NUPLAZID® (pimavanserin) Treatment of Alzheimer's Disease Psychosis

Acadia Pharmaceuticals Inc. (Acadia)

Psychopharmacologic Drugs Advisory Committee

17 June 2022

Introduction

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Acadia

NUPLAZID (pimavanserin) Current and Proposed Indications

Current: **Treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP)**

Recommended dose: 34 mg once daily (QD)

Proposed: **Treatment of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP)**

Recommended dose: 34 mg QD

Substantial Evidence of Effectiveness in ADP (FDA 2019 Regulatory Guidance[1])

ADP Patients
Study 019

Adequate, Well-Controlled Positive Study in Proposed Indication

PDP Patients
Study 020

Confirmatory Evidence Closely Related Approved Indication

DRP Patients
Study 045

Supportive Data from ADP Subgroup in Positive DRP Study

Consistent and Clinically Meaningful Effect Across Multiple Clinical Studies and Measures

- Reduced psychosis symptoms and risk of psychosis relapse
- Responder analyses
- Exposure-response analyses

1. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (FDA, 2019)

Pimavanserin Development and Regulatory History

Parkinson's Disease Psychosis (PDP)
Alzheimer's Disease Psychosis (ADP)

FDA Meetings: Align on Resubmission

Dementia-Related Psychosis (DRP)

- **2016**
  - NUPLAZID FDA Approved for PDP (Study 020)
- **2017**
  - Positive Study 019 in ADP
  - EoP2 Meeting: DRP
  - Breakthrough Therapy Designation: DRP
- **2018**
  - Positive Study 045 in DRP
- **2019**
- **2020**
  - sNDA for DRP Indication
- **2021**
  - FDA Issues Complete Response Letter
- **2022**
  - Resubmission for ADP Indication

EoP2 = End of Phase 2; sNDA = supplemental New Drug Application

Positive Benefit-Risk for Treatment of ADP

- Pimavanserin efficacy across clinical studies and measures
  - Consistent, clinically meaningful benefit in ADP
- Expanded pimavanserin safety dataset corroborates favorable and differentiated safety profile
  - > 1,500 elderly, frail patients with neurodegenerative disease in clinical studies, including patients with ADP
  - > 44,000 PDP patients in postmarketing since approval

Pimavanserin Benefit-Risk in Context of Unmet Medical Need

- No FDA-approved treatments for ADP
  - Increased patient / caregiver distress and risk of morbidity / mortality
- No demonstrated benefit with available antipsychotics and potentially serious safety liabilities
- Pimavanserin reduces psychosis symptoms and risk of relapse, with a favorable safety profile in ADP
  - No adverse impact on cognition or motor function
- Payors require PDP diagnosis: ~ 96% NUPLAZID prescriptions on label for PDP

Agenda

Unmet Need and Current Standard of Care	**Pierre N Tariot, MD** Director, Banner Alzheimer's Institute Research Professor of Psychiatry University of Arizona College of Medicine-Phoenix
Evidence of Efficacy *Studies 019 and 020*	**Clive Ballard, MD** Pro-Vice-Chancellor and Executive Dean Professor of Age-related Diseases College of Medicine and Health University of Exeter, UK
Study 045 and Supportive ADP Analyses	**Suzanne Hendrix, PhD** Statistical Consultant CEO, Pentara Corporation
Safety Profile: Key Aspects	**Mary Ellen Turner, MD, MPH** Corporate Safety Officer, Acadia
Benefit-Risk of Pimavanserin	**Serge Stankovic, MD, MSPH** President, Acadia

Unmet Need and Current Standard of Care

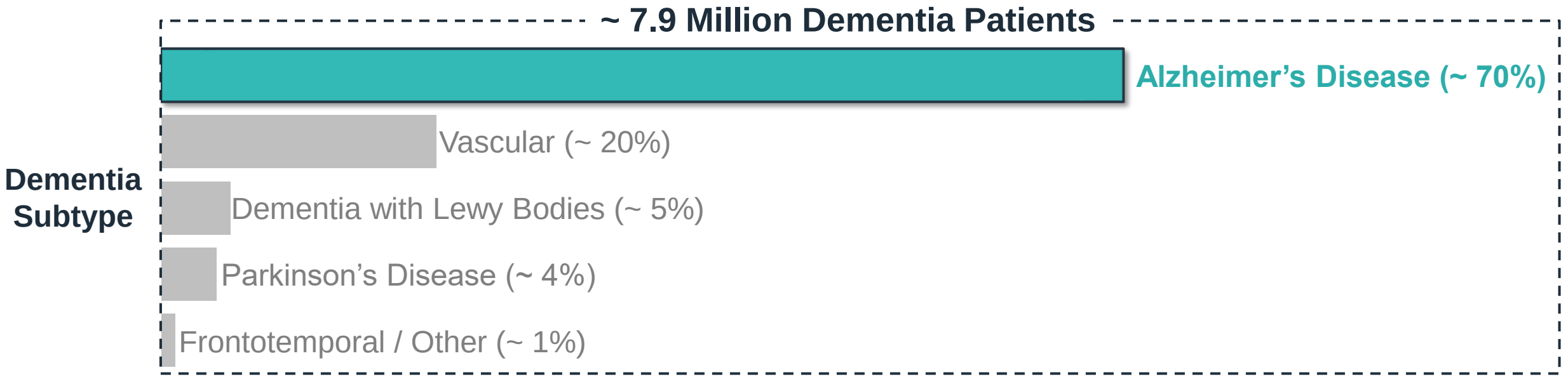
Pierre N Tariot, MD

Director, Banner Alzheimer's Institute

Research Professor of Psychiatry

University of Arizona College of Medicine-Phoenix

Epidemiology of Alzheimer's Disease (AD)



- Psychosis: hallucinations and / or delusions
  - ~ 30% of patients with AD experience psychosis at any given time

Goodman, 2017; Plassman, 2007; Hebert, 2013; Alzheimer's Association 2017; Vann Jones and O'Brien, 2014; Hogan, 2016; Aarsland, 2005

ADP Severity Increases Over Time with Dire Consequences

Social Consequences

- Loss of independence and relationships
- Increased distress and burden to patient, family, and caregivers
- Diminished QoL

Clinical Consequences

- Shorter time to severe dementia
- Worsened functioning
- Increased cognitive impairment
- Accelerated mortality

Public Health Impact

- Increased hospitalizations
- Earlier progression to nursing home care

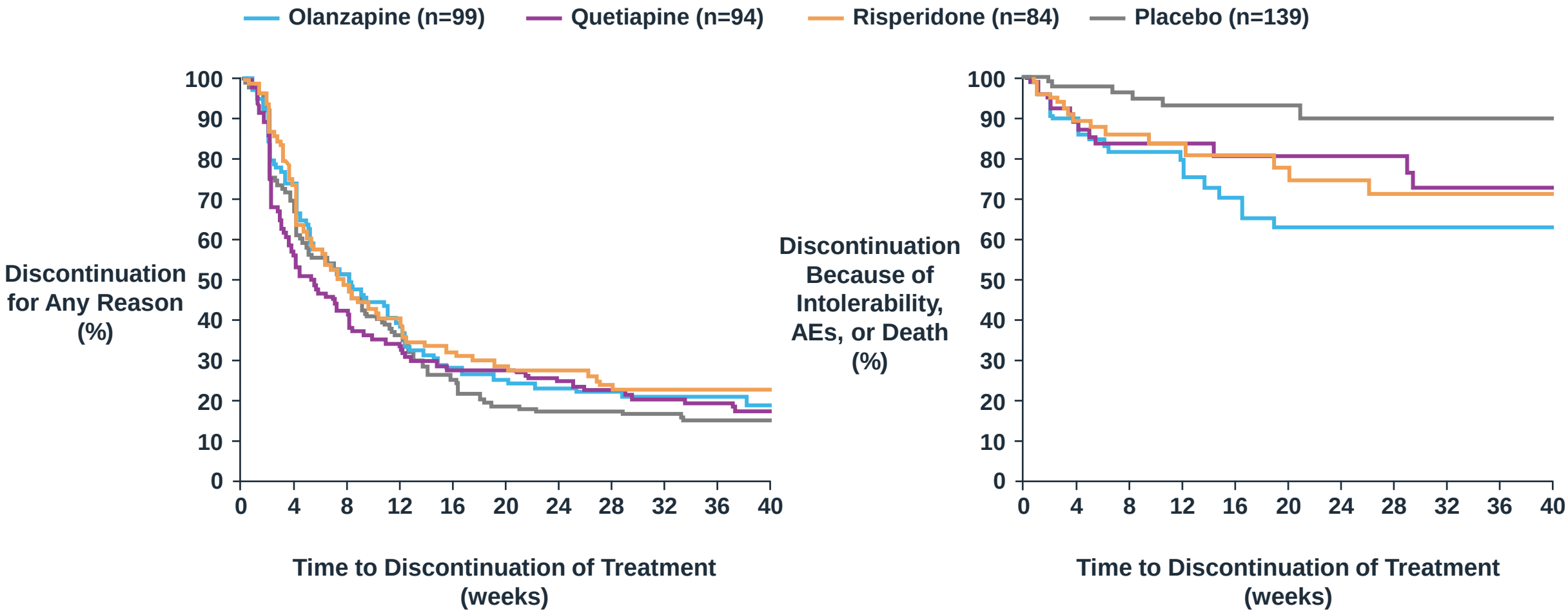
Fernández-Martínez, 2008; Lyketsos, 2002; Karttunen, 2011; Geda, 2013; Brodaty & Donkin, 2009

No FDA Approved Treatments for Patients with ADP

- Non-pharmacological interventions commonly fail
- Antipsychotics used if symptoms frequent, severe, dangerous, or cause distress[1]
  - Medicare claims data 2008-2016: ~ 66% (> 30,000 / 49,509) of patients with DRP prescribed an antipsychotic off-label[2]
- Efficacy is equivocal at best
- Toxicities are significant (80% – 90%)[1]
  - Cognitive impairment, increased mortality, parkinsonism, stroke, metabolic syndrome, hypertension
  - Related to receptor binding at dopaminergic, histaminergic and muscarinic receptors

