 34 mg subgroup (HR=0.35, 95% CI: 0.14, 0.91, two-sided p=0.031) (Figure 3–21; Figure 3–22). When this refined ADP-specific Cox model is applied to the overall DRP population to explore the potential impact of those dementia and psychosis severity related baseline covariates, the resulting HRs are similar to the primary DRP model (0.41 [refined] vs. 0.35 [primary]). This further supports that these covariates are selected to correct for ADP subgroup, not for the overall DRP population which was the original Study 045 design objective.

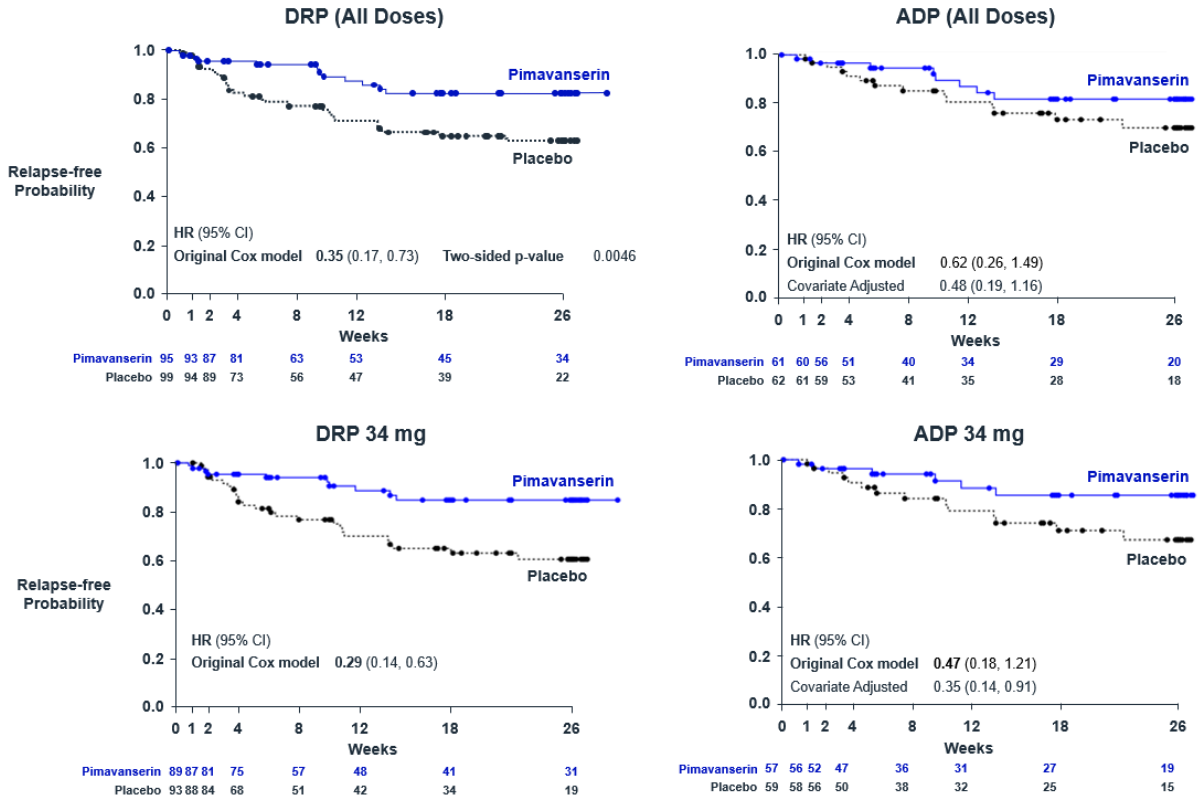
Figure 3–21 Time to Relapse Analyses for DRP and ADP (Primary and Baseline Covariate Adjusted Cox Model) (ITT Analysis Set at IA) – Study 045

	Pimavanserin Events/N	Placebo Events/N	HR (95% CI)	Two-sided p-value
Primary Analysis				
DRP All Doses (Original Cox Model)	12/95	28/99	0.35 (0.17, 0.73)	0.005
Exploratory Analyses				
DRP 34 mg (Original Cox Model)	10/89	27/93	0.29 (0.14, 0.63)	0.002
ADP All Doses				
Original Cox Model	8/61	14/62	0.62 (0.26, 1.49)	0.283
Covariate Adjusted Cox Model	8/61	14/62	0.48 (0.19, 1.16)	0.103
ADP 34 mg				
Original Cox Model	6/57	14/59	0.47 (0.18, 1.21)	0.118
Covariate Adjusted Cox Model	6/57	14/59	0.35 (0.14, 0.91)	0.031



Sources: Study 045 CSR Addendum Tables 14.2.1.5.1, AH14.2.1.5.1.OL34, 14.2.1.10.3, AH14.2.1.5.1.OL34.AD, AH14.2.1.5.1.MODEL5drp, AH14.2.1.5.1.MODEL5adAIC; post resubmission Table AH14.2.1.5.1.MODEL5drp34AIC
Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; CSR=clinical study report; HR=hazard ratio; IA=interim analysis; ITT=Intention-to-treat; PBO=placebo; PIM=pimavanserin; SAPS-H+D=Scale for the Assessment of Positive Symptoms-Hallucinations + Delusions; Y/N=yes/no
Note: The original Cox regression model includes effects for treatment, dementia subgroup (randomization strata) and region; the covariate adjusted Cox regression model includes effects for treatment, antipsychotic use within 14 days of screening (Y/N), OL baseline SAPS-H+D, OL baseline dementia severity (mild versus not mild), and OL baseline antidementia medication use (Y/N).

Figure 3–22 Analyses of Time to Relapse in DRP and the ADP Subgroup, DRP 34 mg and ADP 34 mg Subgroups (ITT Analysis Set at IA) – Study 045



Sources: Study 045 CSR Figures 14.1.1, 14.1.3.4; Study 045 CSR Addendum Figure AH14.1.3.4.34mg, Tables 14.2.1.5.1, 14.2.1.5.1.OL34, 14.2.1.10.3, AH14.2.1.5.1.OL34.AD, AH14.2.1.5.1.MODEL5adAIC; Post-resubmission Figure AH14.1.1.OL34-km-ol34-relapse-itt
Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; CSR=clinical study report; DRP=dementia-related psychosis; HR=hazard ratio; IA=interim analysis; ITT=Intention-to-treat
Note: The original Cox regression model includes effects for treatment, dementia subgroup (randomization strata) and region; the covariate adjusted Cox regression model includes effects for treatment, antipsychotic use within 14 days of screening (Y/N), OL baseline SAPS-H+D, OL baseline dementia severity (mild versus not mild), and OL baseline antidementia medication use (Y/N).

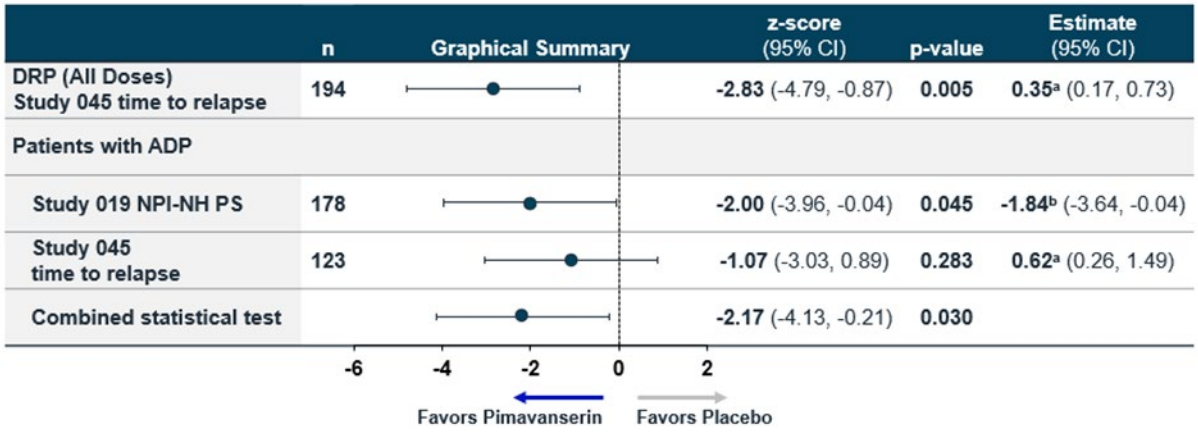
With respect to key secondary endpoint, when the covariate adjusted Cox model was applied, the resulting HRs for the ADP subgroup continued to reflect a clinically meaningful effect when compared to the primary model, both for the overall ADP subgroup (HR=0.61, 95% CI: 0.30, 1.24) and for the ADP 34 mg subgroup (HR=0.53, 95% CI: 0.25, 1.11).

3.6 Efficacy Conclusions

Pimavanserin has demonstrated clinically meaningful and consistent treatment effects in patients with ADP across clinical studies and endpoints, providing substantial evidence of effectiveness in aggregate to support the proposed treatment of ADP indication.

As shown in Figure 3–23, the forest plot of a common metric reflecting the statistical evidence (z-score) for a treatment effect on the various study endpoints, the results for the primary efficacy endpoints in two studies including patients with ADP, as well as the combined statistical test assessing the statistical evidence across these studies, consistently supports a clinically meaningful benefit of pimavanserin for the treatment of patients with ADP.

Figure 3–23 Overall Statistical Evidence for Pimavanserin Treatment Effect in Patients With Psychosis Across Two Studies



Source: Post-submission Figure ForestD-forest-slim-no046

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; DRP=dementia-related psychosis; LSM=least square means; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version psychosis score

Notes: Estimates with 95% CI and 2-sided p-values are from the primary analysis models in each study; z-scores correspond to the p-values based on the standard normal distribution; 95% CI of z-scores are z-scores +/- 1.96 standard error units. Combined Statistical Test z-scores are derived from a bivariate normal distribution with correlation of zero and calculated as (sum of z-scores across 2 studies)/sqrt(2).

[a] Hazard ratio (pimavanserin/placebo)

[b] LSM difference in change from baseline values (pimavanserin – placebo)

In summary:

- The efficacy of pimavanserin for ADP is demonstrated in Study 019 in ADP patients, with confirmatory evidence from a closely-related FDA-approved indication for the treatment of PDP (Study 020, ~25% with cognitive impairment [MMSE 21-24]), and supportive evidence from an overall positive study in DRP Study 045 , the largest subgroup evaluated being ADP.

- Study 019 in patients with ADP that had severe dementia in nursing homes (mean MMSE=10) met the primary endpoint of change from Baseline to NPI-NH PS at Week 6 (p=0.045, effect size=0.32), which is clinically meaningful and larger than atypical antipsychotics (effect size ≤0.2). Responder analyses with single digit NNTs further demonstrated the clinical meaningfulness of the results.
- Study 020 led to pimavanserin's FDA- approval for the treatment of the PDP indication and showed consistent and similar efficacy results as observed in Study 019.
  - A statistically significant treatment effect and clinically meaningful reductions in psychotic symptoms were observed in the pimavanserin group relative to placebo on the primary efficacy endpoint at 6 weeks.
  - Subgroup analysis of patients with cognitive impairment (MMSE <25; ~25% of patients) showed highly meaningful efficacy (p=0.002, effect size=0.99).
- Study 045 was a randomized withdrawal study in DRP patients and met the primary endpoint with highly statistical persuasive results and terminated early at a prespecified efficacy IA (HR=0.35, 95% CI: 0.17, 0.73; one sided p=0.0023).
  - ADP, the largest subgroup (66% of patients), showed the following:
    - Clinically meaningful reductions in hazard of relapse compared to placebo for all ADP (38%) and 34 mg ADP (53%).
    - Symptom severity analyses evaluating severity of hallucinations and delusions over time following randomization into DB period show maintenance of benefit of pimavanserin over placebo.
    - Responder analyses evaluating maximum worsening of symptoms showed pimavanserin was consistently better than placebo (van Elteren test, p=0.04), with single digit NNTs.
    - The consistency of efficacy favoring pimavanserin over placebo across various efficacy measures supports further supports pimavanserin benefit in ADP.
    - A strong exposure-response relationship was observed, with higher exposure associated with lower risk of relapse supporting the proposed therapeutic dose of pimavanserin 34 mg.
    - The proposed therapeutic dose of pimavanserin 34 mg consistently showed greater efficacy on all endpoints.
    - A covariate adjusted Cox model correcting for confounding effects of baseline disease severity variables showed consistent benefit as seen in the primary analysis for all ADP (HR=0.48, 95% CI: 0.19, 1.16) and 34 mg ADP (HR=0.35, 95% CI: 0.14, 0.91).

3.7 Substantial Evidence of Effectiveness for ADP: Studies 019, 020, and 045

In accordance with the FDA's (draft) Guidance on *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (lines 419-430; Dec 2019), substantial evidence of pimavanserin's efficacy for improvement of psychosis symptoms and prevention of relapse in patients with ADP is based on a positive, adequate and well-controlled study (Study 019) in ADP (target indication) and an existing positive study (Study 020) that demonstrated effectiveness for pimavanserin's other, closely-related approved indication for the treatment of PDP. Additional supportive evidence comes from the ADP subgroup analyses in Study 045, an overall positive, randomized withdrawal study in patients with DRP (Figure 3-24).

In Study 045, the ADP subgroup, including the ADP 34 mg subgroup, showed clinically meaningful reduction in the hazard of relapse (38% [all doses] to 53% [34 mg dose]), and although not nominally statistically significant, was clinically meaningful and consistent with the primary outcome across multiple analyses and endpoints. The strong E-R relationship observed indicates that the pimavanserin benefit seen in the ADP subgroup reflects a true treatment response and is not likely to be a chance observation.

Figure 3–24 Substantial Evidence of Effectiveness for ADP

	n	z-score (95% CI)	p-value	Estimate (95% CI)
Study 019 ADP NPI-NH PS	178	**-2.00** (-3.96, -0.04)	**0.045**	-1.84[a] (-3.64, -0.04)
Study 020 PDP SAPS-PD	185	**-3.19** (-5.15, -1.23)	**0.001**	-3.06[a] (-4.91, -1.20)
Study 045 Time to Relapse				
DRP	194	**-2.83** (-4.79, -0.87)	**0.005**	0.35[b] (0.17, 0.73)
ADP All Doses	123	**-1.07** (-3.03, 0.89)	**0.283**	0.62[b] (0.26, 1.49)
ADP 34 mg (covariate adjusted[c])	116	**-2.16** (-4.12, -0.20)	**0.031**	0.35[b] (0.14, 0.91)

Sources: Study 019 CSR Table 14.2.1.1.1; Study 020 CSR Table 14.2.1.1.1; Study 045 CSR Addendum Tables 14.2.1.5.1, 14.2.1.10.3, AH14.2.1.5.1.MODELadAIC

Abbreviations: ADP=Alzheimer's disease psychosis; CI=confidence interval; DRP=dementia-related psychosis; LSM=least square means; N=no; NPI-NH PS=Neuropsychiatric Inventory–Nursing Home Version psychosis score; OL=open-label; SAPS-H+D=Scale for the Assessment of Positive Symptoms–Hallucinations + Delusions; SAPS-PD=Scale for the Assessment of Positive Symptoms in Parkinson's Disease; Y=yes

Notes: Estimates with 95% CI and 2-sided p-values are from the primary analysis models in each study; z-scores correspond to the p-values based on the standard normal distribution; 95% CI of z-scores are z scores +/- 1.96 standard error units. For Study 045, the original Cox regression model includes effects for treatment, dementia subgroup (randomization strata) and region; the covariate adjusted Cox regression model includes effects for treatment group, antipsychotic use within 14 days of screening (Y/N), OL baseline SAPS-H+D, OL baseline dementia severity (mild versus not mild), and OL baseline antidementia medication use (Y/N).

[a] LSM difference in change from Baseline values (pimavanserin – placebo)
[b] Hazard ratio (pimavanserin/placebo)
[c] post-hoc analysis

4 CLINICAL SAFETY

SUMMARY

- Safety data from large numbers of frail, elderly patients with NDD and AD exposed to pimavanserin demonstrate that pimavanserin is well-tolerated in patients with NDD, including ADP.
- Safety data support the conclusion that pimavanserin is not associated with the numerous adverse effects observed with off-label use of other antipsychotic drugs, *importantly* including no evidence for cognitive decline or motor dysfunction.
- The IRR for deaths occurring within the intended treatment period plus 30 days thereafter was 1.28 (0.48, 3.43) for pimavanserin 34 mg treated patients with NDD, NDD being the largest group of patients treated with pimavanserin in placebo-controlled trials.

- Review of accumulating clinical mortality data suggests a positive trend toward balance with placebo, but still relatively limited numbers of patients and wide and overlapping confidence intervals.
- Postmarketing experience of NUPLAZID treatment in >40,000 PDP patients over the 6 years since approval in the US provides further evidence of a well-tolerated profile in a frail, elderly, patient population. Moreover, the results of two recent real-world, observational studies have demonstrated a significant decrease in risk of mortality in PDP patients treated with pimavanserin vs. atypical antipsychotics.

4.1 Safety in NDD

Overall, the cumulative dataset from the pool of NDD studies is a substantial safety dataset, and includes the data submitted for the original PDP NDA in addition to clinical safety data from the PMC studies in frail and elderly patients, with a substantial number of patients with AD. This dataset provides the greatest power for detecting potentially drug-related safety signals and is used to inform adverse reactions (ARs) for the label. The NDD pool is the pool of parallel group, placebo-controlled studies in patients with NDD. This safety dataset shows that pimavanserin is very well tolerated in patients with NDD, including AD, and is not associated with the numerous adverse effects observed with off-label use of other antipsychotic drugs in NDD patients, including no evidence for cognitive decline or motor dysfunction with chronic use. Most notably, there is no indication of increased mortality with pimavanserin use in NDD compared to placebo in any of the safety pools examined, although an increase in risk cannot be definitively ruled out.

4.1.1 Summary of Safety in NDD Patients

As of 08 September 2021, Acadia has compiled a large, pooled, clinical study safety database in 1683 frail, elderly patients with NDD exposed to pimavanserin (Table 4–1). Specifically, data are available from 14 clinical studies, of which 721 patients had a clinical diagnosis of AD, 572 of whom had psychosis. The integrated safety database for the Day 120 Safety Update (16 June 2020 data cutoff) included 1502 frail, elderly patients with NDD who were exposed to pimavanserin. (See Appendix Section 7.2 for the main design features of key studies.)

Table 4–1 Duration of Pimavanserin Exposure in Patients With NDD (including AD) From Completed Studies and Unblinded Interim Analyses

Patient Population	<3 months	≥3 months	≥6 months	≥12 months	Total pimavanserin at data cutoff
Total NDD population[a]	766	917	740	394	1683
Subset of patients with AD[b]	260	461	288	160	721
Subset of patients with ADP[b]	226	346	180	97	572

Sources: sNDA Section 2.7.4.1.2.1; Section 5.3.5.3 Tables RADPIMEXT.1.6 and RADPPIMEXT.1.6

Abbreviations: AD=Alzheimer's disease; ADP=Alzheimer's disease psychosis; IA2=second interim analysis; NDD=neurodegenerative disease; sNDA=supplemental new drug application

Note: For ongoing Studies 046 and 047, exposure is calculated only for the subset of subjects unblinded in IA2 for Study 046. For Study 047, exposure is calculated to 08Sep2021.

[a] Clinical studies contributing patients: 005, 006, 010, 012, 014, 015, 020, 048, 019, 032, 033, 045, 046 (IA2), 047 (IA2)

[b] Clinical studies contributing patients: 019, 032, 033, 045, 046 (IA2), 047 (IA2)

The safety conclusions resulting from a comprehensive review of pimavanserin clinical data in patients with NDD are summarized as follows. The proportions of patients with a target TEAE are presented as study-adjusted percentages to account for various sample sizes across studies.

Overall, pimavanserin was well tolerated with TEAE frequencies generally similar to placebo. Events reported in at least 2% of patients (study-adjusted) in the pimavanserin 34 mg group and at a rate at least 1% greater than the placebo group were peripheral edema and confusional state (Table 4–2). In addition, the incidence of TEAEs was similar between the pimavanserin 34 mg and placebo group across all exposure periods (≤2 weeks, >2 to ≤4 weeks, >4 to ≤6 weeks, and >6 weeks). Similar findings were observed when comparing the overall pimavanserin group (all doses) with placebo.

Table 4–2 Adverse Reactions Reported Events in at Least 2% of Pimavanserin Patients and at Least 1% Greater Than the Placebo Rate (NDD Pool)

Percentage of Patients Reporting Adverse Reaction		
	Pimavanserin 34 mg	Placebo
	N=580	N=575
Peripheral edema	3%	1%
Confusional state	3%	1%

Source: D120 Safety Update Table 2.7.4.2-7

Abbreviations: D120=Day 120

While the study-adjusted frequency of serious TEAEs was low, an increased frequency of serious TEAEs was observed in the pimavanserin 34 mg group compared to the placebo group in patients in the pool of parallel group, placebo-controlled studies in patients with NDD (NDD pool) (7.1% pimavanserin 34 mg vs. 4.2% placebo). Similar findings were

observed when comparing the overall pimavanserin group (all doses) with placebo in the NDD pool.

The serious TEAEs reported in at least 2 patients in either treatment group and at a higher rate in the pimavanserin 34 mg group than in the placebo group were urinary tract infection (UTI) (0.9% vs. 0.2%, respectively); fall and mental status changes (0.3% vs. 0.2% each, respectively); and agitation, psychotic disorder, and hallucination (0.3% vs. 0% each, respectively). Review of the cases did not reveal any pattern suggestive of a drug effect. Similar findings were observed when comparing the overall pimavanserin group (all doses) with placebo, with the exception of the additional serious TEAEs of sepsis (0.4% vs. 0%, respectively), and femoral neck fracture, hip fracture, encephalopathy, Parkinson's disease, and syncope (0.2% vs. 0% each, respectively).

A total of 5.8% of pimavanserin 34 mg-treated patients and 4.7% placebo-treated patients (study adjusted) discontinued because of TEAEs. The TEAEs that occurred in more than one patient and with an incidence at least twice that of placebo were depressed level of consciousness (0.4% pimavanserin vs. 0% placebo), psychotic disorder (0.8% pimavanserin vs. 0.2% placebo), hallucination (0.7% pimavanserin vs. 0.2% placebo), and fatigue (0.3% pimavanserin vs. 0% placebo). Similar findings were observed when comparing the overall pimavanserin group (all doses) with placebo, with the exception of the additional events of delusion (0.2% vs. 0%, respectively), syncope (0.2% vs. 0%, respectively), and confusional state (0.3% vs. 0%, respectively).

Mortality has been analyzed using two different timeframes to allow comparison with the Schneider et al. (2005) and FDA meta-analyses of mortality and atypical antipsychotics:

- deaths occurring within 30 days of the last dose
- deaths occurring within the intended treatment period plus 30 days thereafter.

The incident rate ratios and odds ratios of deaths occurring within 30 days of last dose and of deaths occurring within the intended treatment period plus 30 days thereafter are presented for NDD patients who took pimavanserin 34 mg or placebo in the NDD pool in Table 4–3. Mortality rates associated with pimavanserin treatment (pimavanserin 34 mg vs. placebo) in the overall NDD patient population were relatively balanced versus placebo; the IRR (95% CI) of deaths was 1.02 (0.36, 2.90) for deaths occurring within 30 days of the last dose and 1.28 (0.48, 3.43) for deaths occurring within the intended treatment period plus 30 days thereafter. Similar results were observed in the NDD pool for patients who received placebo or pimavanserin (all doses).

Table 4–3 Comparison of Pimavanserin Mortality Rate in NDD With Published Meta-Analyses

	Deaths Within 30 Days of the Last Dose	Deaths Occurring Within the Intended Period of Treatment plus 30 Days Thereafter
Pimavanserin 34 mg (N=580), n (%)	7 (1.2)	9 (1.6)
Pimavanserin all doses (N=833), n (%)	8 (1.0)	10 (1.2)
Placebo (N=649), n (%)	7 (1.1)	8 (1.2)
IRR (pimavanserin 34 mg/placebo) (95% CI)	1.02 (0.36, 2.90)	1.28 (0.48, 3.43)
IRR (pimavanserin all doses/placebo) (95% CI)	1.01 (0.37, 2.80)	1.22 (0.46, 3.23)
OR (pimavanserin 34 mg/placebo) (95% CI)	0.99 (0.34, 2.85)	1.28 (0.47, 3.47)
OR (pimavanserin all doses/placebo) (95% CI)	1.00 (0.36, 2.81)	1.24 (0.47, 3.31)
FDA Meta-Analysis: All drugs: IRR (95% CI)		1.71 (1.38, 2.11)
FDA Meta-Analysis: Atypical: IRR (95% CI)		1.65 (1.29, 2.09)
Meta-Analysis, Schneider et al. 2005: Antipsychotics OR (95% CI)	1.54 (1.06, 2.23)	

Sources: Section 5.3.5.3 Tables NPG.3.4.2, AH.NPG.3.4.1.INTRTDUR
Abbreviations: CI=confidence interval; FDA=Food and Drug Administration; IRR=incidence rate ratio; OR=odds ratio; NDD=neurodegenerative disease

Note: The pimavanserin mortality rate is based on data from the NDD pool, which included pimavanserin treated patients with neurodegenerative disease in double-blind, placebo-controlled, parallel-group studies.

The IRR (CI) of 1.28 (0.48, 3.43) for pimavanserin 34 mg versus placebo (for deaths in the NDD pool occurring within the intended treatment period plus 30 days thereafter) is nominally lower than the value FDA calculated for antipsychotic drugs in their 17-study meta-analysis, IRR (CI) 1.71 (1.38, 2.11), but the confidence intervals overlap (Table 4–3, FDA Email Correspondence).

Similarly, the OR (CI) of 0.99 (0.34, 2.85) for pimavanserin 34 mg versus placebo for deaths in the NDD pool occurring within 30 days of the last dose is nominally lower than the value Schneider et al. (2005) calculated for antipsychotic drugs in their meta-analysis, OR (CI) 1.54 (1.06, 2.23), but the confidence intervals overlap (Table 4–3).

In contrast to what has been reported for other antipsychotic drugs, there was no evidence for decline in a measure of cognitive function (MMSE) and no negative effect on motor function across studies in frail patients with neurodegenerative disease.

4.1.2 Summary of Safety in AD Patients in the Context of NDD

The safety conclusions resulting from a comprehensive review of pimavanserin clinical data in patients with AD, in the context of safety in patients with NDD, are summarized as follows.

Frequencies of TEAEs, TEAEs leading to study drug discontinuation or study termination, and deaths within 30 days of last dose were generally similar between pimavanserin 34 mg and placebo and are summarized in Table 4-4 for the patients with neurodegenerative disease in double-blind, placebo-controlled, parallel-group studies (NDD pool) and for patients with AD in double-blind, placebo-controlled, parallel-group studies (AD pool). Serious TEAEs occurred at slightly higher frequency in pimavanserin treated patients. Similar findings were observed when comparing the overall pimavanserin group (all doses) with placebo in both the NDD and AD pools.

Table 4-4 Overall Summary of TEAEs in Patients With NDD and AD in the Pimavanserin Clinical Study Safety Database (Safety Analysis Sets) – Study-Adjusted

TEAE	NDD		AD	
	PIM 34 mg (N=580) %	PBO (N=575) %	PIM 34 mg (N=292) %	PBO (N=282) %
Any TEAE	53.9	54.5	55.5	56.3
Any serious TEAE	7.1	4.2	8.0	5.6
Any TEAE leading to study drug discontinuation or study termination	5.8	4.7	5.2	7.0
Death within 30 days of last dose	1.2	1.2	1.4	1.8

Sources: Tables RADPG.2.13; RADPG.2.14; RADPG.2.15; RADPG.2.16; NPG.2.13; NPG.2.14; NPG.2.15; NPG.2.16

Abbreviations: AE=adverse event; IA2=second interim analysis; placebo-controlled pool; PBO=placebo; PIM=pimavanserin; TEAE=treatment-emergent adverse event

Notes: A TEAE was an AE with an onset date on or after the first study dose date and no later than the last study dose date plus 30 days. The NDD pool included Studies 005, 006, 012, 014, 019, 020, 032, and 046IA2. The AD pool included Studies 019, 032, and 046IA2. Study adjusted % is a weighted average of the study specific percentages for the dose group. The weight for a study is the number of subjects included in the analysis from the study divided by the number of subjects across all studies that are included in the analysis.

When the data from AD patients are examined, compared with NDD data, a similar low number of deaths was observed on pimavanserin 34 mg treatment versus placebo (the IRR [95% CI] of deaths was 0.82 [0.22, 3.05] for deaths occurring within 30 days of the last dose and 0.99 [0.29, 3.41] for deaths occurring within the intended treatment period plus 30 days thereafter [Table 4–3]).

No new safety signals were observed in the additional integrated analysis of patients with AD as compared to patients with NDD. Safety analyses in patients with AD revealed similar or more favorable safety that that found for patients with NDD.

Overall, the clinical safety and tolerability profile for pimavanserin continues to support the positive benefit-risk of treatment of hallucinations and delusions in patients with ADP.

Analyses provided below demonstrate the lack of negative effect on cognition and motor function in patients with ADP.