1. American Psychiatric Association (APA) guidelines 2016; 2. Rashid, 2022

CATIE-AD: Limited Efficacy and High Discontinuation for Atypical Antipsychotics



CATIE-AD: Clinical Antipsychotic Trials of Intervention Effectiveness – Alzheimer's Disease

Adapted from Schneider, Tariot et al NEJM 2006

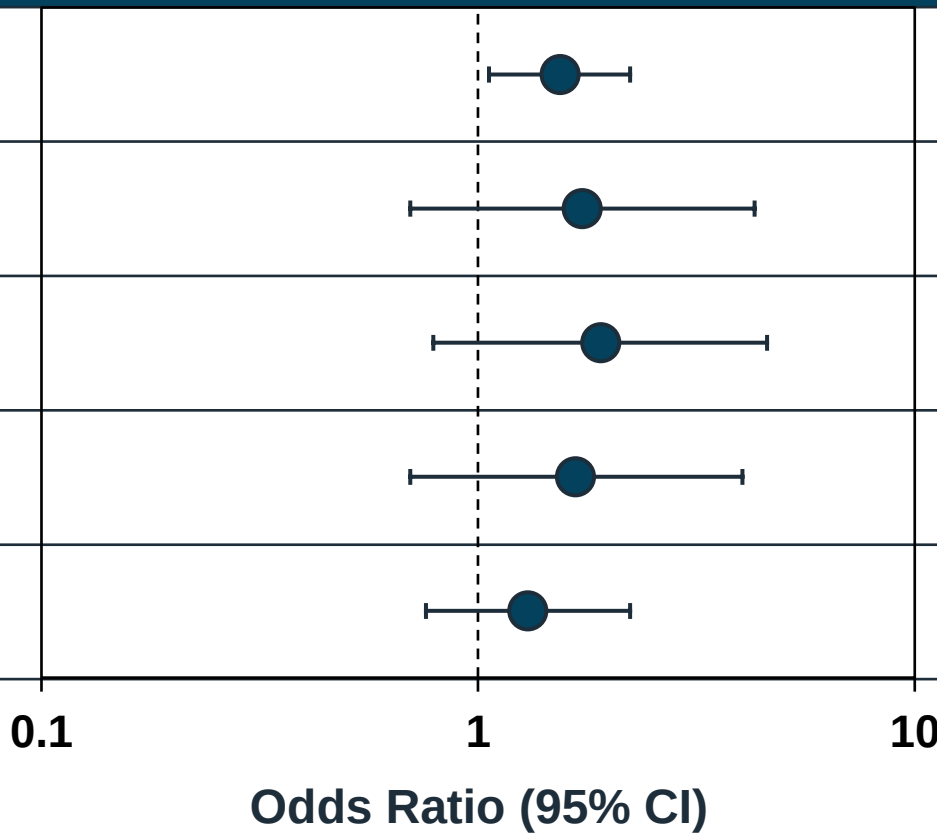
CATIE-AD: Atypical Antipsychotics Associated with Cognitive Decline

- Patients showed steady, significant declines over time in cognitive function
  - MMSE: -2.4 points over 36 weeks
  - Decline experienced consistent with 1 years' deterioration in dementia
- Physicians likely to switch medications due to lack of efficacy or AEs

Vigen, 2011; Schneider, Tariot et al NEJM 2006

Mortality Risk of Atypical Antipsychotics

	% (Events / N)		Favors Treatment ←	→ Favors Placebo	OR (95% CI)
	Treatment	Placebo			
Total	**4%** (118 / 3353)	**2%** (41 / 1851)			**1.54** (1.06, 2.23)
Aripiprazole	**3%** (21 / 603)	**2%** (6 / 348)			**1.73** (0.70, 4.30)
Olanzapine	**3%** (31 / 1184)	**1%** (6 / 478)			**1.91** (0.79, 4.59)
Quetiapine	**5%** (21 / 391)	**3%** (7 / 246)			**1.67** (0.70, 4.03)
Risperidone	**4%** (45 / 1175)	**3%** (22 / 779)			**1.30** (0.76, 2.23)



Schneider, 2006

APA Guidelines Recommend Judicious Use of Antipsychotics

- Individualized treatment plan developed with patients and their families
- Antipsychotic non-response
  - No significant response after 4 weeks, medication withdrawn
- Antipsychotic response
  - Withdraw medication within 4 months of treatment initiation due to known toxicities

American Psychiatric Association (APA) guidelines 2016

Patients with ADP Deserve More Than Current Off-Label Options

- ADP is serious and symptomatic consequences are life-altering
- Patients, their families, healthcare system at large
  - Need an effective therapy not associated with significant toxicities
  - Need therapy recognized by health authorities as appropriate for clinical use

Evidence of Efficacy: Clinical Studies 019 and 020

Clive Ballard, MD

Pro-Vice-Chancellor and Executive Dean

Professor of Age-related Diseases

College of Medicine and Health

University of Exeter, UK

Evidence of Efficacy Supporting Pimavanserin for Patients with ADP

- Primary evidence - Study 019
  - Positive placebo-controlled study in ADP (target indication)
- Confirmatory evidence - Study 020
  - Positive placebo-controlled study in PDP (closely related approved condition)
- Supportive evidence - Study 045
  - Positive randomized withdrawal study in DRP
  - ADP subgroup analyses support consistent benefit

Studies 019 and 020: Key Discussion Points

- Relationship between ADP and PDP
  - Biologic evidence (neuropathology and pathophysiology)
  - Similar symptoms of psychosis and treatment response
- Study 019: positive, adequate and well-controlled study in ADP
  - NPI-NH PS: validated measure of H+D
  - Treatment effect clinically meaningful and relevant
  - Durability of effect
  - Secondary outcomes evaluated non-psychotic symptoms (e.g. agitation/aggression); not statistically significant
- Study 020: pivotal study leading to pimavanserin approval in PDP

NPI-NH PS = Neuropsychiatric Inventory–Nursing Home Psychosis Score; H+D = Hallucinations and Delusions

Neurobiological Similarities Between PDP and ADP

Mechanisms of Psychosis

- Post-mortem, genetic, and neuroimaging studies supports similarity
- Common brain areas
  - Delusions – frontal cortex
  - Visual hallucinations – Occipital Cortex and visual association areas[1]
- Importance of serotonergic system – post-mortem, functional neuroimaging, and genetic polymorphism studies[2]

Pathological Overlap

- 90% of patients with PD dementia have substantial AD pathology[3]
- Almost all patients with PD have at least some amyloid plaque pathology[4]

1. Ktrola, 1995, Mega, 2009, Lenka, 2015; 2. Huot, 2010, Ballanger, 2010, Garcia-Allozal, 2005, Creese, 2014; 3. Ballard, 2006; 4. Perry, 2003

Clinical Similarities of ADP and PDP

- Similar phenomenology of visual hallucinations, hallucinations in other modalities, and delusions[1]
  - PDP: higher frequency of visual hallucinations and reduced rate of spontaneous recovery[2]
- Visual hallucinations: people, animals, strangers
- Auditory hallucinations: often associated with visual hallucinations
- Delusions: theft, harm (e.g., being poisoned), infidelity

1. Aarsland, 2001; 2 Ballard, 2001

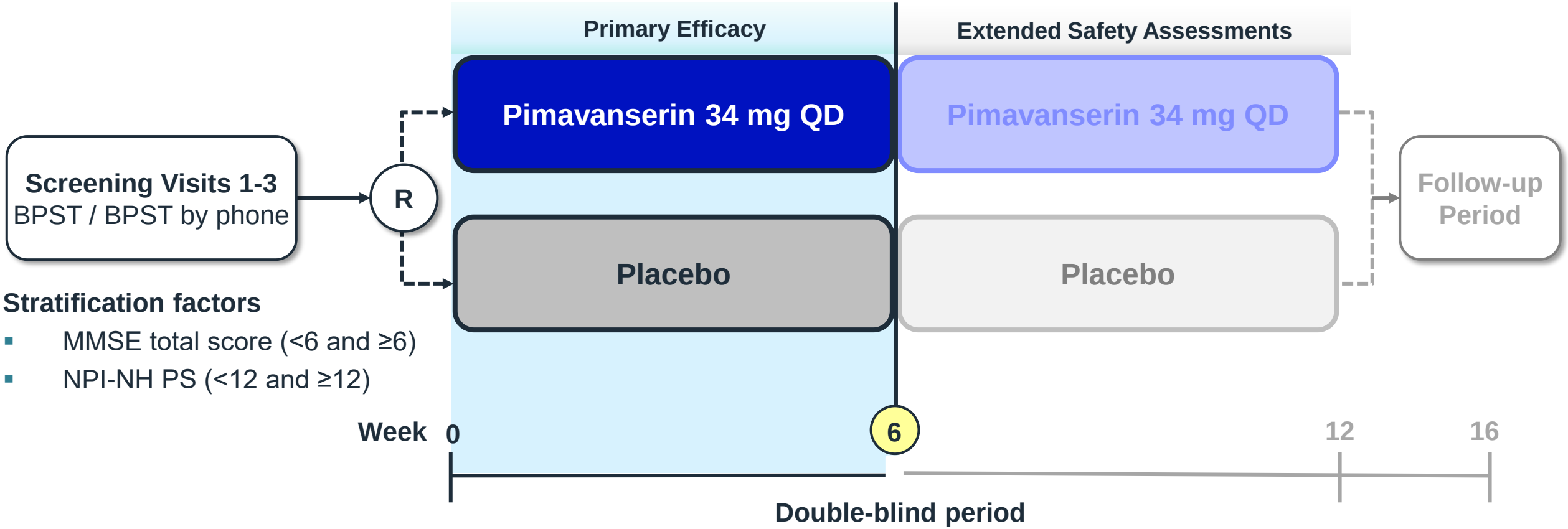
Natural History of Psychosis in ADP Informing Trial Design

- Psychosis resolution[1]
  - 68% of patients by 12 weeks
    - 50% experienced recurrence in 12-month follow-up
    - Month to month fluctuation of symptoms
- 59% experience new psychotic symptom different than presenting symptom during the 12 months[1]
- 26% experience persistent symptoms through 12 months
- Placebo response[2, 3]
  - 50% improvement in symptoms common at week 4