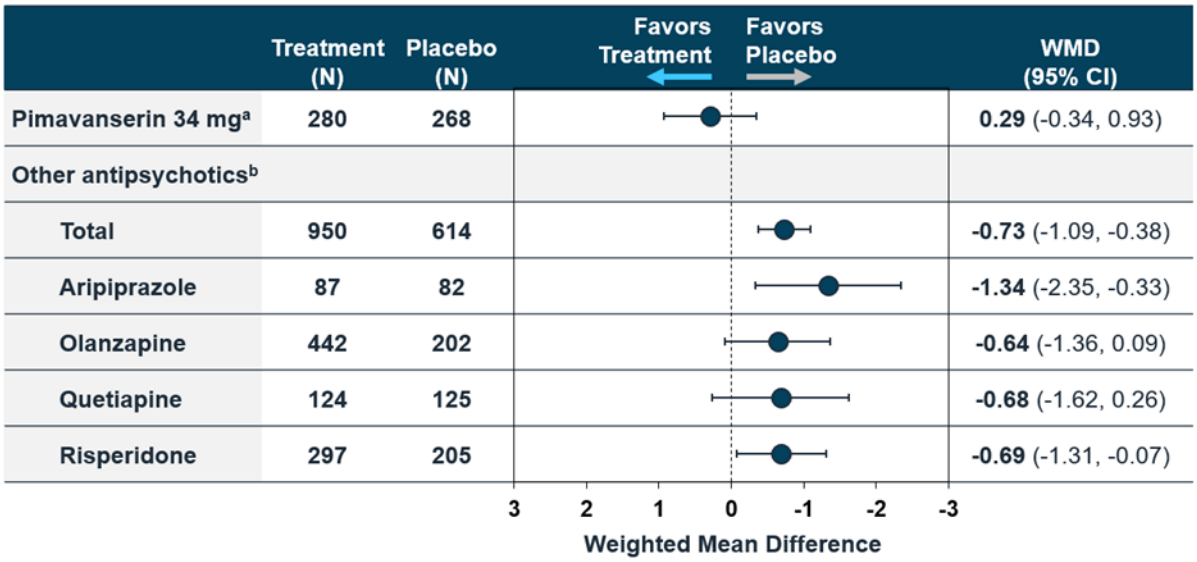
4.2 Cognitive Function

Acceleration of cognitive decline is of clear clinical detriment to the dementia patient population, in which cognitive impairment is a core symptom of the disease.

Unlike pimavanserin's selective antagonist/partial agonist activity at serotonergic 5-HT_{2A} receptors, conventional and atypical antipsychotics principally act as dopamine receptor antagonists as well as having activity at several other receptors (e.g., muscarinic, histaminergic, and adrenergic). Dopamine receptor antagonist activity is a significant concern because AD is linked to decreased levels of dopaminergic neurotransmitters (Pan et al. 2019) and the common symptom of apathy and related dysfunction (Levy and Czernecki 2006; Hongisto et al. 2018; Udo et al. 2020). Consequently, their use is associated with increased cognitive impairment, as well as with other significant safety liabilities such as extrapyramidal symptoms, sedation, and falls, which can be especially problematic for use in frail, elderly patients with dementia (Schneider et al. 2006a; Schneider et al. 2006b).

Pimavanserin treatment did not result in evidence for a decline in MMSE in any study and had no negative impact on cognition. Further, data from the integrated clinical development program in AD patients showed no evidence of a decline in cognition, as measured by MMSE score with pimavanserin 34 mg treatment compared with placebo in short-term studies. Based on the meta-analyses (Figure 4–1), pimavanserin 34 mg has shown a numerical improvement on MMSE compared with placebo with a difference of 0.29; however, other antipsychotics significantly worsened the MMSE scores as compared with placebo with a difference of -0.73. When comparing pimavanserin treatment (all doses) with placebo, a similar trend of a numerical improvement on MMSE is observed, with a difference of 0.07.

Figure 4–1 Meta-Analysis of Cognitive Function Measured by Changes in MMSE Scores by Drug



Source: Section 5.3.5.3 Figure RADPG.1.1.1

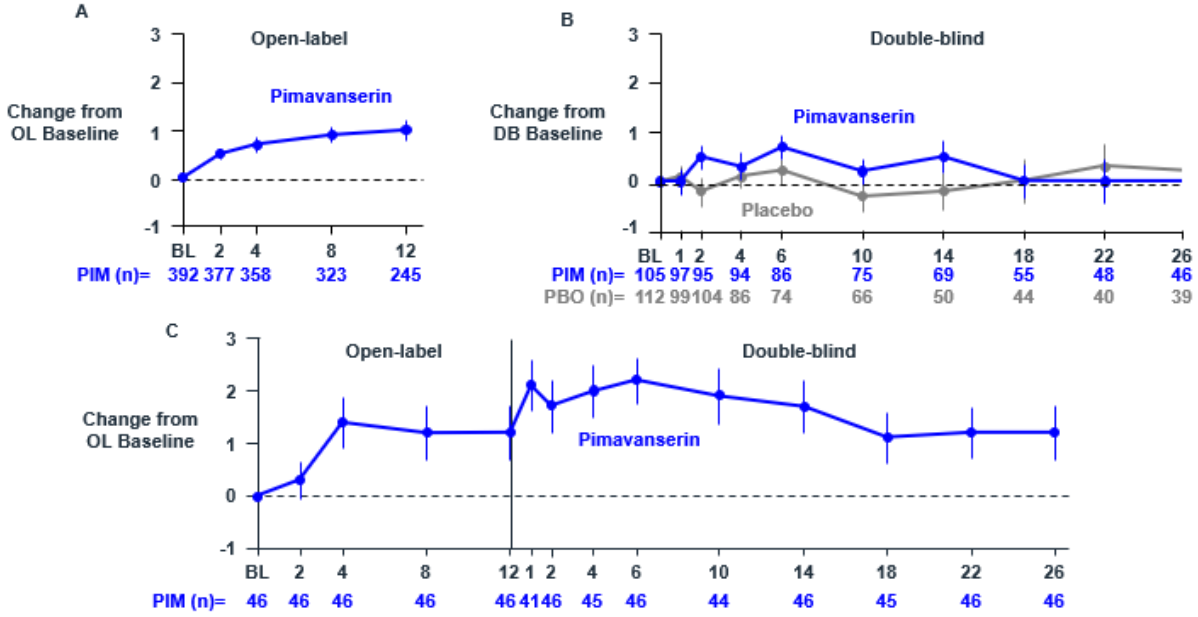
Abbreviations: CI=confidence interval; MMSE=Mini-Mental State Examination; WMD=weighted mean difference

a This meta-analysis compares pimavanserin 34 mg treatment to placebo treatment group for Alzheimer's disease patients in Studies 019, 032 and 046 (AD pool).

b Adapted from Schneider et al. 2006a

In addition, there was no observed decline in mean MMSE in pimavanserin-treated patients or difference from placebo-treated patients in Study 045 (Figure 4–2 A and B, respectively). The mean change from OL Baseline (SE) for patients treated with pimavanserin for the entire duration of the study (9 months) was 1.2 (0.51) (Figure 4–2 C).

Figure 4–2 MMSE Score Changes From Baseline by Visit (Mean ±SE; OC) During the Open-Label and Double-Blind Period: Double-Blind Safety Analysis Set - Study 045

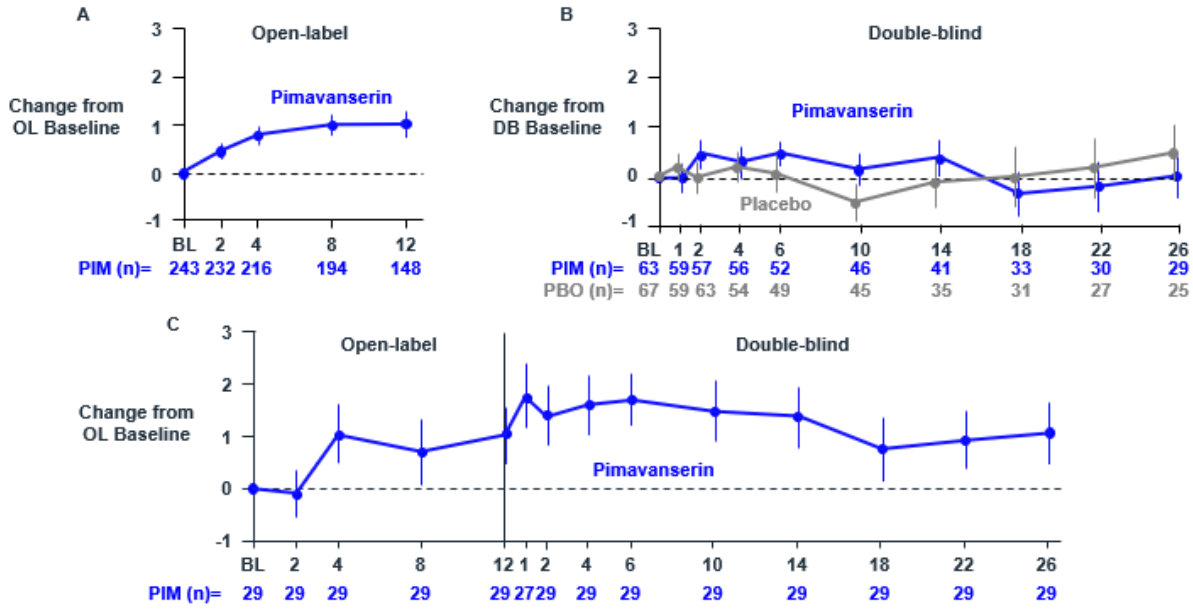


Sources: sNDA Figure 2.7.4.4-3, Figure 2.7.4.4-4, and Figure 2.7.4.4-5

Abbreviations: BL=baseline; DB=double-blind; MMSE=Mini-Mental State Examination; OC=observed cases; OL=open-label; PBO=placebo; PIM=pimavanserin; SE=standard error; sNDA=supplemental new drug application

Consistent with the results in the DRP population, in the ADP subgroup in the OL phase of Study 045 the mean (SE) change in MMSE from Baseline to OL Week 12 was 1.0 (0.26) for pimavanserin 34 mg (Figure 4–3 A). In the DB phase, the mean (SE) change in MMSE from DB Baseline to DB Week 26 was 0.0 (0.40) for pimavanserin 34 mg and 0.5 (0.56) for placebo (Figure 4–3 B). Patients exposed to pimavanserin 34 mg for the entire duration of the study (up to 9 months: OL period and DB period) did not demonstrate a decline in mean MMSE (change from OL Baseline to DB Week 26: 1.1 [0.61]) (Figure 4–3 C). Results were similar in those AD patients who received pimavanserin (all doses).

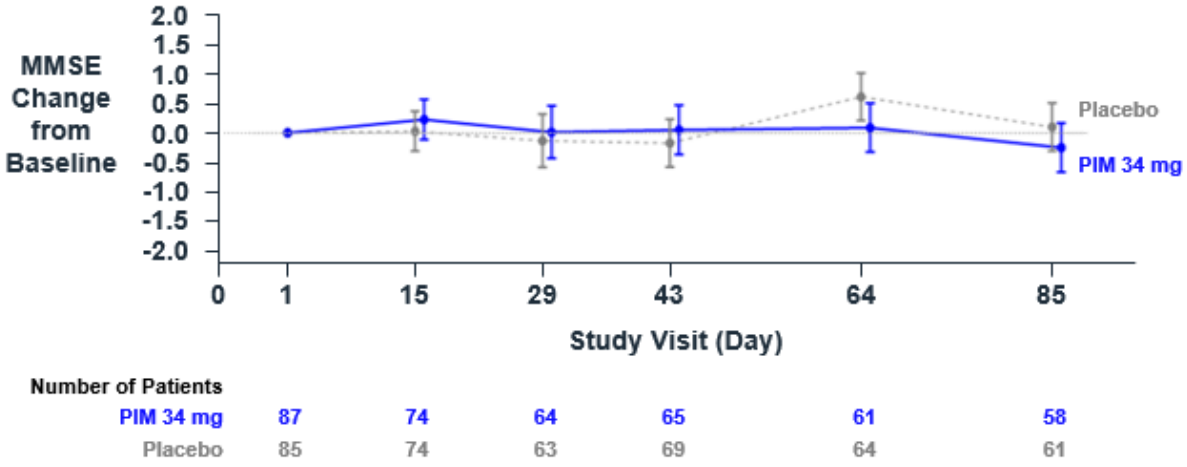
Figure 4–3 MMSE Score Changes from Baseline by Visit (Mean ±SE; OC) During the Open-Label and Double-Blind Period: Double-Blind Safety Analysis Set - Study 045 ADP 34 mg Subgroup



Sources: Study 045 CSR Addendum Figures R.AH14.4.8.ADP34, R.AH14.3.8.ADP34, R.AH14.4.9.ADP34.DB26
Abbreviations: BL=baseline; CSR=clinical study report; DB=double-blind; MMSE=Mini-Mental State Examination; OC=observed cases; OL=open-label; PBO=placebo; PIM=pimavanserin; SE=standard error

Furthermore, individual data from three parallel-group, placebo-controlled studies with pimavanserin (Study 019, Study 032, and Study 046) showed no evidence of a decline in cognition. Study 019 was a 12-week study with an assessment of the primary efficacy endpoint at 6 weeks and safety at 12 weeks. The results are shown for Study 019 in Figure 4-4. Measurement of MMSE was included to assess the potential effects of pimavanserin on cognition in these frail, elderly patients, most of whom were suffering from dementia.

Figure 4–4 MMSE Score Changes From Baseline by Visit (LS Mean±SE) (OC; MMRM): Safety Analysis Set - Study 019



Source: Study 019 CSR Figure 8

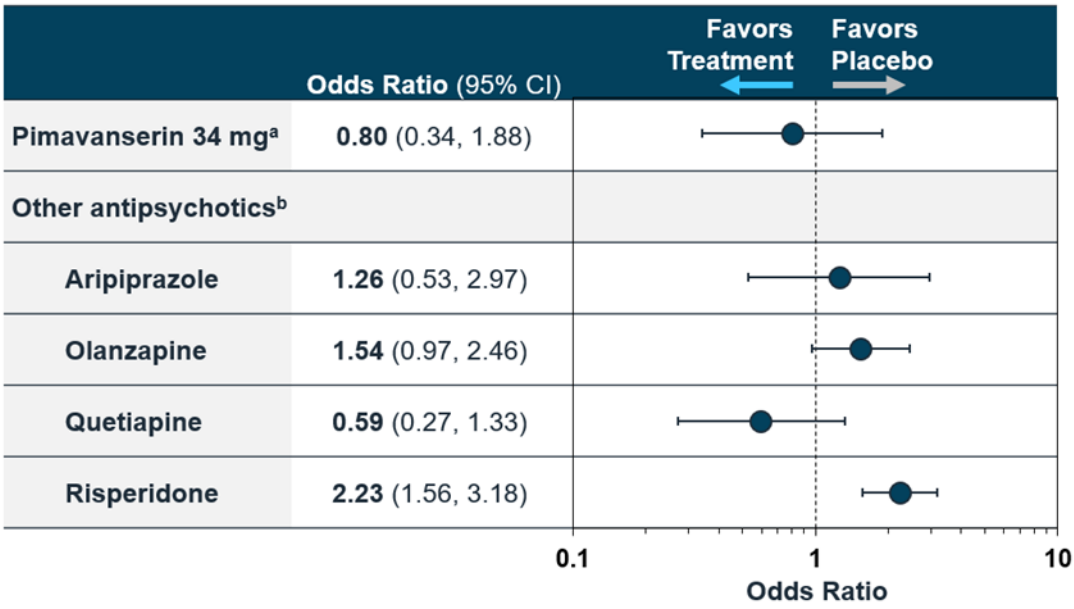
Abbreviations: CSR=clinical study report; LS=least squares; MMRM=mixed-effects model repeated measures; MMSE= Mini-Mental State Examination; OC=observed cases; PIM=pimavanserin; SE=standard error

4.3 Motor Function

Approved multi-receptor acting antipsychotics with dopamine blocking activity are associated with the emergence of extrapyramidal symptoms. Multiple DB placebo-controlled studies in DRP (including ADP) and PDP patients have evaluated the potential for this adverse effect using the UPDRS and the ESRS-A scale. Overall, and as predicted by the selective serotonergic mechanism of action and data from initial approval of pimavanserin in PDP, no negative impact of pimavanserin on motor function was seen in any study.

No clinically significant negative impact of pimavanserin on motor function was seen in any study. Further, data from the integrated clinical development program in patients with AD showed no evidence of a worsening of motor function, as measured by extrapyramidal syndrome events with 34 mg pimavanserin treatment compared with placebo in short-term studies. Based on the meta-analyses (Figure 4–5), pimavanserin 34 mg has shown a numerical improvement on motor function compared with placebo with a difference of 0.80. Pimavanserin (all doses) in these short-term studies also showed a numerical improvement compared with placebo (0.71).

Figure 4–5 Meta-analysis of Motor Function Measured by Adverse Events of EPS by Drug



Source: Section 5.3.5.3 Figure RADPG.1.2.1

Abbreviations: CI=confidence interval; EPS=extrapyramidal symptoms

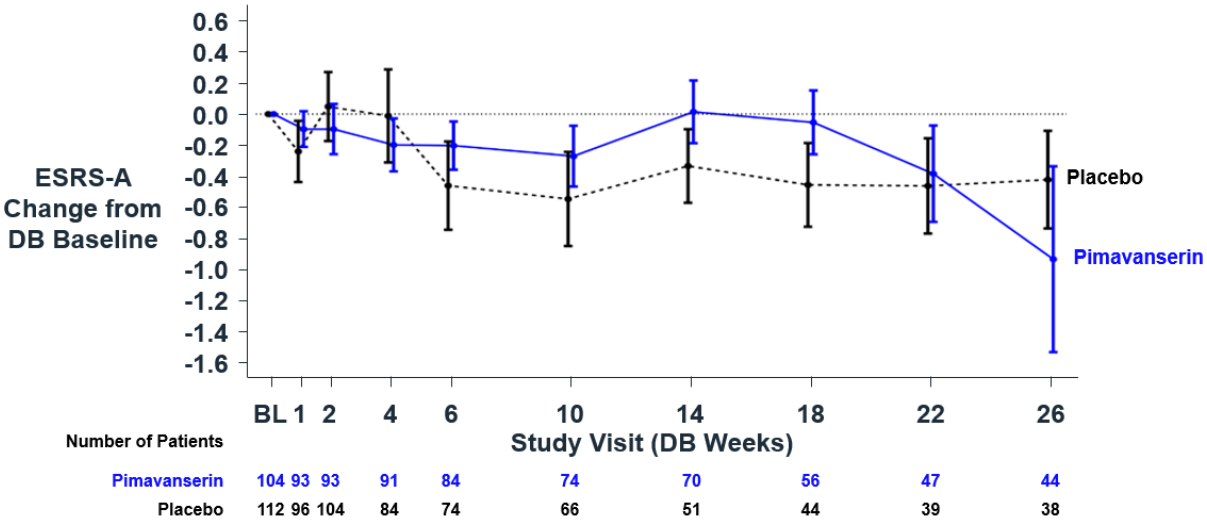
Note: The odds ratio is calculated using a logistic regression model which includes the binary outcome of Extrapyramidal syndrome events (Yes, No), with the factor of treatment group.

[a] This meta-analysis compares pimavanserin 34 mg to placebo for Alzheimer's disease patients in Studies 019, 032 and 046 (AD pool). In Study 032, subjects who were in the pimavanserin 20 mg group were excluded from this analysis.

[b] From Yunusa et al. 2019.

In addition, there was no observed worsening in motor function in pimavanserin-treated patients in Study 045. During the OL period, the mean (SE) change in total ESRS-A score was minimal and trended toward improvement and not worsening of motor function (change at OL Week 12: -0.7 [0.17]). During the DB period, the mean (SE) change from DB Baseline in total ESRS-A was small and similar in the two treatment groups at all timepoints (change at DB Week 26: -0.4 [0.32] and -0.9 [0.60] for placebo and pimavanserin, respectively) (Figure 4–6). Patients exposed to pimavanserin for the entire duration of the study (up to 9 months: OL period and DB period) did not demonstrate worsening in motor function (change from OL Baseline to DB Week 26: -1.2 [0.37]). Results were similar in those patients who received pimavanserin 34 mg. The results reflected no effect of pimavanserin on motor function.

Figure 4–6 ESRS-A Total Score (Mean ±SE) Change From DB Baseline by Visit: Safety Analysis Set - Study 045

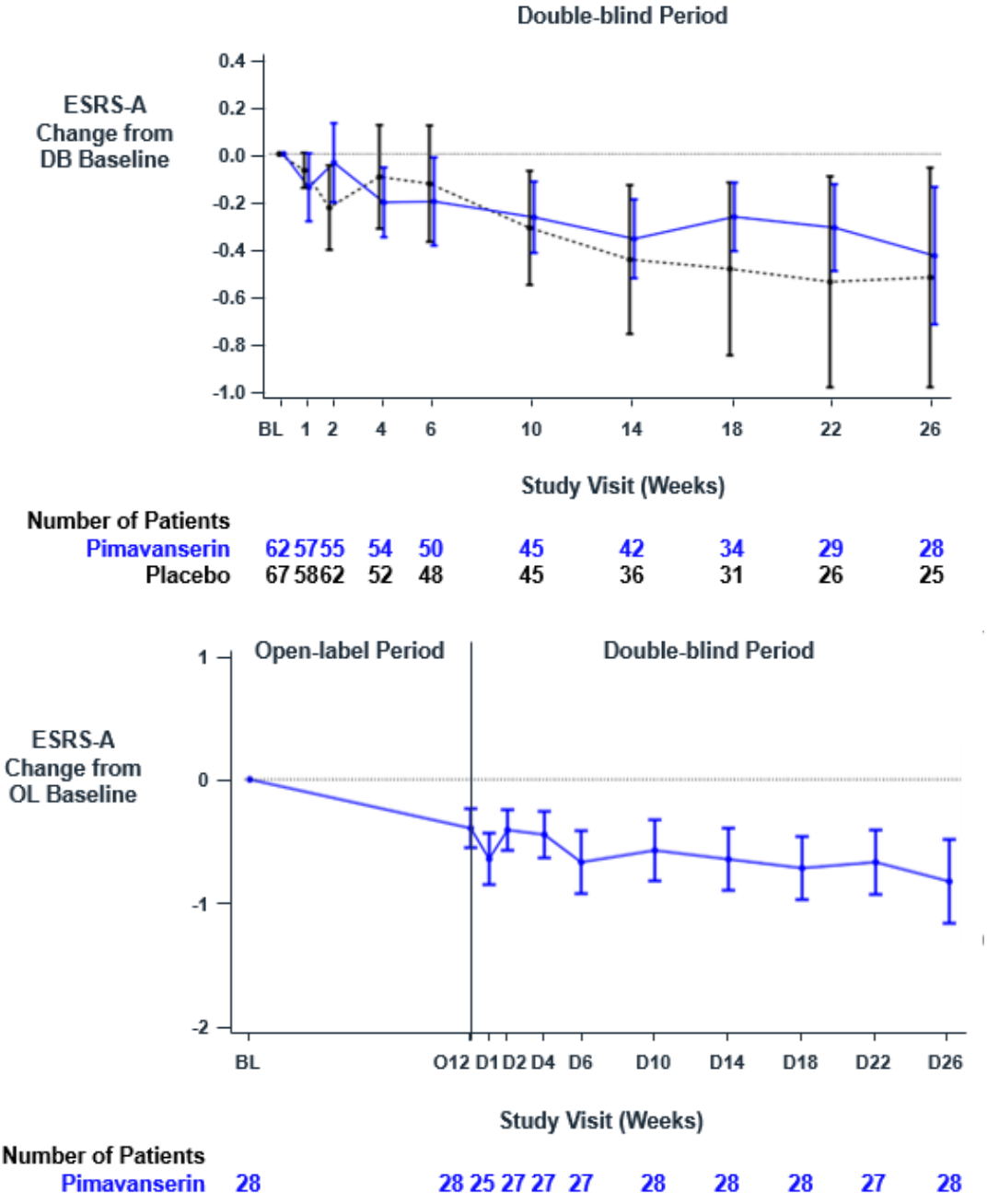


Source: Tariot et al. 2021

Abbreviations: BL=baseline; DB=double-blind; ESRS-A=Extrapyramidal Symptom Rating Scale–Abbreviated

Consistent with the results in the DRP population, in the ADP subgroup in the OL phase of Study 045, the mean (SE) change in ESRS-A from Baseline to OL Week 12 was -0.3 (0.14) for pimavanserin 34 mg. In the DB phase, the mean (SE) change in ESRS-A from DB Baseline to DB Week 26 was -0.4 (0.29) for pimavanserin 34 mg and -0.5 (0.47) for placebo (Figure 4–7 top). Patients exposed to pimavanserin 34 mg for the entire duration of the study (up to 9 months: OL period and DB period) did not demonstrate worsening in motor function (change from OL Baseline to DB Week 26: -0.8 [0.35]) (Figure 4–7 bottom). Results were similar in those AD patients who received pimavanserin (all doses).

Figure 4–7 ESRS-A Total Score Changes from Baseline by Visit (Mean ±SE) (OC) - Double-Blind Period (top panel); Open-Label Period through Double-Blind Period for Pimavanserin Patients With ESRS-A Total Scores at DB Week 26 (bottom panel) - Study 045 ADP 34 mg Subgroup

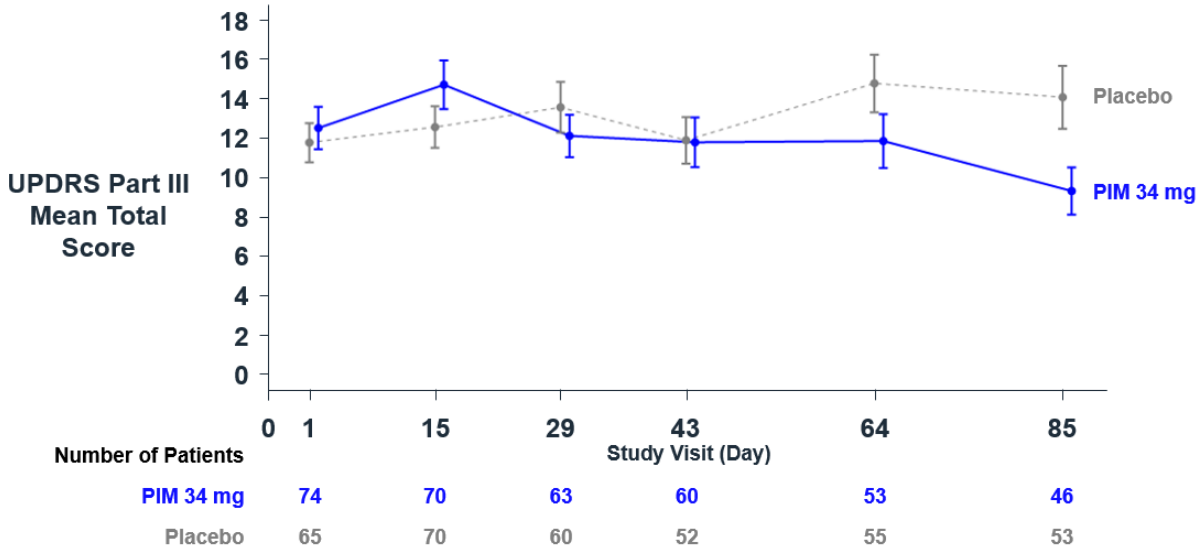


Sources: Study 045 CSR Addendum Figures R.AH.SRSA.DB.ADP34, R.AH.SRSA.ADP34.DB26

Abbreviations: BL=baseline; CSR=clinical study report; DB=double-blind; ESRS-A=Extrapyramidal Symptom Rating Scale–Abbreviated; OC=observed cases; OL=open-label; SE=standard error

In Study 019, pimavanserin was not associated with worsening motor function, as measured by UPDRS Part III score (Figure 4–8).

Figure 4–8 UPDRS Part III Total Score by Visit (Mean ±SE) (OC): Safety Analysis Set – Study 019



Source: Study 019 CSR Figure AH9.1

Abbreviations: CSR=clinical study report; OC=observed cases; PIM=pimavanserin; SE=standard error; UPDRS=Unified Parkinson's Disease Rating Scale

4.4 Worldwide Marketing Experience

NUPLAZID® (pimavanserin 34 mg) was approved in the US for the treatment of PDP on 29 April 2016 and was launched on 31 May 2016. As of 28 October 2021, more than 44,000 patients have been exposed to NUPLAZID in the postmarketing setting, representing at least 35,000 person-years. Due to PDP diagnosis eligibility requirements and payer restrictions, postmarketing experience with NUPLAZID consists almost exclusively of PDP patients. Periodic adverse drug experience reports (PADERs) have been submitted to the FDA in accordance with 21 CFR 314.80 for postmarketing surveillance, and since the sNDA submission, no new safety risks have been identified. The PADERs have included a death reporting rate based on fatal reports and exposure calculated from Acadia's Reimbursement Hub/Specialty Pharmacy distribution system that tracks unique patient exposure and collects AE reports in the course of frequent contact with patients. The use of specialty pharmacies (SPs) to distribute pimavanserin has allowed Acadia to identify a representative sample of pimavanserin patients and to obtain important information such as age, gender, and time on drug, as well as collect "solicited" AEs, including deaths with less uncertainty of under-

reporting seen with voluntary spontaneous reports. In fact, the post-marketing death reporting rate is consistent with the rates seen in observational studies. (Layton 2022).

Since the sNDA submission, the frequency of the most frequently reports adverse events and reported cause of death remains essentially unchanged compared with data presented in the Day 120 (D120) sNDA update with the exception of new reports of COVID-19 cases (72 with fatal outcome).

Overall, the analyses of AEs, SAEs, death reporting rates, and reported cause of death in the SP NUPLAZID cohort continue to be consistent with the advanced age and comorbidities as seen in the general PDP population. Extensive and periodic evaluation of postmarketing deaths and reported AEs showed no patterns or trends suggesting a common underlying pathology.