1. Ballard, 1991; Ballard, 1995; 2. De Deyn, 2005; 3. Katz, 2007

Study 019: Randomized, Double-Blind, Placebo-Controlled Study

Change from Baseline in NPI-NH PS
Primary endpoint at Week 6



Stratification factors

- MMSE total score (<6 and ≥6)
- NPI-NH PS (<12 and ≥12)

Study results published in Lancet Neurology; Ballard et al., 2018

BPST = Brief Psychosocial Therapy for Psychosis; MMSE = mini mental state examination; NPI-NH PS = Neuropsychiatric Inventory–Nursing Home Psychosis Score

NPI-NH PS: Validation and Reliability

- NPI: most common primary measure, used in > 300 studies of neuropsychiatric symptoms of AD
  - Overall internal consistency α = 0.67[a]
  - Test-retest reliability ICC: Delusions = 0.89 (95% CI: 0.79–0.94)[b]; Hallucinations = 0.74 (95% CI: 0.51–0.86)[b]
  - Convergent validity between NPI-NH Psychosis Factor and GSNAP psychotic features: r = 0.54[a]
- NPI-NH PS measures 2 domains of hallucinations and delusions to assess symptom severity and frequency (maximum score 24)

a. Lang, 2004; b. Chen, 2018

GSNAP=Scale for Nursing Assessment in Geriatric Psychiatry

Study 019: Investigators Trained on NPI-NH PS

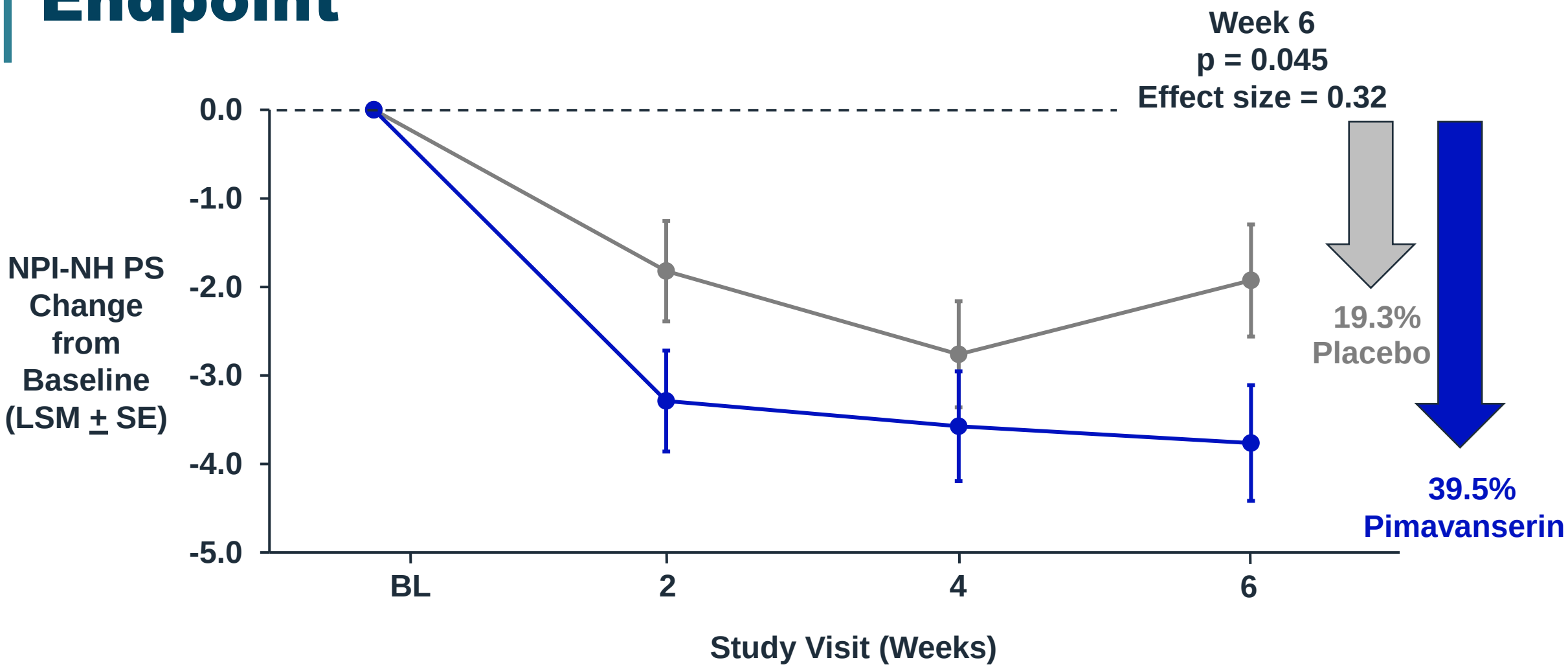
- Different NPI-NH PS raters at consecutive visits for same patient to mitigate expectancy biases
- NPI-NH PS raters trained by MedAvante
  - Centralized training and adherence to standardized procedures
  - Continuous calibration of raters to reduce drift and scoring variability
  - Raters provided feedback and refresher events
  - Caregivers all key workers and knew participants well
  - Caregivers trained in NPI-NH PS to improve quality of informant information

High inter-rater reliability (>0.9) achieved in Study 019

Study 019: Study Population – Elderly / Frail Patients with ADP

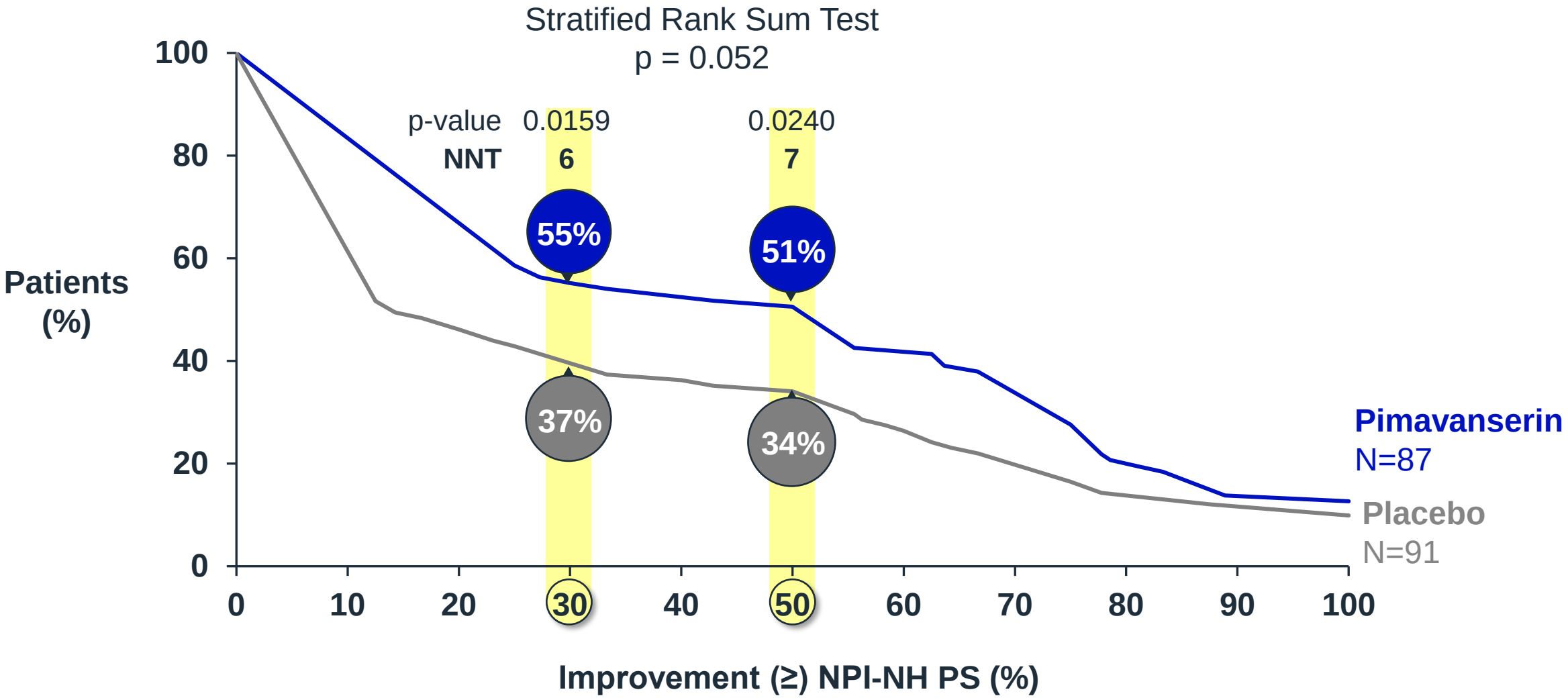
Baseline Characteristics	Pimavanserin N=90	Placebo N=91
Age (years), mean	86	86
Female, %	81%	80%
White, %	93%	98%
NPI-NH PS score, mean	9.5	10.0
MMSE, mean	10.2	9.8
≥ 5 non-anti-dementia concomitant medications, %	82%	85%