Finally, the results of the analysis of this large postmarketing cohort of SP patients and supporting observational studies are consistent with the favorable safety profile seen in the pimavanserin clinical studies.

4.5 Real World Evidence

Since launch several large observational studies in PD and PDP patients have provided additional real world evidence that confirms the favorable safety profile of pimavanserin compared to atypical antipsychotics.

An observational cohort study in US commercial insurance and supplementary Medicare claims (2015-2019) evaluating the risk of falls/fractures among patients with PDP treated with pimavanserin versus other comparator atypical antipsychotics found that the crude incidence rates (95% CI) for composite falls/fractures were 17.8 (7.7, 35.0) for pimavanserin and 40.8 (35.0, 47.4) for comparators (Layton et al. 2022). All characteristics were well balanced after propensity score matching with a matched IRR (pimavanserin vs. comparator) of 0.71 (95% CI: 0.27, 1.67) and sensitivity analysis IRR estimates were consistently below 1.00, with a sensitivity analysis not requiring a diagnosis of psychosis resulting in an IRR estimate of 0.55 (95% CI: 0.34, 0.86).

Two observational studies in Medicare beneficiaries with PD and PDP reported an overall and numerically similar decreased risk of mortality associated with pimavanserin use compared with use of atypical antipsychotics.

A study of Medicare beneficiaries with PD presented by academic and government scientists, including FDA authors, reported an overall decreased risk of mortality associated with pimavanserin use compared with use of atypical antipsychotics, with the largest reductions in mortality risk seen in the first 180 days after treatment (Mosholder et al. 2020). All-cause

mortality was assessed in Medicare beneficiaries with PD who initiated pimavanserin (N=3227) or atypical antipsychotics (N=18,448) during the first 3 years of marketing. Pimavanserin use was associated with significantly lower mortality compared to atypical antipsychotics (HR=0.78, 95% CI: 0.65, 0.94), and was similar in patients with and without dementia. However, the reduced mortality was restricted to patients not in nursing homes.

A subsequent Acadia-sponsored Medicare safety study by an independent epidemiology group submitted to FDA as part of this re-submission reviewed mortality risk associated with pimavanserin use compared with atypical antipsychotics in patients with PDP and showed similar results. The matched HR for mortality for pimavanserin vs. comparator was 0.78 (95% CI: 0.67, 0.91). In LTC/SNF residents the HR was 0.78 (95% CI: 0.60, 1.01.) Estimated HRs were similar across all sensitivity analyses (including patients without a psychosis diagnosis) and subgroups (sex, age, dementia diagnosis, and LTC residence) (Layton 2022).

Overall, the totality of pimavanserin experience in the large postmarketing cohort of patients and supporting observational studies is consistent with the favorable safety profile seen in the pimavanserin clinical studies.

4.6 Safety Conclusions

In conclusion, pimavanserin data from the integrated pimavanserin clinical development program support a differentiated safety profile from currently approved antipsychotics used off-label, particularly with regards to two important aspects: lack of negative impact on cognition and no adverse effects on motor function. Overall pimavanserin safety and tolerability is supportive of a positive benefit-risk in ADP patients. Furthermore, postmarketing data from greater than 40,000 patients in the approved PDP indication continue to support its favorable benefit-risk. Additional real world observational data evaluating mortality rates and falls in PD and PDP patients receiving pimavanserin versus atypical antipsychotics have also supported the favorable safety profile of NUPLAZID.

5 BENEFIT-RISK ANALYSIS

SUMMARY

- Pimavanserin demonstrated the reduction, maintenance of reduction, and prevention of reoccurrence of psychotic symptoms in ADP patients in acute and long-term settings
- Benefits were meaningful and observed consistently across studies and endpoints
  - Study 019 in ADP: effect size at Week 6 = 0.32, p=0.045
  - Study 045 ADP subgroup: 38% (all doses) to 53% (34 mg dose) reduction in hazard of relapse
  - Multiple secondary endpoints and sensitivity analyses confirm benefit
  - Exposure-response analysis and modeling further confirms true treatment effect
- Substantial Evidence of Effectiveness
  - Positive Study 019 in target indication of ADP
  - Confirmatory evidence in positive Study 020 in a closely- related approved indication for the treatment of PDP
  - Supportive evidence of pimavanserin's benefit for the treatment of ADP is observed in the positive randomized withdrawal study in patients with DRP, Study 045, in which the largest dementia subgroup, the ADP subgroup, showed consistent and clinically meaningful benefit of pimavanserin treatment.
- Well-characterized and favorable safety profile
  - Largest antipsychotic clinical study program in patients with NDD
  - >6 years post-marketing safety data with >44,000 patients with PDP with continued favorable safety and tolerability profile supported by real world evidence studies.
  - Differentiated safety profile as compared to off-label antipsychotics used, with lack of negative effect on cognition and motor function
- Pimavanserin fulfills an important unmet medical need.

5.1 Benefits of Pimavanserin Treatment of Alzheimer's Disease Psychosis

Across studies, pimavanserin showed statistically significant and clinically meaningful improvements in the frequency and severity of psychotic symptoms and maintenance of effect in patients with ADP (see Section 3).

In ***Study 019***, pimavanserin 34 mg demonstrated clinically meaningful efficacy in patients with ADP, with an effect size (Cohen's *d*) of 0.32, which is larger than those reported in the literature with currently used off-label treatments (effect size ≤0.2) (Ma et al. 2014; Tampi et

al. 2016; Maher et al. 2011). In the prespecified subgroup of patients with more severe psychosis, the magnitude of efficacy was more than double the overall ADP population (p=0.011, effect size=0.73). NPI-NH PS responder analyses also supported the significant and clinically relevant treatment effect of pimavanserin. Compared with placebo, a greater proportion of patients responded to pimavanserin across all prespecified responder cutoffs, with nominal statistical significance reached at ≥30% and ≥50% improvement and single digit NNTs in all patients. The efficacy benefits were achieved without a negative impact on cognitive or motor function. Additionally, pimavanserin displayed a favorable tolerability profile without off-target toxicities usually associated with atypical antipsychotics.

Study 020: Confirmatory evidence supportive of pimavanserin's benefit for the treatment of ADP comes from an existing positive study (Study 020) that demonstrated effectiveness for pimavanserin's other, closely-related approved indication of PDP. Importantly, the magnitude of symptom reduction observed in Study 019 is similar with that of Study 020, further supporting the consistency of effects of pimavanserin across closely related indications of ADP and PDP.

Study 045: Further, supportive evidence comes from an overall positive study in DRP (Study 045) with highly robust and statistically persuasive treatment effect (HR=0.35, 95% CI: 0.17, 0.73, one-sided p=0.0023). While the study was not powered to yield statistical significance by dementia subgroup, clinically meaningful reductions in the hazard of relapse were observed across dementia subgroups, demonstrating a directionally consistent response across dementia subgroups. Specifically, in patients with ADP, the largest subgroup in Study 045, remarkable consistency of benefit with the overall study population was demonstrated in the pimavanserin arm. Study 045 provides supportive evidence for antipsychotic efficacy for the ADP subgroup of both short-term response to treatment and stabilization (through OL treatment) and long-term relapse prevention (through DB, placebo-controlled treatment).

Evidence of benefit for stabilization is as follows:

- A significant majority (60%) of eligible ADP patients (N=229) had a sustained response to OL pimavanserin treatment, meeting prespecified response criteria at both Week 8 and Week 12.
- Other endpoints included safety evaluations of cognition and motor function (MMSE and ESRS-A) that showed no decline during the 12 weeks of OL treatment in ADP patients.

Evidence of benefit for maintenance of efficacy for the ADP subgroup is as follows:

- Patients with ADP who remained on pimavanserin were 38% (all doses) less likely to experience a relapse of psychotic symptoms compared with those on placebo (HR=0.62, CI: 0.26, 1.49). Analyses of the ADP 34 mg subgroup (the recommended dose for the proposed indication) showed a larger (53%) risk reduction (HR=0.47, CI: 0.18, 1.21). Patients with more severe psychosis at Baseline also had greater (~50%) risk reduction with pimavanserin treatment versus placebo (HR=0.49, CI: 0.10, 2.26).
- Pimavanserin reduced the risk of all-cause discontinuation in ADP subgroup (HR=0.66, 95% CI: 0.33, 1.33) and ADP 34 mg subgroup (HR=0.57, CI: 0.27, 1.18).
- Analyses of psychosis symptom severity (SAPS-H+D) and all exploratory efficacy scales showed consistent benefit of pimavanserin treatment over placebo.
- Responder analyses showed pimavanserin was consistently better than placebo, with single digit NNTs for multiple clinically meaningful cutoffs, as evaluated by maximum worsening of symptoms in the DB period.
- A strong E-R relationship was observed with higher exposure showing lower risk of relapse.
- Evaluations of cognition and motor function (MMSE and ESRS-A) showed no decline with pimavanserin versus placebo during the DB period in ADP patients.

5.2 Risks of Pimavanserin Treatment of Alzheimer's Disease Psychosis

As of 16 June 2020, approximately 3579 patients have been exposed to pimavanserin in all ongoing and completed studies in all indications. Of the 1502 patients with NDD in this group, 329 patients (22%) were exposed to pimavanserin for ≥1 year, including 180 patients (12%) exposed to pimavanserin for ≥2 years. The median age of NDD patients in placebo-controlled studies (NDD pool) was 74 years (range 40-99 years).

Among 1683 patients with NDD exposed to pimavanserin as of 08 September 2021, 721 patients had AD (median age 76 years, range 53-99 years), of which 572 patients had ADP, and 180 of these patients were exposed to pimavanserin for ≥6 months with 97 exposed for ≥12 months.

The safety results in patients with AD are similar to those observed in NDD patients.

A comprehensive review of pimavanserin clinical data (see Section 4) points to the following safety considerations:

- Safety data from large numbers of frail, elderly patients with NDD and AD exposed to pimavanserin demonstrate that pimavanserin is well tolerated in patients with NDD, including AD.

- In the AD patient population specifically, pimavanserin was well tolerated with TEAE frequencies generally similar to placebo.
- While the frequency of serious TEAEs were low, an increased frequency of serious TEAEs was observed in the pimavanserin group in the pooled analyses. Review of the cases did not reveal any pattern suggestive of a drug effect. This population is particularly challenged due to their underlying progressive neurodegenerative disease, comorbidities, as well as their advanced age. Patients have increased risk for many diseases reflected in the events reported, including respiratory and cardiovascular disease.
- Pimavanserin prolongs the QT interval by approximately 5-8 ms compared to placebo. This risk is communicated in the Prescribing Information for NUPLAZID (Appendix Section 7.1).
- As described already in NUPLAZID labeling for the treatment of PDP (same 34 mg QD dose as proposed for the treatment of ADP), metabolism of pimavanserin is significantly affected by strong cytochrome P450 (CYP)3A4 inhibitors. A lower dose (10 mg) is available for patients who concomitantly receive strong CYP3A4 inhibitors.
- Pimavanserin safety data support conclusion that pimavanserin is not associated with the numerous adverse effects observed with off-label use of other antipsychotic drugs.

Importantly, pimavanserin clinical trials demonstrate no evidence of cognitive or motor impairing effects, a known liability of existing antipsychotics used off-label today.

Antipsychotic class labeling, including a Boxed Warning and warning/precaution, exists regarding increased risk of mortality in elderly patients with DRP which is based on a meta-analysis of studies with antipsychotics that did not include studies of pimavanserin. Review of accumulating pimavanserin clinical data suggests a positive trend toward balance with placebo in respect to mortality, but the risks cannot be discounted due to still relatively limited numbers of patients and wide and overlapping confidence intervals. Two recent observational studies have reported a significant decrease in risk of mortality in PDP patients treated with pimavanserin versus atypical antipsychotics. Nevertheless, Acadia proposes to keep but modify the existing Boxed Warning for NUPLAZID in a manner consistent with the approach taken by the FDA as part of the original approval of NUPLAZID for the treatment of PDP to now also accommodate the proposed indication of ADP.

In conclusion, pimavanserin was well tolerated in a large clinical program and with a safety profile that has been well-characterized through clinical studies and postmarketing

surveillance. Identified risks are considered manageable, including through labeling, and monitorable through routine pharmacovigilance.

5.3 Benefit-Risk Conclusion

ADP is a serious medical condition with no approved drugs available. The selective serotonergic receptor binding profile of pimavanserin is markedly different from approved multi-receptor acting antipsychotics used off-label to treat ADP (and PDP), which are associated with serious safety risk, including negative impacts on cognitive and motor function, with marginal or no efficacy.

The efficacy of pimavanserin as a treatment for hallucinations and delusions associated with ADP has been demonstrated in a positive ADP study (Study 019) and supported by data from ADP subgroup in a positive DRP study (Study 045). Consistent and clinically meaningful benefit of pimavanserin treatment in ADP patients was observed across different studies, across different efficacy endpoints and over time.

In summary, the pimavanserin clinical database provides consistent and convincing evidence of clinically meaningful benefit of pimavanserin with improvement in hallucinations and delusions in the treatment of ADP. Safety data from large numbers of frail, elderly patients with neurodegenerative disease exposed to pimavanserin demonstrate that pimavanserin is well tolerated in patients with NDD, including ADP. Taken together, the aggregate data support a positive benefit-risk profile for pimavanserin as a treatment for hallucinations and delusions associated with ADP.

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7 APPENDICES

7.1 NUPLAZID PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUPLAZID safely and effectively. See full prescribing information for NUPLAZID.

NUPLAZID® (pimavanserin) capsules, for oral use
NUPLAZID® (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)**

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.2) 11/2020

----------INDICATIONS AND USAGE----------
NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose is 34 mg taken orally once daily, without titration. (2.1)
- Can be taken with or without food. (2.2)
- Capsules may be swallowed whole or opened and entire contents sprinkled over a tablespoon of certain types of soft food. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 34 mg (3)
- Tablets: 10 mg (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to NUPLAZID or any of its components. (4)

----------WARNINGS AND PRECAUTIONS----------
- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Acadia Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose to 10 mg once daily. (2.3, 7.1)
- Strong or Moderate CYP3A4 Inducers: Avoid concomitant use of NUPLAZID. (2.3, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

NUPLAZID® is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of NUPLAZID is 34 mg taken orally once daily, without titration.

2.2 Administration Information

NUPLAZID can be taken with or without food *[see Clinical Pharmacology (12.3)]*.

NUPLAZID capsules can be taken whole, or opened and the entire contents sprinkled over a tablespoon (15 mL) of applesauce, yogurt, pudding, or a liquid nutritional supplement. Consume the drug/food mixture immediately without chewing; do not store for future use.

2.3 Dosage Modifications for Concomitant Use with CYP3A4 Inhibitors and Inducers

- Coadministration with Strong CYP3A4 Inhibitors
  The recommended dose of NUPLAZID when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) is 10 mg, taken orally as one tablet once daily *[see Drug Interactions (7.1)]*.
- Coadministration with Strong or Moderate CYP3A4 Inducers
  Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID *[see Drug Interactions (7.1)]*.