Study 019: Positive Efficacy on Primary Endpoint

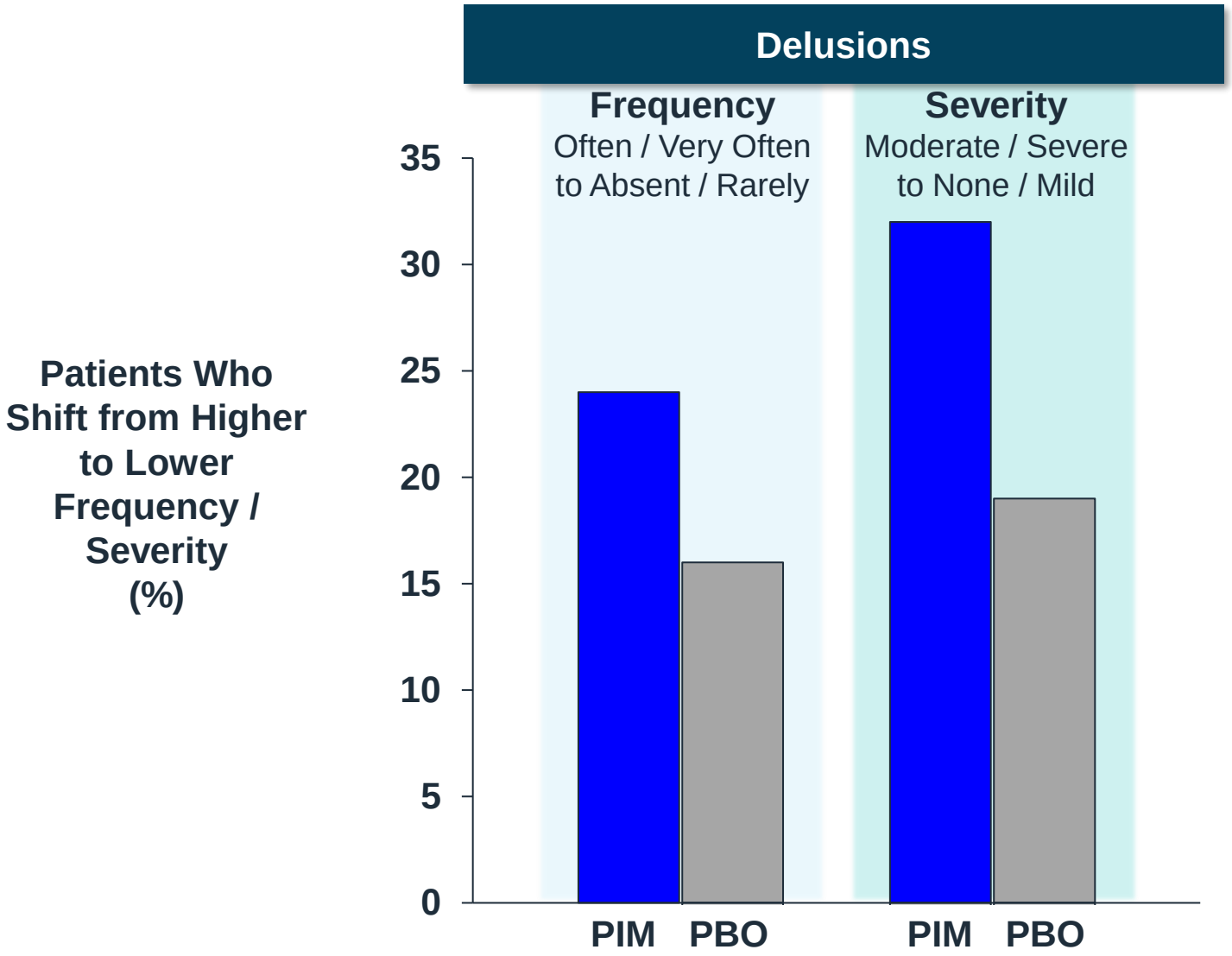


Pimavanserin (n)	87	85	80	76
Placebo (n)	91	85	86	81

Study 019: Clinically Meaningful Efficacy Shown by Responder Analysis at Primary Endpoint

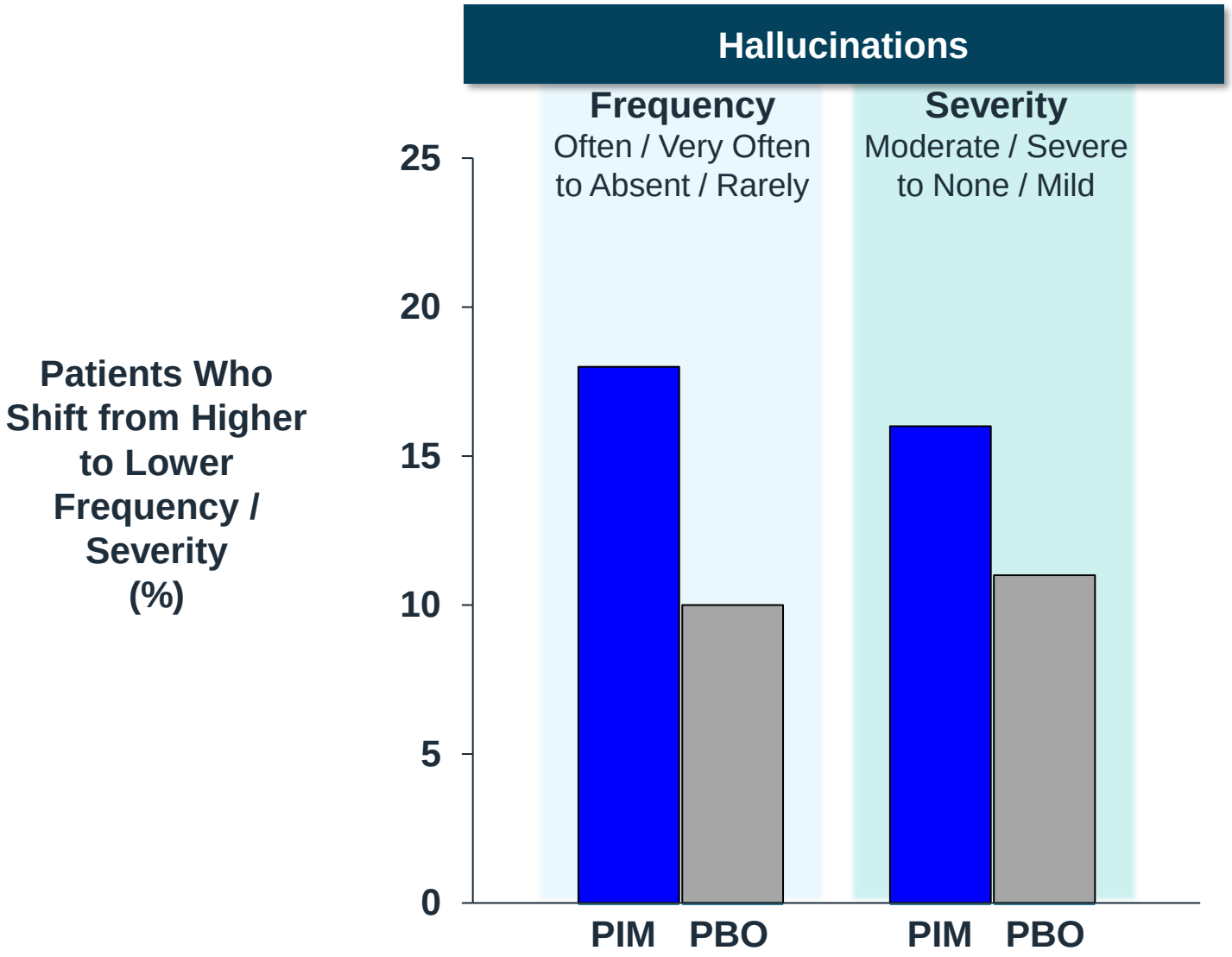


Study 019: Meaningful Improvement Observed on Frequency and Severity of Delusions



PIM = pimavanserin; PBO = placebo

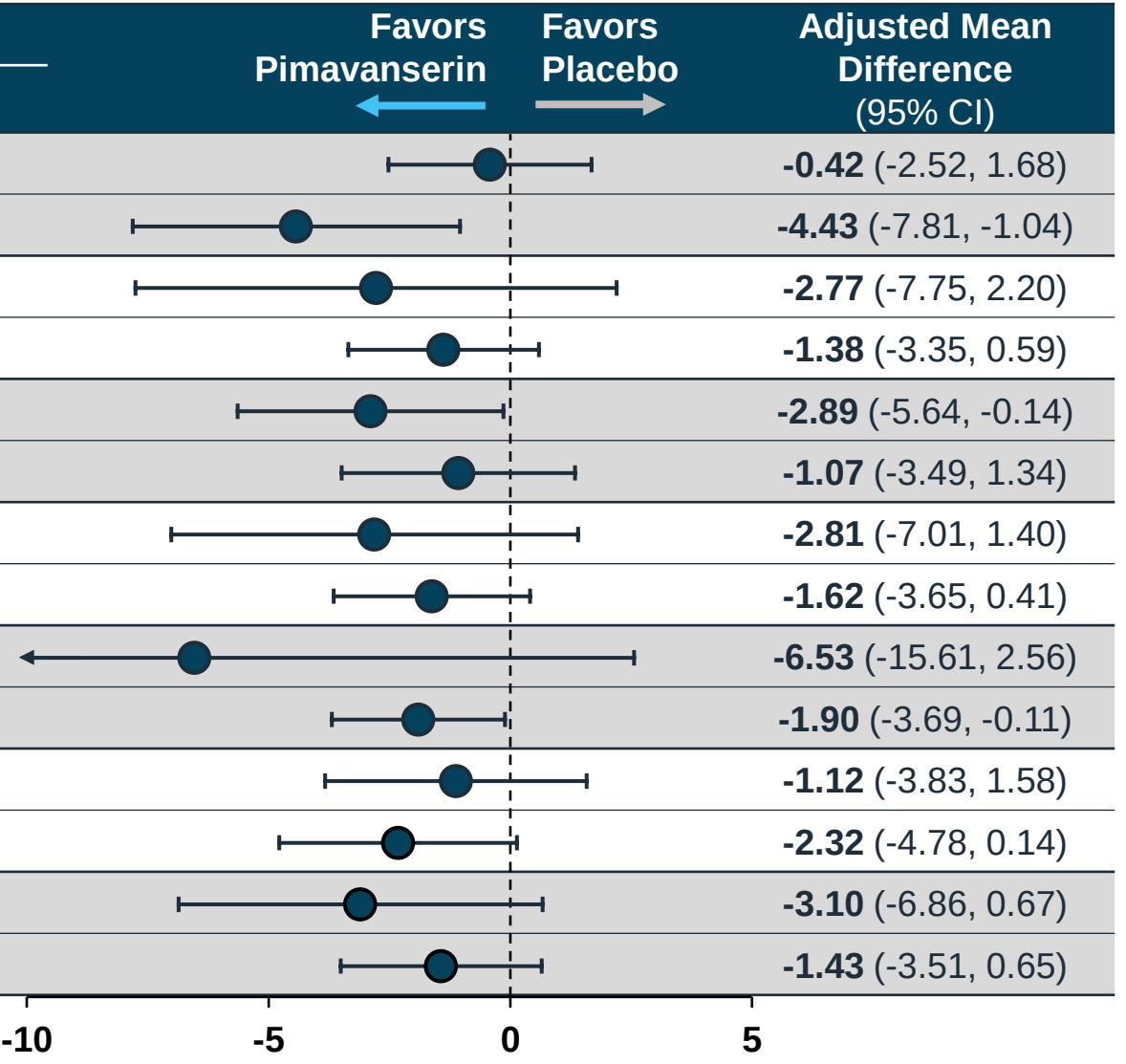
Study 019: Meaningful Improvement Observed on Frequency and Severity of Hallucinations



PIM = pimavanserin; PBO = placebo

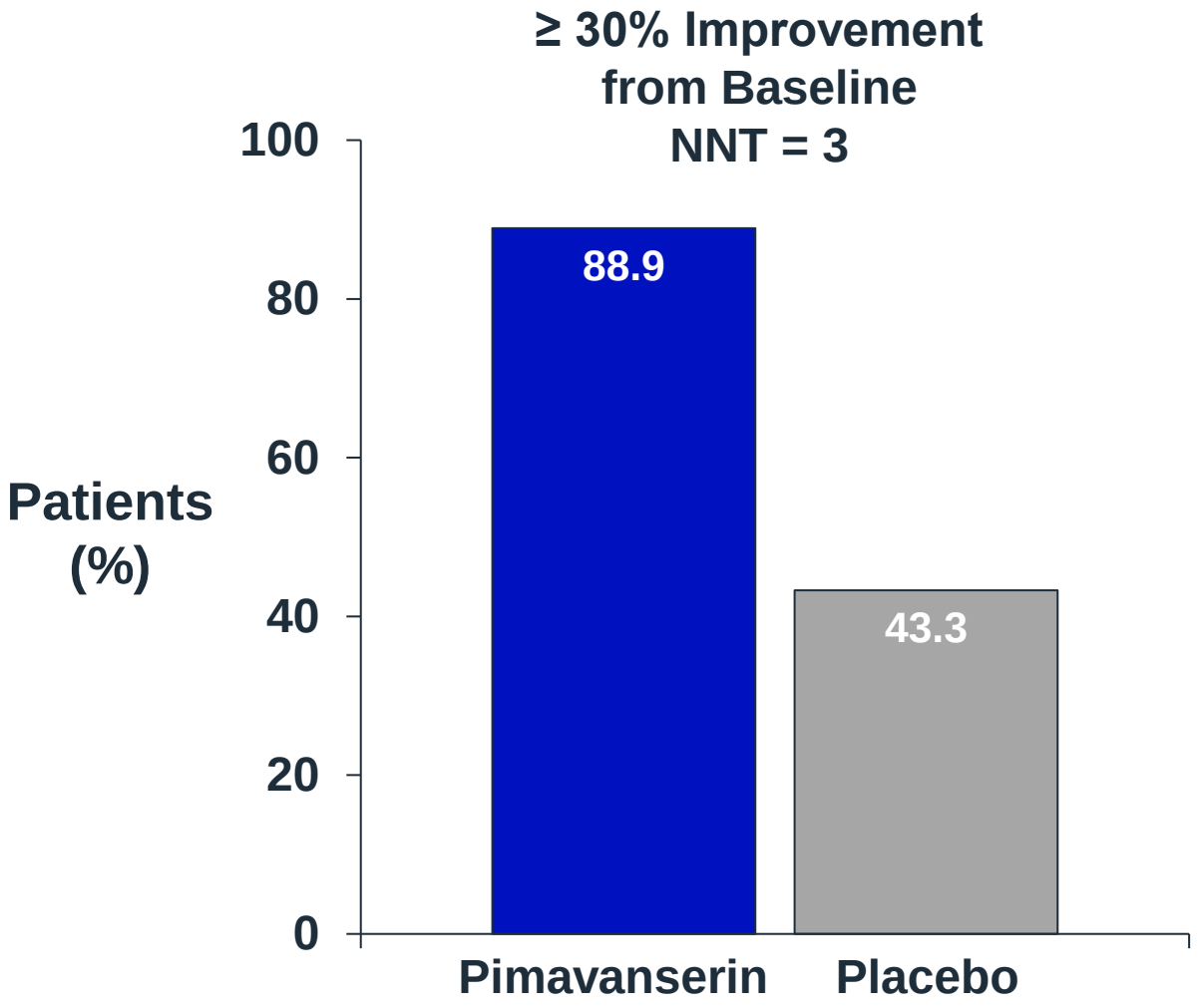
Study 019: Subgroup Analyses for NPI-NH PS at Week 6

Subgroup Analyses for NPI-NH Psychosis Score	N PIM	N PBO	Adjusted Mean Difference (95% CI)
Baseline NPH-NH PS < 12	49	56	**-0.42** (-2.52, 1.68)
Baseline NPH-NH PS ≥ 12	27	25	**-4.43** (-7.81, -1.04)
Baseline MMSE < 6	14	14	**-2.77** (-7.75, 2.20)
Baseline MMSE ≥ 6	59	62	**-1.38** (-3.35, 0.59)
Age ≤ 85 years	33	37	**-2.89** (-5.64, -0.14)
Age > 85 years	43	44	**-1.07** (-3.49, 1.34)
Men	11	17	**-2.81** (-7.01, 1.40)
Women	65	64	**-1.62** (-3.65, 0.41)
Previous antipsychotic use	10	4	**-6.53** (-15.61, 2.56)
No previous antipsychotic use	66	77	**-1.90** (-3.69, -0.11)
Anti-dementia medication use	29	37	**-1.12** (-3.83, 1.58)
No anti-dementia medication use	47	44	**-2.32** (-4.78, 0.14)
SSRI use	18	18	**-3.10** (-6.86, 0.67)
No SSRI use	58	63	**-1.43** (-3.51, 0.65)



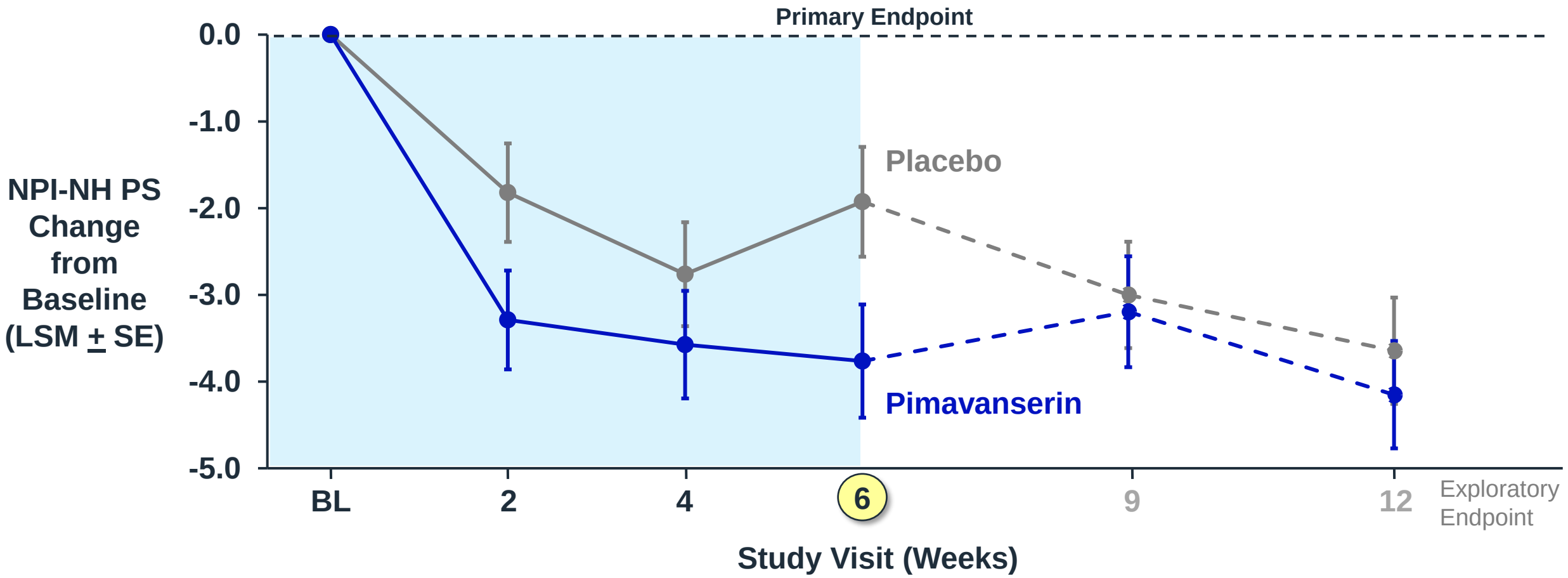
Ballard, Lancet Neurology, 2018

Study 019: Change from Baseline in Patients with Severe Psychosis (NPI-NH PS ≥ 12)