3 DOSAGE FORMS AND STRENGTHS

NUPLAZID (pimavanserin) is available as:

- 34 mg strength capsules. The capsules are opaque white and light green with "PIMA" and "34" printed in black.
- 10 mg strength tablets. The orange, round, coated tablets are debossed on one side with a "P" and "10" on the reverse side.

4 CONTRAINDICATIONS

NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs) revealed a risk of death in the drug-treated patients of between 1.6- to 1.7-times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Boxed Warning]*.

5.2 QT Interval Prolongation

NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin) *[see Drug Interactions (7.1)]*. NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical trial database for NUPLAZID consists of over 1200 subjects and patients exposed to one or more doses of NUPLAZID. Of these, 616 were patients with hallucinations and delusions associated with Parkinson's disease psychosis (PDP). In the placebo-controlled setting, the majority of experience in patients comes from studies evaluating once-daily NUPLAZID doses of 34 mg (N=202) compared to placebo (N=231) for up to 6 weeks. In the controlled trial setting, the study population was approximately 64% male and 91% Caucasian, and the mean age was about 71 years at study entry. Additional clinical trial experience in patients with hallucinations and delusions associated with PDP comes from two open-label, safety extension studies (total N=497). The majority of patients receiving long-term treatment received 34 mg once-daily (N=459). Over 300 patients have been treated for more than 6 months; over 270 have been treated for at least 12 months; and over 150 have been treated for at least 24 months.

The following adverse reactions are based on the 6-week, placebo-controlled studies in which NUPLAZID was administered once daily to patients with hallucinations and delusions associated with PDP.

Common Adverse Reactions (incidence ≥5% and at least twice the rate of placebo): peripheral edema (7% NUPLAZID 34 mg vs. 2% placebo) and confusional state (6% NUPLAZID 34 mg vs. 3% placebo).

Adverse Reactions Leading to Discontinuation of Treatment

A total of 8% (16/202) of NUPLAZID 34 mg-treated patients and 4% (10/231) of placebo-treated patients discontinued because of adverse reactions. The adverse reactions that occurred in more than one patient and with an incidence at least twice that of placebo were hallucination (2% NUPLAZID vs. <1% placebo), urinary tract infection (1% NUPLAZID vs. <1% placebo), and fatigue (1% NUPLAZID vs. 0% placebo).

Adverse reactions that occurred in 6-week, placebo-controlled studies and that were reported at an incidence of ≥2% and >placebo are presented in **Table 1**.

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

Percentage of Patients Reporting Adverse Reaction		
	NUPLAZID 34 mg	**Placebo**
	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination	5%	3%
Confusional state	6%	3%

Adverse Reactions in Demographic Subgroups

Examination of population subgroups in the 6-week, placebo-controlled studies did not reveal any differences in safety on the basis of age (≤75 vs. >75 years) or sex. Because the study population was predominantly Caucasian (91%; consistent with reported demographics for PD/PDP), racial or ethnic differences in the safety profile of NUPLAZID could not be assessed. In addition, in the 6-week, placebo-controlled studies, no clinically relevant differences in the incidence of adverse reactions were observed among those with a Mini-Mental State Examination (MMSE) score at entry of <25 versus those with scores ≥25.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of NUPLAZID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include rash, urticaria, reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea), somnolence, falls, agitation, and aggression.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with NUPLAZID

Table 2 Clinically Important Drug Interactions with NUPLAZID

QT Interval Prolongation	
Clinical Impact:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of NUPLAZID and increase the risk of cardiac arrhythmia.
Intervention:	Avoid the use of NUPLAZID in combination with other drugs known to prolong QT interval *[see Warnings and Precautions (5.2)]*.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: gatifloxacin, moxifloxacin
Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of NUPLAZID with a strong CYP3A4 inhibitor increases pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	If NUPLAZID is used with a strong CYP3A4 inhibitor, reduce the dosage of NUPLAZID *[see Dosage and Administration (2.3)]*.
Examples:	itraconazole, ketoconazole, clarithromycin, indinavir
Strong or Moderate CYP3A4 Inducers	
Clinical Impact:	Concomitant use of NUPLAZID with strong or moderate CYP3A4 inducers reduces pimavanserin exposure *[see Clinical Pharmacology (12.3)]*.
Intervention:	Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID *[see Dosage and Administration (2.3)]*.
Examples:	Strong inducers: carbamazepine, St. John's wort, phenytoin, rifampin Moderate inducers: modafinil, thioridazine, efavirenz, nafcillin

7.2 Drugs Having No Clinically Important Interactions with NUPLAZID

Based on pharmacokinetic studies, no dosage adjustment of carbidopa/levodopa is required when administered concomitantly with NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data on NUPLAZID use in pregnant women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no adverse developmental effects were seen when pimavanserin was administered orally to rats or rabbits during the period of organogenesis at doses up to 10- or 12-times the maximum recommended human dose (MRHD) of 34 mg/day, respectively. Administration of pimavanserin to pregnant rats during pregnancy and lactation resulted in maternal toxicity and lower pup survival and body weight at doses which are 2-times the MRHD of 34 mg/day *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pimavanserin was not teratogenic in pregnant rats when administered during the period of organogenesis at oral doses of 0.9, 8.5, and 51 mg/kg/day, which are 0.2- and 10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC at mid and high doses, respectively. Maternal toxicity included reduction in body weight and food consumption at the highest dose.

Administration of pimavanserin to pregnant rats during pregnancy and lactation at oral doses of 8.5, 26, and 51 mg/kg/day, which are 0.14- to 14-times the MRHD of 34 mg/day based on AUC, caused maternal toxicity, including mortality, clinical signs including dehydration, hunched posture, and rales, and decreases in body weight, and/or food consumption at doses ≥26 mg/kg/day (2-times the MRHD based on AUC). At these maternally toxic doses there was a decrease in pup survival, reduced litter size, and reduced pup weights, and food consumption. Pimavanserin had no effect on sexual maturation, neurobehavioral function including learning and memory, or reproductive function in the first generation pups up to 14-times the MRHD of 34 mg/day based on AUC.

Pimavanserin was not teratogenic in pregnant rabbits during the period of organogenesis at oral doses of 4.3, 43, and 85 mg/kg/day, which are 0.2- to 12-times the MRHD of 34 mg/day based on AUC. Maternal toxicity, including mortality, clinical signs of dyspnea and rales, decreases in body weight and/or food consumption, and abortions occurred at doses 12-times the MRHD of 34 mg/day based on AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of pimavanserin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUPLAZID and any potential adverse effects on the breastfed infant from NUPLAZID or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of NUPLAZID have not been established in pediatric patients.

8.5 Geriatric Use

No dose adjustment is required for elderly patients.

Parkinson's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the 6-week clinical studies with NUPLAZID *[see Adverse Reactions (6.1)]* was 71 years, with 49% 65-75 years old and 31% >75 years old. In the pooled population of patients enrolled in 6-week, placebo-controlled studies (N=614), 27% had MMSE scores from 21 to 24 compared to 73% with scores ≥25. No clinically meaningful differences in safety or effectiveness were noted between these two groups.

8.6 Patients with Renal Impairment

No dosage adjustment for NUPLAZID is needed in patients with mild to severe renal impairment or end stage renal disease (ESRD); however, increased exposure (C_{max} and AUC) to NUPLAZID occurred in patients with severe renal impairment (CrCL <30 mL/min, Cockcroft-Gault) in a renal impairment study *[see Clinical Pharmacology (12.3)]*.

NUPLAZID should be used with caution in patients with severe renal impairment and end stage renal disease.

In a renal impairment study, dialysis did not appear to significantly affect the concentrations of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment
No dosage adjustment for NUPLAZID is recommended in patients with hepatic impairment based on the exposure differences observed in patients with and without hepatic impairment in a hepatic impairment study *[see Clinical Pharmacology (12.3)]*.

8.8 Other Specific Populations
No dosage adjustment is required based on patient's age, sex, ethnicity, or weight. These factors do not affect the pharmacokinetics of NUPLAZID *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
NUPLAZID is not a controlled substance.

9.2 Abuse
NUPLAZID has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence.

While short-term, placebo-controlled and long-term, open-label clinical trials did not reveal increases in drug-seeking behavior, the limited experience from the clinical trials do not predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

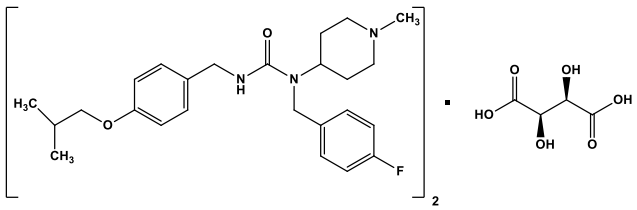
10 OVERDOSAGE

10.1 Human Experience
The pre-marketing clinical trials involving NUPLAZID in approximately 1200 subjects and patients do not provide information regarding symptoms with overdose. In healthy subject studies, dose-limiting nausea and vomiting were observed.

10.2 Management of Overdose
There are no known specific antidotes for NUPLAZID. In managing overdose, cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias *[see Warnings and Precautions (5.2)]*. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of NUPLAZID *[see Drug Interactions (7.1)]*. Consider the long plasma half-life of pimavanserin (about 57 hours) and the possibility of multiple drug involvement. Consult a Certified Poison Control Center (1-800-222-1222) for up-to-date guidance and advice.

11 DESCRIPTION

NUPLAZID contains pimavanserin, an atypical antipsychotic, which is present as pimavanserin tartrate salt with the chemical name, urea, *N*-[(4-fluorophenyl)methyl]-*N*-(1-methyl-4-piperidinyl)-*N*'-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1). Pimavanserin tartrate is freely soluble in water. Its molecular formula is $(C_{25}H_{34}FN_3O_2)_2 \cdot C_4H_6O_6$ and its molecular weight is 1005.20 (tartrate salt). The chemical structure is:



The molecular formula of pimavanserin free base is $C_{25}H_{34}FN_3O_2$ and its molecular weight is 427.55.

NUPLAZID capsules are intended for oral administration only. Each capsule contains 40 mg of pimavanserin tartrate, which is equivalent to 34 mg of pimavanserin free base. Inactive ingredients include magnesium stearate and microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the capsule shell: black iron oxide, FD&C blue #1, hypromellose, titanium dioxide, and yellow iron oxide.

NUPLAZID tablets are intended for oral administration only. Each round, orange, immediate-release, film coated tablet contains 11.8 mg of pimavanserin tartrate, which is equivalent to 10 mg pimavanserin free base. Inactive ingredients include magnesium stearate, pregelatinized starch, and silicified microcrystalline cellulose. Additionally, the following inactive ingredients are present as components of the film coat: polyethylene glycol, polyvinyl alcohol, red iron oxide, talc, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of pimavanserin in the treatment of hallucinations and delusions associated with Parkinson's disease psychosis is unclear. However, the effect of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at serotonin 5-HT_{2C} receptors.

12.2 Pharmacodynamics

In vitro, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity (K_i value 0.087 nM) and at serotonin 5-HT_{2C} receptors with lower binding affinity (K_i value 0.44 nM). Pimavanserin shows low binding to sigma 1 receptors (K_i value 120 nM) and has no appreciable affinity (K_i value >300 nM), to serotonin 5-HT_{2B}, dopaminergic (including D_2), muscarinic, histaminergic, or adrenergic receptors, or to calcium channels.

Cardiac Electrophysiology

The effect of NUPLAZID on the QTc interval was evaluated in a randomized placebo- and positive-controlled double-blind, multiple-dose parallel thorough QTc study in 252 healthy subjects. A central tendency analysis of the QTc data at steady-state demonstrated that the maximum mean change from baseline (upper bound of the two-sided 90% CI) was 13.5 (16.6) msec at a dose of twice the therapeutic dose. A pharmacokinetic/ pharmacodynamic analysis with NUPLAZID suggested a concentration-dependent QTc interval prolongation in the therapeutic range.

In the 6-week, placebo-controlled effectiveness studies, mean increases in QTc interval of ~5-8 msec were observed in patients receiving once-daily doses of NUPLAZID 34 mg. These data are consistent with the profile observed in a thorough QT study in healthy subjects. Sporadic QTcF values ≥500 msec and change from baseline values ≥60 msec were observed in subjects treated with NUPLAZID 34 mg; although the incidence was generally similar for NUPLAZID and placebo groups. There were no reports of torsade de pointes or any differences from placebo in the incidence of other adverse reactions associated with delayed ventricular repolarization in studies of NUPLAZID, including those patients with hallucinations and delusions associated with PDP *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg (0.5- to 7.5-times the recommended dosage). The pharmacokinetics of pimavanserin are similar in both the study population and healthy subjects. The mean plasma half-lives for pimavanserin and the active metabolite (*N*-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively.

Absorption

The median T_{max} of pimavanserin was 6 (range 4-24) hours and was generally unaffected by dose.
The bioavailability of pimavanserin oral tablet and pimavanserin solution was essentially identical.
The formation of the major circulating *N*-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median T_{max} of 6 hours.

Administration of one 34 mg capsule once daily results in plasma pimavanserin concentrations that are similar to exposure with two 17 mg tablets once daily.

Effect of Food

Ingestion of a high-fat meal had no significant effect on rate (C_{max}) and extent (AUC) of pimavanserin exposure. C_{max} decreased by about 9% while AUC increased by about 8% with a high-fat meal.

Distribution

Pimavanserin is highly protein bound (~95%) in human plasma. Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14. Following administration of a single dose of NUPLAZID (34 mg), the mean (SD) apparent volume of distribution was 2173 (307) L.

Elimination

Metabolism

Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

Based on *in vitro* studies, transporters play no significant role in the disposition of pimavanserin.

AC-279 is neither a reversible or irreversible (metabolism-dependent) inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). AC-279 does not cause clinically significant CYP3A induction and is not predicted to cause induction of any other CYP enzymes involved in drug metabolism.

Excretion

Approximately 0.55% of the 34 mg oral dose of ^{14}C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days.

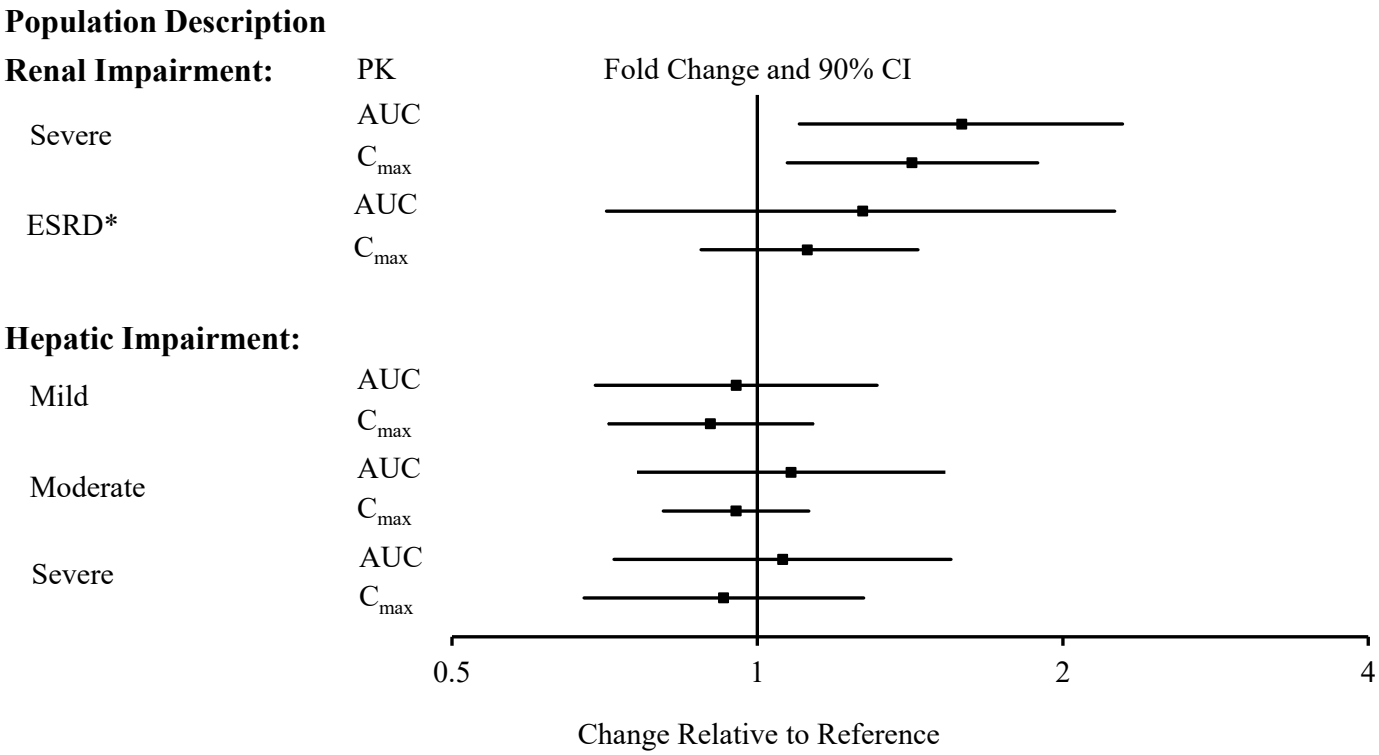
Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.

Specific Populations

Population PK analysis indicated that age, sex, ethnicity, and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin. In addition, the analysis indicated that exposure of pimavanserin in patients with mild to moderate renal impairment was similar to exposure in patients with normal renal function.

The effects of other intrinsic factors on pimavanserin pharmacokinetics is shown in **Figure 1** *[see Use in Specific Populations (8.6 and 8.7)]*.

Figure 1 Effects of Intrinsic Factors on Pimavanserin Pharmacokinetics



*Less than 10% of the administered dose of NUPLAZID was recovered in the dialysate.

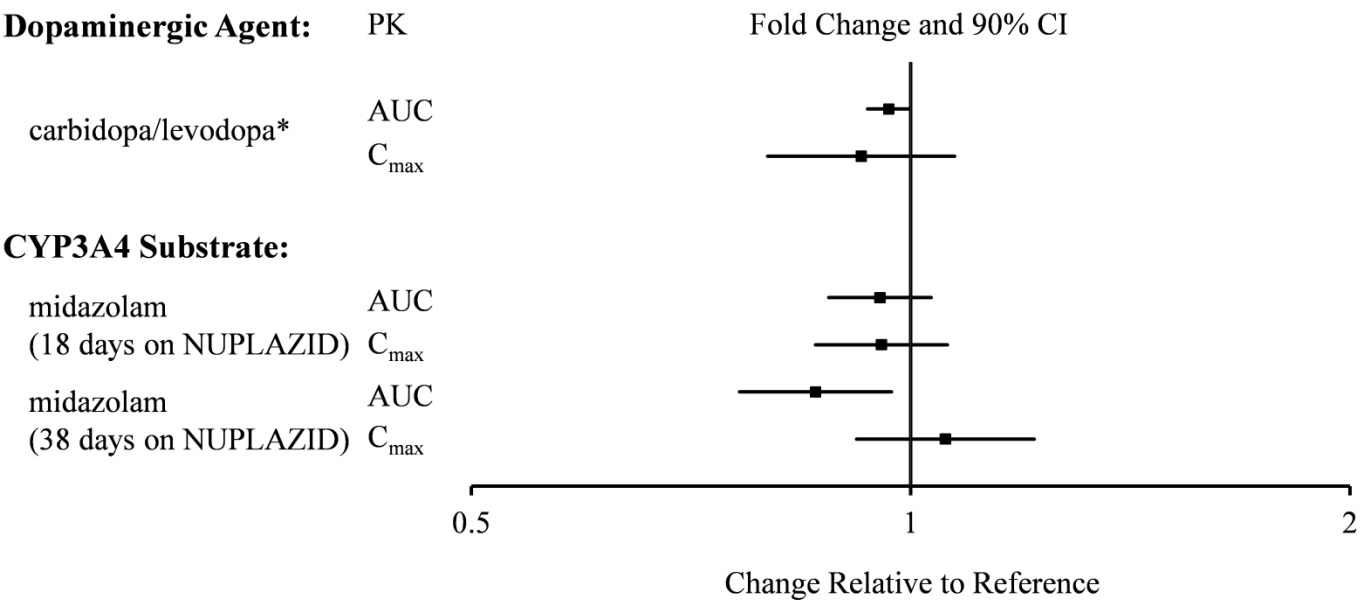
Drug Interaction Studies

CYP3A4 Inhibitor: ketoconazole, a strong inhibitor of CYP3A4, increased pimavanserin C_{max} by 1.5-fold and AUC by 3-fold. Population PK modeling and simulation show that steady-state exposure ($C_{max,ss}$ and AUC_{tau}) for 10 mg pimavanserin with ketoconazole is similar to exposure for 34 mg pimavanserin alone *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

CYP3A4 Inducer: In a clinical study where single doses of 34 mg pimavanserin were administered on Days 1 and 22, and 600 mg rifampin, a strong inducer of CYP3A4, was given daily on Days 15 through 21, pimavanserin C_{max} and AUC decreased by 71% and 91%, respectively, compared to pre-rifampin plasma concentrations. In a simulation with a moderate CYP3A4 inducer (efavirenz), physiologically based pharmacokinetic (PBPK) models predicted pimavanserin $C_{max,ss}$ and AUC_{tau} at steady state decreased by approximately 60% and 70%, respectively *[see Dosage and Administration (2.3) and Drug Interactions (7.1)]*.

There is no effect of pimavanserin on the pharmacokinetics of midazolam, a CYP3A4 substrate, or carbidopa/levodopa as shown in **Figure 2**.

Figure 2 Effects of Pimavanserin on the Pharmacokinetics of Other Drugs



*AUC and C_{max} depict levodopa levels.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of pimavanserin to mice or rats for 2 years. Mice were administered pimavanserin at oral doses of 2.6, 6, and 13 (males)/8.5, 21, and 43 mg/kg/day (females) which are 0.01- to 1- (males)/0.5- to 7- (females) times the MRHD of 34 mg/day based on AUC. Rats were administered pimavanserin at oral doses of 2.6, 8.5, and 26 (males)/4.3, 13, and 43 mg/kg/day (females) which are 0.01- to 4- (males)/0.04- to 16- (females) times the MRHD of 34 mg/day based on AUC.

Mutagenesis

Pimavanserin was not mutagenic in the *in vitro* Ames reverse mutation test, or in the *in vitro* mouse lymphoma assay, and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Pimavanserin was administered orally to male and female rats before mating, through mating, and up to Day 7 of gestation at doses of 8.5, 51, and 77 mg/kg/day, which are approximately 2-, 15-, and 22-times the maximum recommended human dose (MRHD) of 34 mg/day based on mg/m^2, respectively. Pimavanserin had no effect on fertility or reproductive performance in male and female rats at doses up to 22-times the MRHD of 34 mg based on mg/m^2. Changes in uterine parameters (decreases in the number of corpora lutea, number of implants, viable implants, and increases in pre-implantation loss, early resorptions and post-implantation loss) occurred at the highest dose which was also a maternally toxic dose. Changes in sperm parameters (decreased density and motility) and microscopic findings of cytoplasmic vacuolation in the epididymis occurred at doses approximately 15-times the MRHD of 34 mg/day based on mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (foamy macrophages and/or cytoplasmic vacuolation) was observed in multiple tissues and organs of mice, rats, and monkeys following oral daily administration of pimavanserin. The occurrence of phospholipidosis was both dose- and duration-dependent. The most severely affected organs were the lungs and kidneys. In rats, diffuse phospholipidosis was associated with increased lung and kidney weights, respiratory-related clinical signs including rales, labored breathing, and gasping, renal tubular degeneration, and, in some animals, focal/multifocal chronic inflammation in the lungs at exposures ≥10-times those at the maximum recommended human dose (MRHD) of 34 mg/day based on AUC. Phospholipidosis caused mortality in rats at exposures ≥16-times the MRHD of 34 mg/day based on AUC. The chronic inflammation in the rat lung was characterized by minimal to mild focal collagen positive fibroplasia as shown by specialized staining. Chronic inflammation of the lungs was not seen in monkeys treated for 12 months (exposures 9-times the MRHD). Based on the exposures at the estimated No Observed Effect Level (NOEL) for chronic lung inflammation in rats, there is a 5- to 9-times safety margin after 6-months of treatment and a 2- to 4-times safety margin after 24-months (lifetime) treatment compared to exposure at the MRHD. The relevance of these findings to human risk is not clear.

14 CLINICAL STUDIES

The efficacy of NUPLAZID 34 mg as a treatment of hallucinations and delusions associated with Parkinson's disease psychosis was demonstrated in a 6-week, randomized, placebo-controlled, parallel-group study. In this outpatient study, 199 patients were randomized in a 1:1 ratio to NUPLAZID 34 mg or placebo once daily. Study patients (male or female and aged 40 years or older) had a diagnosis of Parkinson's disease (PD) established at least 1 year prior to study entry and had psychotic symptoms (hallucinations and/or delusions) that started after the PD diagnosis and that were severe and frequent enough to warrant treatment with an antipsychotic. At entry, patients were required to have a Mini-Mental State Examination (MMSE) score ≥21 and to be able to self-report symptoms. The majority of patients were on PD medications at entry; these medications were required to be stable for at least 30 days prior to study start and throughout the study period.

The PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate the efficacy of NUPLAZID 34 mg. SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS. Each item is scored on a scale of 0-5, with 0 being none and 5 representing severe and frequent symptoms. Therefore, the SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement. Primary efficacy was evaluated based on change from baseline to Week 6 in SAPS-PD total score.

As shown in **Table 3**, **Figure 3**, and **Figure 4**, NUPLAZID 34 mg (n=95) was statistically significantly superior to placebo (n=90) in decreasing the frequency and/or severity of hallucinations and delusions in patients with PDP as measured by central, independent, and blinded raters using the SAPS-PD scale. An effect was seen on both the hallucinations and delusions components of the SAPS-PD.

Table 3 Primary Efficacy Analysis Result Based on SAPS-PD (N=185)

Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
SAPS-PD	NUPLAZID	15.9 (6.12)	-5.79 (0.66)	-3.06* (-4.91, -1.20)
	Placebo	14.7 (5.55)	-2.73 (0.67)	--
SAPS-PD Hallucinations[b]	NUPLAZID	11.1 (4.58)	-3.81 (0.46)	-2.01 (-3.29, -0.72)
	Placebo	10.0 (3.80)	-1.80 (0.46)	--
SAPS-PD Delusions[b]	NUPLAZID	4.8 (3.59)	-1.95 (0.32)	-0.94 (-1.83, -0.04)
	Placebo	4.8 (3.82)	-1.01 (0.32)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Supportive analysis.
* Statistically significantly superior to placebo.

The effect of NUPLAZID on SAPS-PD improved through the six-week trial period, as shown in **Figure 3**.