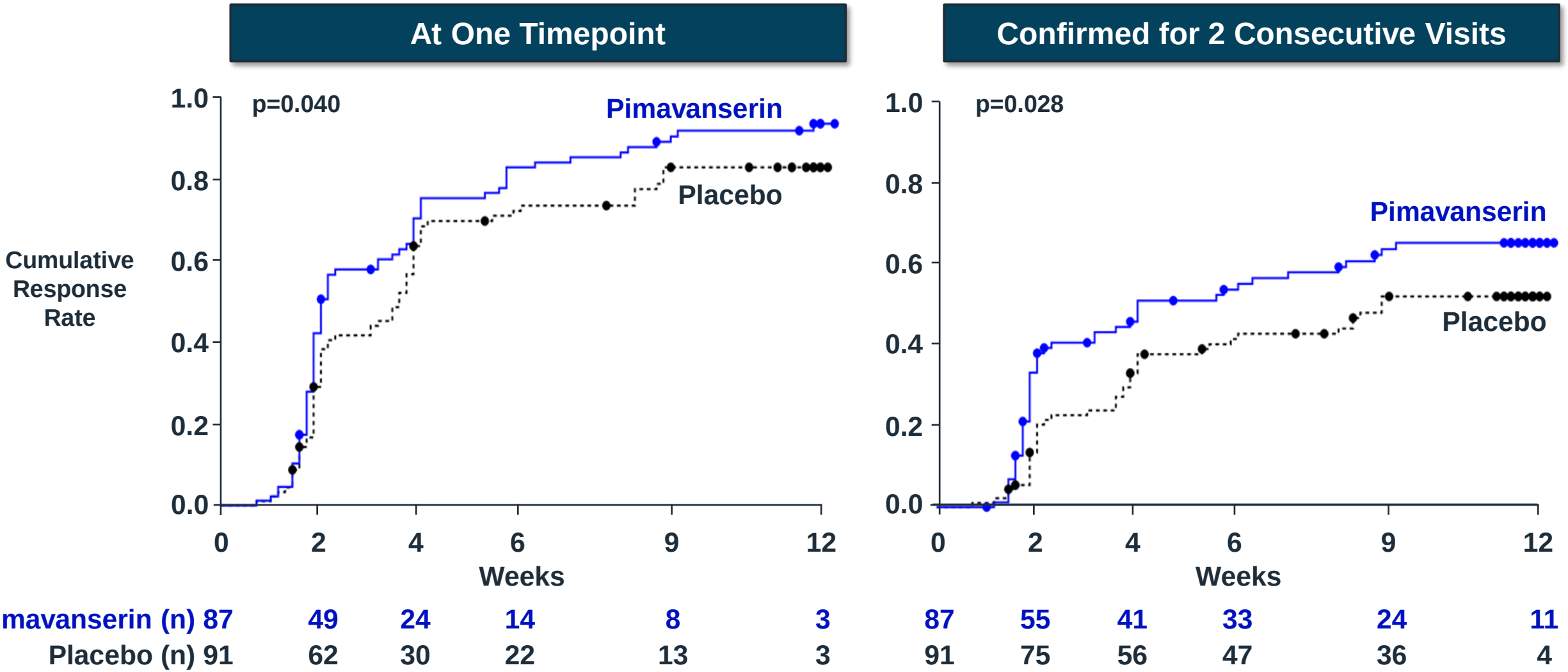
	Point Change at Week 6	Effect Size	p-value
Pimavanserin	-10.2	0.73	0.011
Placebo	-5.7		

Study 019: Exploratory Efficacy Assessments After Week 6

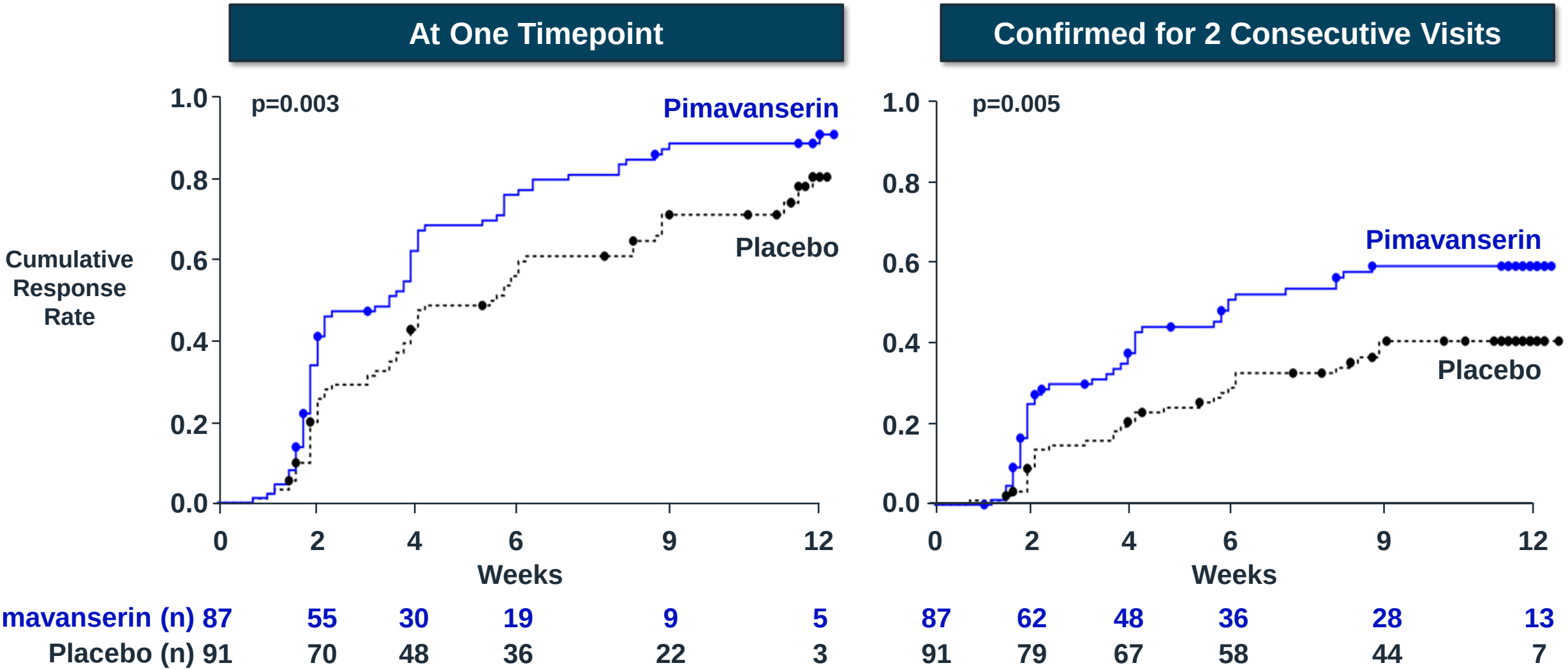


Pimavanserin (n)	87	85	80	76	71	69
Placebo (n)	91	85	86	81	77	70

Study 019: Time to Improvement of ≥ 30% from Baseline on NPI-NH PS



Study 019: Time to Improvement of ≥ 50% from Baseline on NPI-NH PS

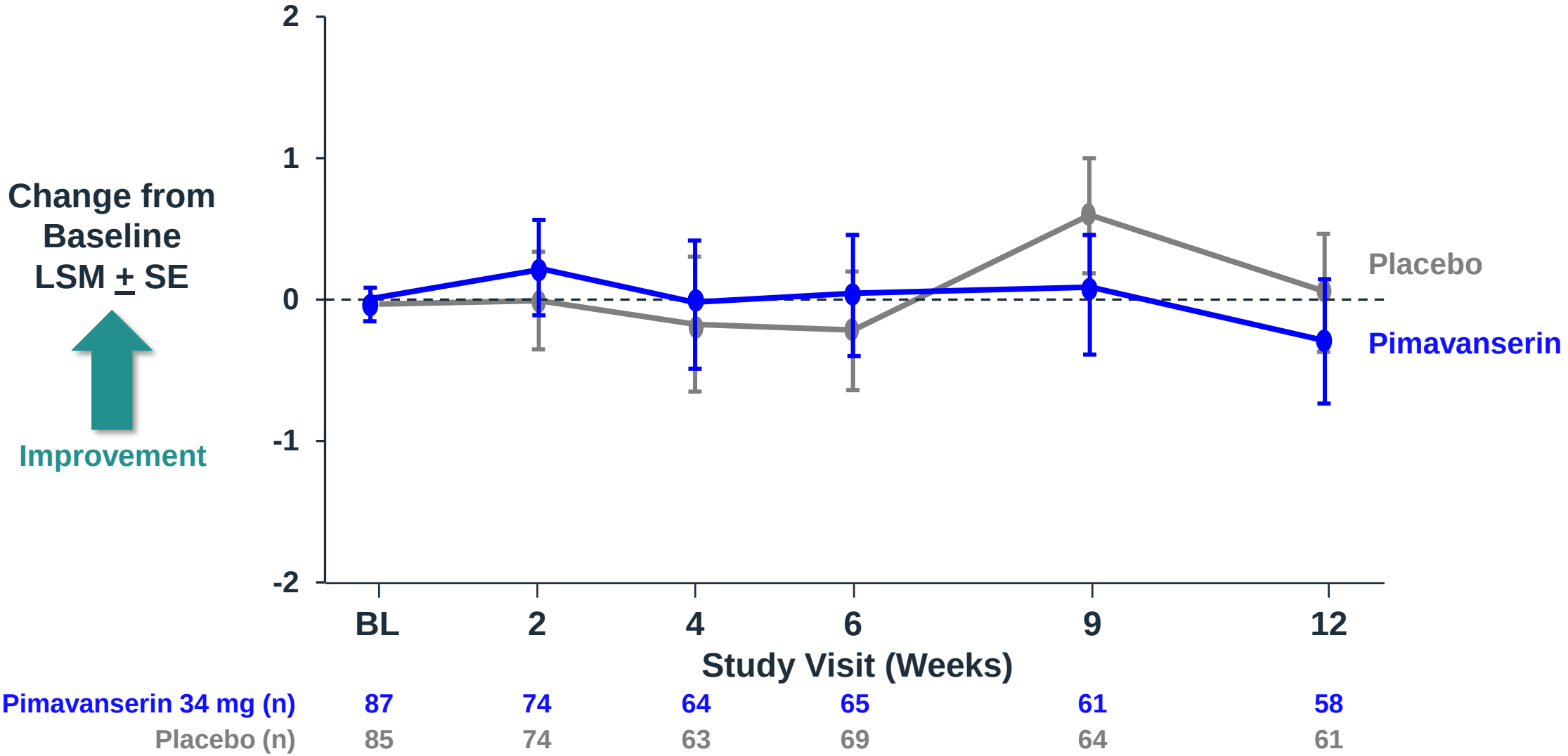


Study 019: Secondary Outcomes Evaluated Non-Psychotic Neuropsychiatric Symptoms

	MMRM LSM (SE)			
	PIM (N=87)	Placebo (N=91)	Difference (95% CI)	p-value
ADCS-CGIC Rating	**3.71 (0.14)**	**3.59 (0.14)**	**0.13** (-0.26, 0.51)	**0.514**
NPI-NH Agitation/Aggression (Domain C)	**-1.13 (0.41)**	**-0.47 (0.40)**	**-0.66** (-1.80, 0.48)	**0.254**
NPI-NH Sleep and Nighttime Behavior Disorders (Domain K)	**-0.84 (0.32)**	**-0.42 (0.31)**	**-0.42** (-1.30, 0.46)	**0.344**
CMAI-SF (14-item) Total Score	**-2.07 (0.85)**	**-2.36 (0.83)**	**0.30** (-2.04, 2.63)	**0.803**
CMAI-SF Aggressive Behavior Subdomain Score	**-0.45 (0.30)**	**-0.74 (0.29)**	**0.30** (-0.52, 1.11)	**0.475**
CMAI-SF Physically Nonaggressive Behavior Subdomain Score	**-0.27 (0.38)**	**-0.45 (0.37)**	**0.18** (-0.87, 1.23)	**0.734**
CMAI-SF Verbally Agitated Behavior Subdomain Score	**-1.35 (0.43)**	**-1.18 (0.42)**	**-0.17** (-1.35, 1.02)	**0.782**

ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; CMAI-SF = Cohen-Mansfield Agitation Inventory Short Form

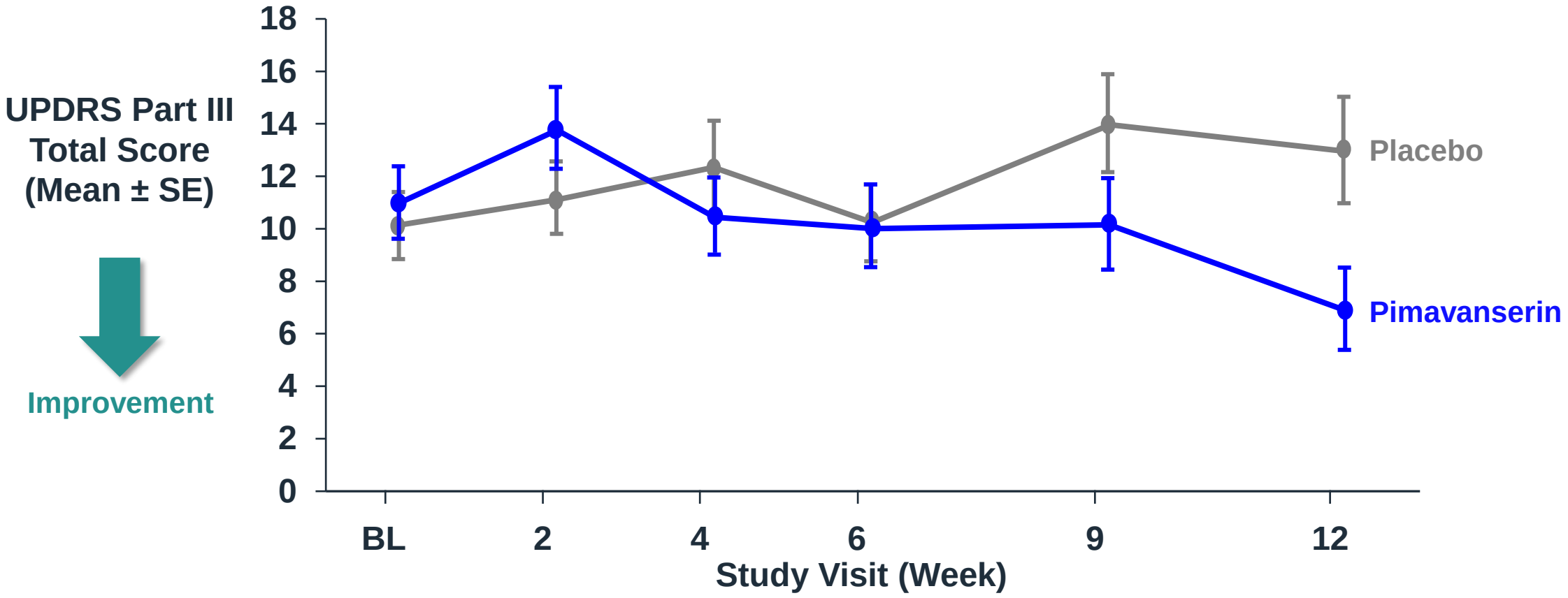
Study 019: No Observed Negative Impact on Cognitive Function Measured by MMSE



	BL	2	4	6	9	12
Pimavanserin 34 mg (n)	87	74	64	65	61	58
Placebo (n)	85	74	63	69	64	61

MMSE = Mini-Mental State Examination

Study 019: No Observed Negative Impact on Motor Function Measured by UPDRS Part III



Pimavanserin 34 mg (n)	74	70	63	60	53	46
Placebo (n)	65	70	60	52	55	53

UPDRS = Unified Parkinson's Disease Rating Scale

Study 019 Demonstrated Positive and Meaningful Efficacy of Pimavanserin in ADP

- Statistically significant result on primary endpoint
- Clinically meaningful treatment response
- Pimavanserin accelerated time to symptom improvement
- Severe patients experienced greatest benefits
- Safety endpoints demonstrated no negative impact on cognitive or motor functions

Study 020: Pivotal Study Leading to Pimavanserin Approval in PDP

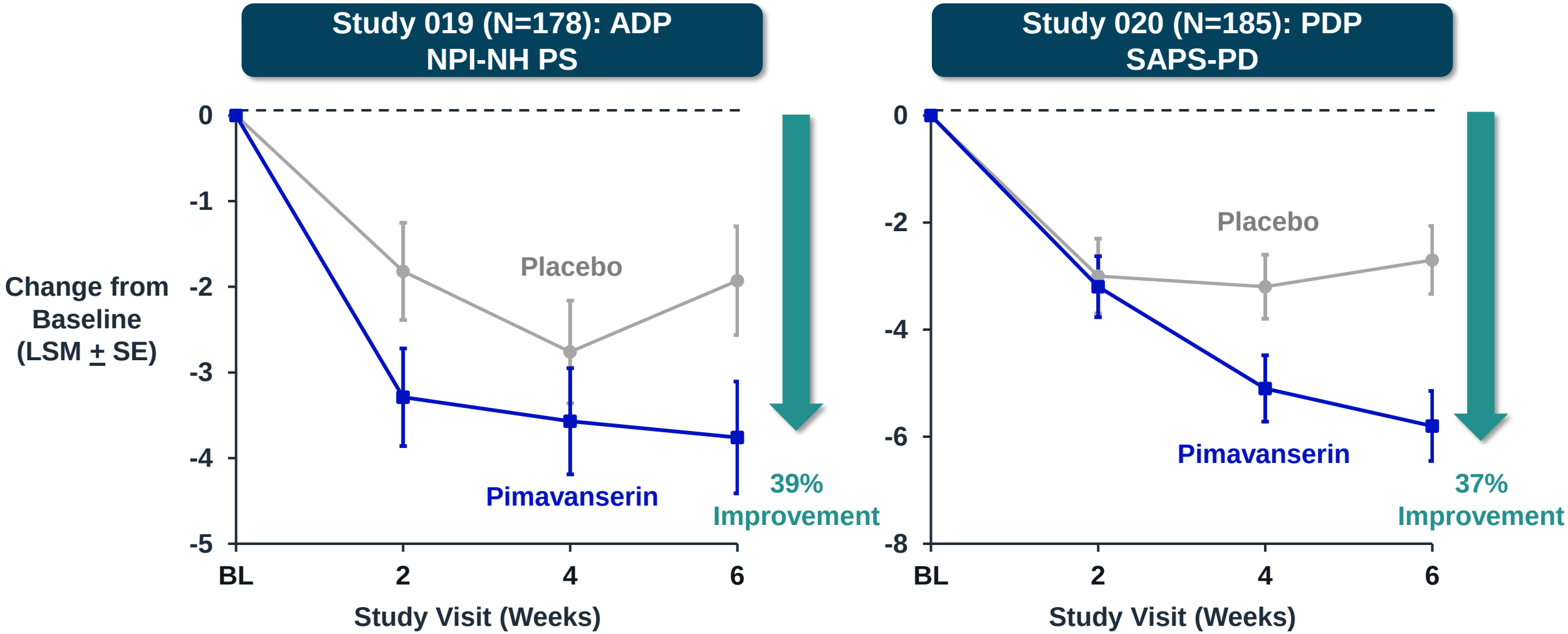
Study 020 (PDP): Overview

- Randomized, double-blind, placebo-controlled, outpatient study in patients with PDP (N=199)
  - Mean age ~ 72 years
  - Mean SAPS-PD at baseline = 15
  - MMSE ≥ 21
- Randomized 1:1 ratio to placebo or pimavanserin 34 mg QD
- Primary efficacy endpoint
  - Mean change in SAPS-PD from baseline to week 6
- Treatment difference: -3.06 (p=0.001, effect size=0.50)
- Treatment difference (MMSE score = 21 – 24): -5.71 (p=0.002, effect size=0.99)

Study results published in Lancet; Cummings et al., 2014

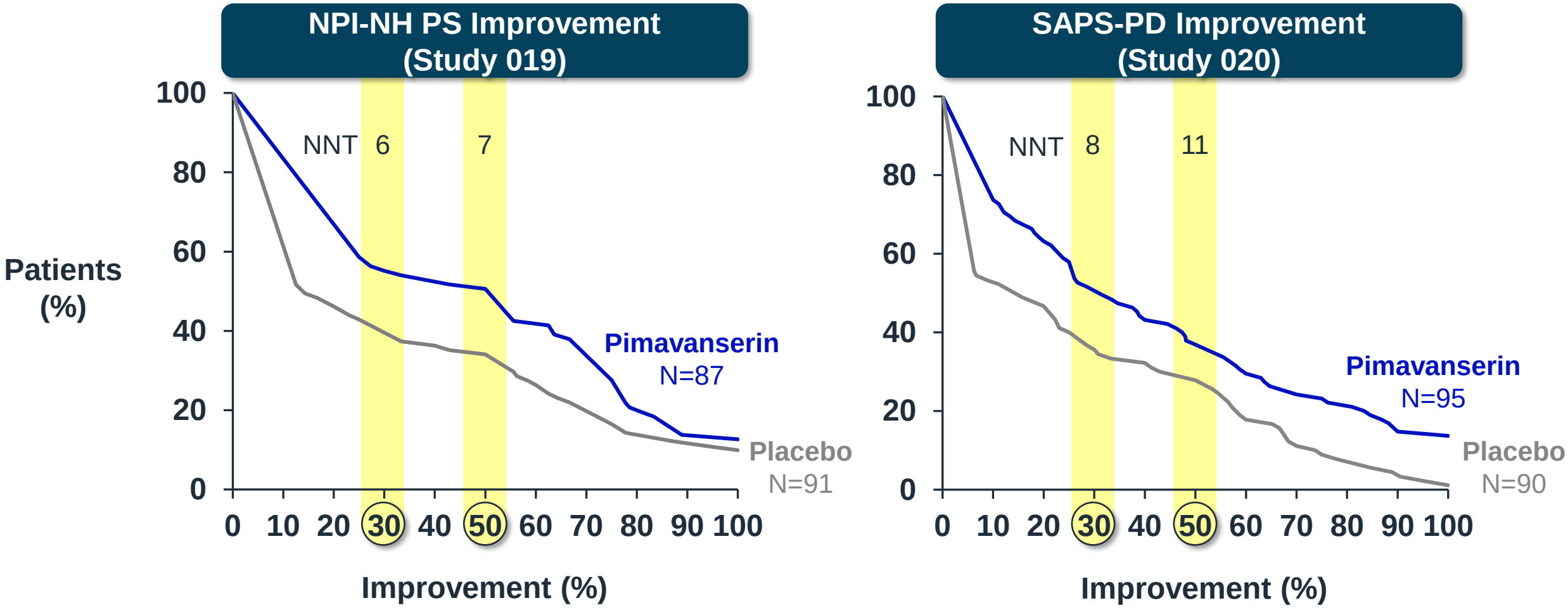
SAPS-PD = Scale for the Assessment of Positive Symptoms in PD