Figure 3 SAPS-PD Change from Baseline through 6 Weeks Total Study Treatment

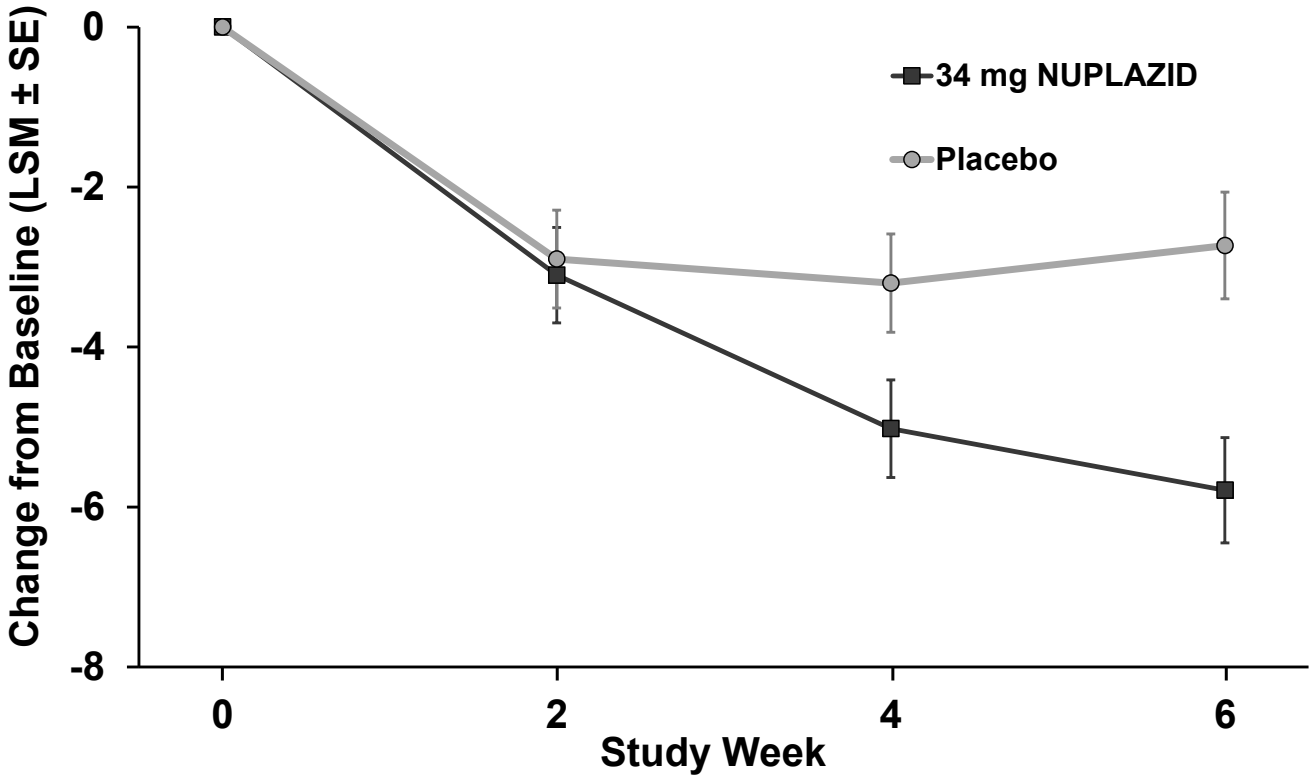
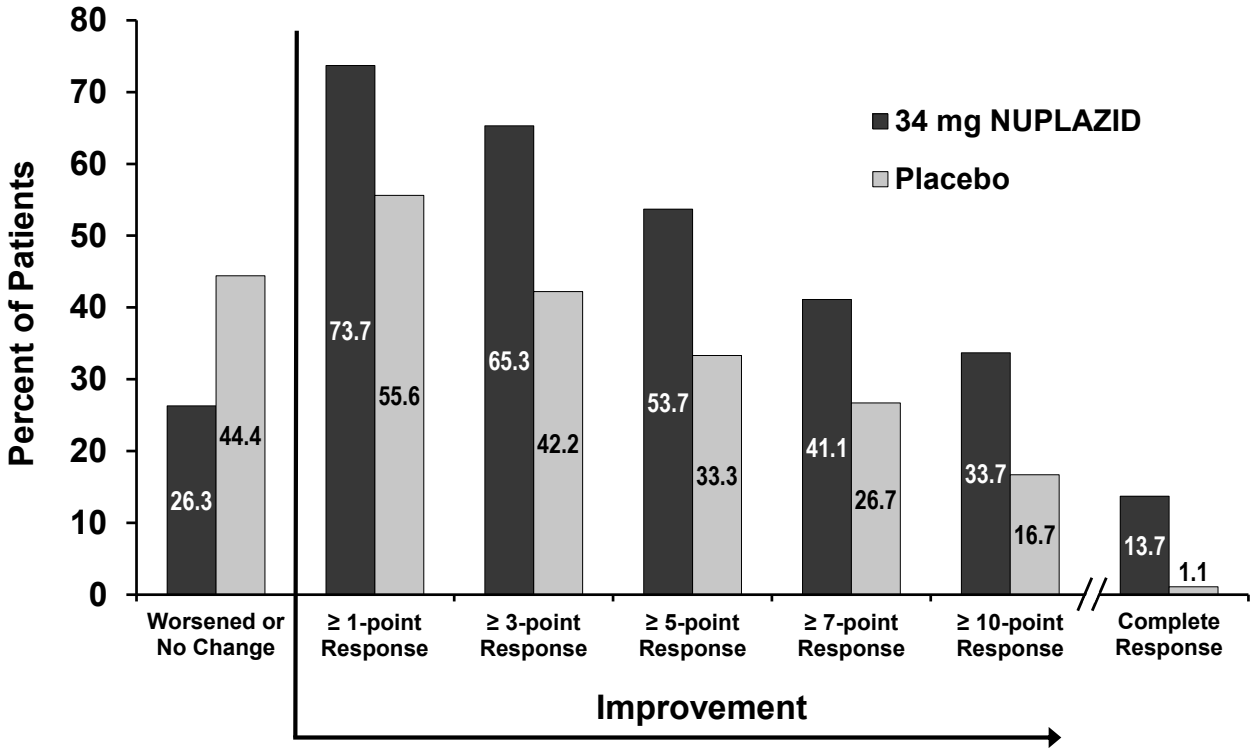


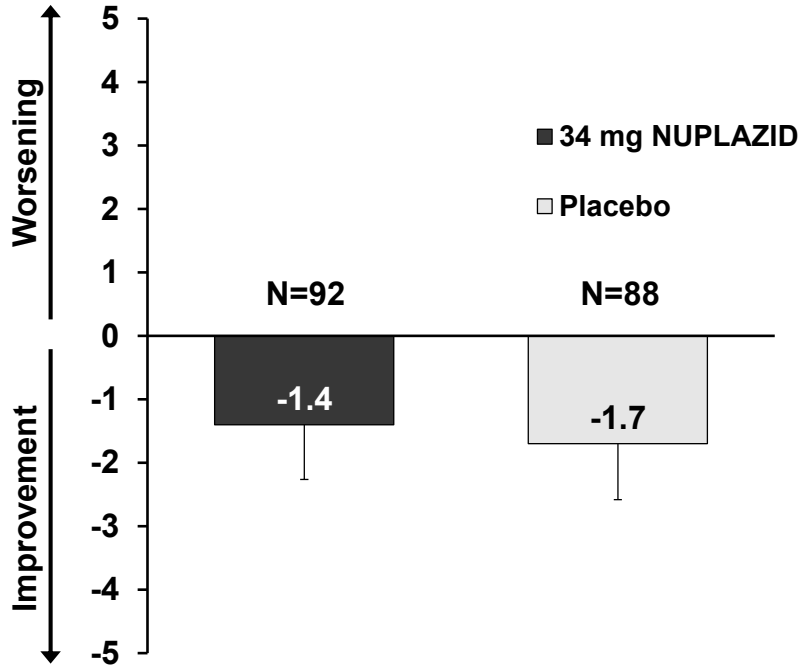
Figure 4 Proportion of Patients with SAPS-PD Score Improvement at the End of Week 6 (N=185)



Complete response = SAPS-PD score reduced to zero from baseline value.
Patients with missing values were counted as non-responders.

Motor Function in Patients with Hallucinations and Delusions Associated with Parkinson's Disease Psychosis
NUPLAZID 34 mg did not show an effect compared to placebo on motor function, as measured using the Unified Parkinson's Disease Rating Scale Parts II and III (UPDRS Parts II+III) (**Figure 5**). A negative change in score indicates improvement. The UPDRS Parts II+III was used to assess the patient's Parkinson's disease state during the 6-week double-blind treatment period. The UPDRS score was calculated as the sum of the 40 items from activities of daily living and motor examination, with a range of 0 to 160.

Figure 5 Motor Function Change from Baseline to Week 6 in UPDRS Parts II+III (LSM - SE)



LSM: least-squares mean; SE: standard error. The error bars extend one SE below the LSM.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUPLAZID (pimavanserin) is available as:

34 mg Capsule:
Opaque white and light green capsule with "PIMA" and "34" printed in black.
Bottle of 30: NDC 63090-340-30

10 mg Tablet:
Orange, round, coated tablet debossed with "P" on one side and "10" on the reverse.
Bottle of 30: NDC 63090-100-30

Storage
34 mg Capsule:
Store at 20°C to 25°C (68ºF to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. To prevent potential capsule color fading, protect from light.

10 mg Tablet:
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Concomitant Medication
Advise patients to inform their healthcare providers if there are any changes to their current prescription or over-the-counter medications, since there is a potential for drug interactions *[see Warnings and Precautions (5.2), Drug Interactions (7)]*.

Administration Instructions
Advise patients to take the capsule whole or sprinkled over a tablespoon (15 mL) of applesauce, yogurt, pudding, or a liquid nutritional supplement. Advise patients to consume the drug/food mixture immediately and not to store for future use *[see Dosage and Administration (2.2)]*.

Distributed by:
Acadia Pharmaceuticals Inc.
San Diego, CA 92130 USA

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7.2 Main Design Features of Key Studies

Study	Status	Objective	Endpoints	Phase	Disease Population	Design	Blinding	Treatment (Once Daily)	Planned Treatment Duration
ACP-103-045	completed	To evaluate relapse prevention and time to discontinuation for any reason in subjects with DRP treated with pimavanserin compared to placebo and to evaluate the safety and tolerability of pimavanserin compared to placebo in subjects with DRP who had been stabilized on pimavanserin therapy	Primary: time from randomization to relapse in the DB period. Key secondary: time from randomization to discontinuation from the DB period for any reason. Safety: TEAEs, SAEs, withdrawals due to AEs, PCI changes in other safety assessments, GCAS score, MMSE score, ESRS-A score.	3	DRP	randomized withdrawal	OL Period	PIM 20 or 34 mg	12 weeks
							DB Period	PIM 20 or 34 mg, PBO	up to 26 weeks
ACP-103-020	completed	To demonstrate the antipsychotic efficacy of pimavanserin in subjects with PDP as measured by a decrease in the severity and/or frequency of hallucinations and/or delusions	Primary: the mean absolute change from Baseline (Day 1) in the SAPS-PD score on Day 43.	3	PDP	placebo-controlled, randomized	DB	PIM 34 mg, PBO	6 weeks

7.2 Main Design Features of Key Studies (Continued)

Study	Status	Objective	Endpoints	Phase	Disease Population	Design	Blinding	Treatment (Once Daily)	Planned Treatment Duration
ACP-103-019	completed	To assess the efficacy and evaluate the safety and tolerability of pimavanserin in subjects with ADP	Primary: change from Baseline to Day 43 in the NPI-NH psychosis score (Delusions+Hallucinations domains A and B). Safety: AEs, physical examinations, height and weight, vital signs, ECGs, and clinical laboratory tests, MMSE. UPDRS Part III.	2	ADP	placebo-controlled, randomized	DB	PIM 34 mg, PBO	12 weeks
ACP-103-032	completed	To evaluate the safety and efficacy of pimavanserin at doses of 34 mg and 20 mg compared to placebo in the treatment of agitation and aggression in subjects with probable AD	Primary: the change from Baseline to Week 12 in the CMAI total score.	2	AD-AA	placebo-controlled, randomized	DB	PIM 20 or 34 mg, PBO	12 weeks
ACP-103-046 Interim analysis[a]	ongoing	To assess the safety and tolerability of pimavanserin compared to placebo in adult and elderly subjects with neuropsychiatric symptoms related to NDD	Primary: TEAEs.	3b	NDD	placebo-controlled, randomized	DB	PIM 34 mg, PBO	8 weeks

7.2 Main Design Features of Key Studies (Continued)

Study	Status	Objective	Endpoints	Phase	Disease Population	Design	Blinding	Treatment (Once Daily)	Planned Treatment Duration
ACP-103-033	completed	To evaluate the safety and tolerability of pimavanserin treatment for up to 52 weeks of exposure (approximately 64 weeks total for subjects who received pimavanserin in Study ACP-103-032) in subjects with probable AD who had symptoms of agitation and aggression	Primary: TEAEs.	2	AD-AA	long-term safety, open-label extension of ACP-103-032	OL	PIM 20 or 34 mg flexible dose	52 weeks
ACP-103-047	ongoing	To assess the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to NDD	Primary: TEAEs.	3b	NDD	long-term safety, open-label extension of ACP-103-046	OL	PIM 34 mg, can be lowered to 20 mg after Baseline visit	52 weeks

Abbreviations: AD-AA=agitation and aggression in Alzheimer's disease; ADP=Alzheimer's disease psychosis; AE=adverse event; CMAI= Cohen-Mansfield Agitation Inventory; DB=double blind; DRP=dementia-related psychosis; ESRS-A=Extrapyramidal Symptoms Rating Scale–A; GCAS=Global Clinician Assessment of Suicidality; MMSE=Mini-Mental State Examination; NPI-NH=Neuropsychiatric Inventory – Nursing Home Version; NDD=neurodegenerative disease; OL=open-label; PCI=potentially clinically important; PDP=Parkinson's disease psychosis; PIM=pimavanserin; PBO=placebo; SAPS=Scale for the Assessment of Positive Symptoms; SAPS=Modified 9-item SAPS-Hallucinations and Delusions; SAE=serious adverse event; TEAE=treatment-emergent adverse event; UPDRS=Unified Parkinson's Disease Rating Scale.

a Interim Analysis 2 (IA2) data cut (16JUN2020) presented; study is ongoing.

7.3 Efficacy and Safety Measures

7.3.1 Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions Subscales (SAPS-H+D and SAPS-PD)

The SAPS (Andreasen 1984) was designed to measure positive psychotic symptoms, including hallucinations, delusions, abnormalities in language and behavior, and disordered thought processes. The SAPS-H+D subscales consist of 20 items, including 2 global ratings of severity for hallucinations (H7) and delusions (D13). Each of the 20 items was scored on a 6-point scale (0=none, 1=questionable, 2=mild, 3=moderate, 4=marked, and 5=severe). The SAPS-H+D total score was the sum of the 20 item scores with a possible range of 0 to 100. Higher scores denote more severe symptoms. The hallucinations score (SAPS-H) was the sum of the 7 hallucinations item scores, and the delusions score (SAPS-D) was the sum of the 13 delusions item scores.

The SAPS-PD is a modified version of the SAPS-H+D that includes 9 of the 20 items of the SAPS-H+D: 5 items for assessment of hallucinations (auditory hallucinations, voices conversing, somatic or tactile hallucinations, visual hallucinations, and global rating of severity of hallucinations) and 4 items for assessment of delusions (persecutory, delusions of jealousy, ideas and delusions of references, and global rating of severity of delusions) (Voss et al. 2013).

7.3.2 Clinical Global Impression –Severity and –Improvement Scales (CGI-S and CGI-I)

The CGI-S scale is a clinician-rated, 7-point scale that is designed to rate the severity of the hallucinations and delusions at the time of assessment using the Investigator's judgment and past experience with patients who have the same disorder (i.e., DRP) (Guy 1976).

The possible scores for the CGI-S scale are 1=normal, not at all ill, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, and 7=among the most extremely ill patients.

The CGI-I scale is a clinician-rated, 7-point scale that is designed to rate the improvement in the hallucinations and delusions relative to the symptoms at Baseline.

The possible scores for the CGI-I scale are 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse.

7.3.3 Neuropsychiatric Inventory–Nursing Home Version (NPI-NH)

NPI-NH consisted of 12 neuropsychiatric disturbances 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, represented the product of symptom frequency and severity. The NPI-NH psychosis subscale (delusions+hallucinations domains) was used to assess psychosis.

7.3.4 Mini-Mental State Examination (MMSE)

The MMSE is a brief 30-point questionnaire that is used to quantitatively assess cognition (Folstein et al. 1975). The MMSE includes simple questions and problems in a number of areas: the time and place of testing, repeating lists of words, arithmetic, language use and comprehension, and copying a drawing. The MMSE was used in the pimavanserin studies to screen for cognitive impairment.

7.3.5 Zarit Burden Interview

The ZBI was designed to assess the stress experienced by caregivers of patients with dementia (Zarit et al. 1980). The ZBI was administered as an interview. The interview consists of 22 statements reflecting how people sometimes feel when taking care of another person. The statements are phrased as questions for the family member study partner/caregiver to indicate how often they feel the way described in the statement. Responses are Never, Rarely, Sometimes, Quite Frequently, and Nearly Always. When the study partner/caregiver is not a family member, this scale will not be completed.

7.3.6 EQ-5D-5L

The EQ-5D-5L is a standardized instrument used as a measure of health outcome (Kind 1996). It measures 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which has 5 potential responses. The responses record 5 levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. The EQ-5D-5L Proxy version 1 was be used. For this version, a study partner/caregiver (the proxy) was asked to rate subject's health-related quality of life in their (the proxy's) opinion.