ADP and PDP Closely Related Conditions: Supported by Data from Studies 019 and 020 (Psychosis Severity Rating Scales)



Both studies statistically significant at primary efficacy endpoint (Week 6)

ADP and PDP Closely Related Conditions: Supported by Data from Studies 019 and 020 (Responder Analysis-Psychosis Severity Scales)



Studies 019 and 020 Provide Evidence of Efficacy for ADP

- Study 019 in ADP
  - Adequate and well-controlled study
  - Met primary endpoint demonstrating statistically and clinically meaningful treatment response
- Study 020 in PDP
  - Closely related condition
  - Consistency of treatment response supports common clinical presentations of psychosis

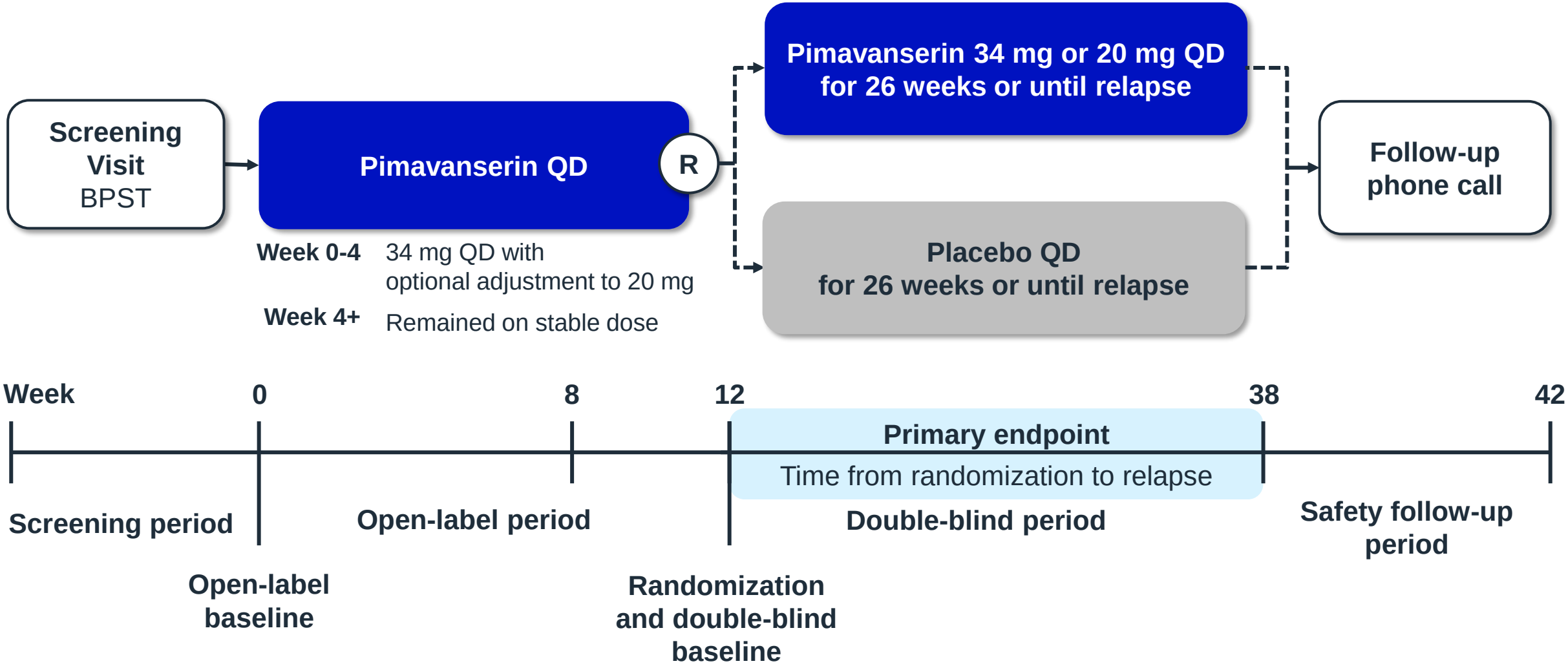
Study 045 and Supportive ADP Subgroup Analyses

Suzanne Hendrix, PhD

Statistical Consultant

CEO, Pentara Corporation

Study 045: Double-Blind, Placebo-Controlled, Randomized Withdrawal Study in DRP



Study results published in NEJM; Tariot et al., 2021

Sparse PK samples collected in OL and DB periods

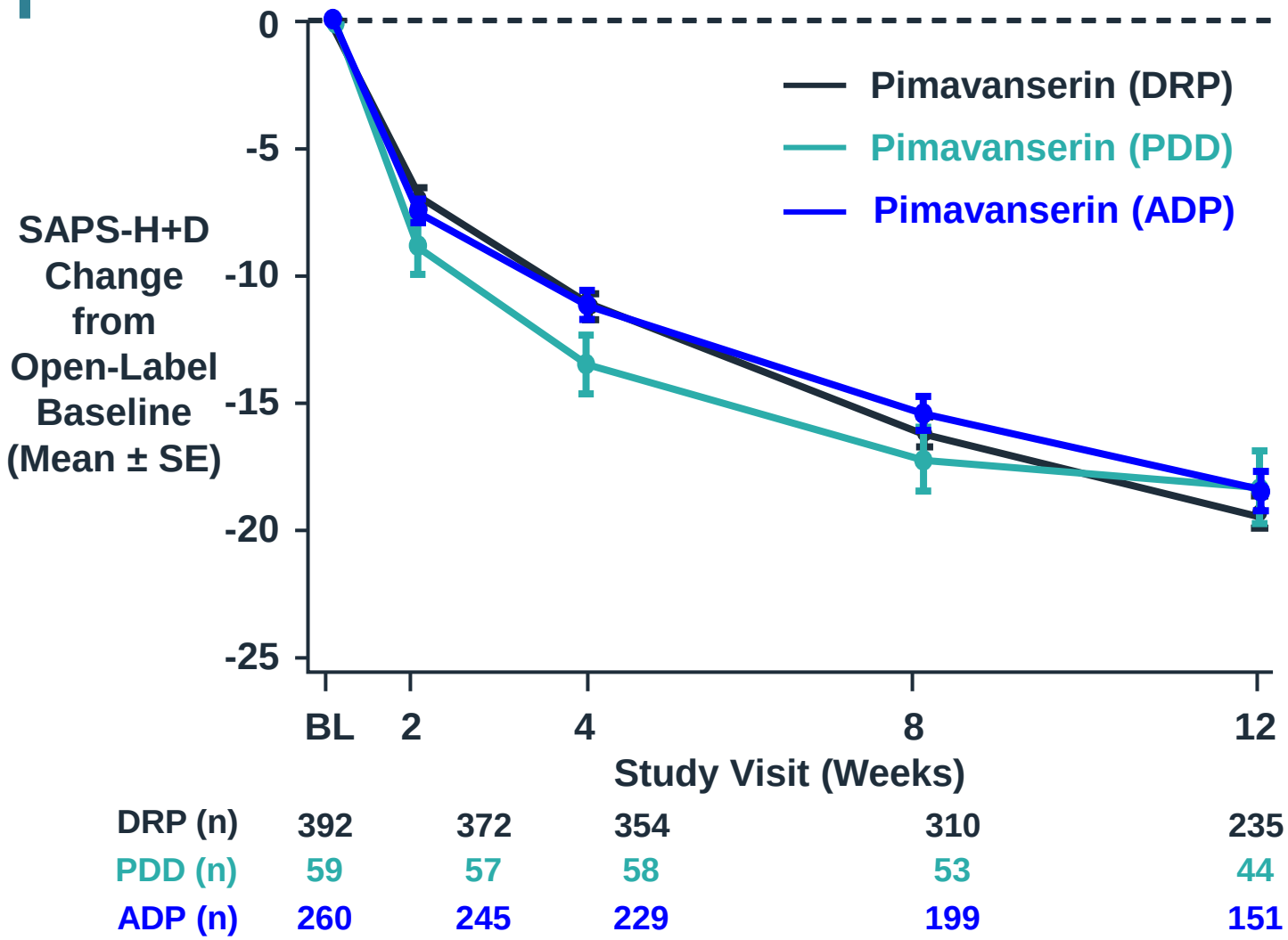
Study 045: Primary Endpoint and Statistical Analysis Plan

- Primary endpoint: time from randomization to relapse of psychosis in double-blind period
- Prespecified interim efficacy analysis (after 40 relapses) with stopping criteria
  - One-sided p-value less than O'Brien-Fleming stopping boundary of alpha = 0.0033
- All analyses prespecified for full analysis set in all DRP patients

Study 045: Study Population – Psychosis in Patients with Dementia

Baseline Characteristics	Open-Label Period N=392	Double-Blind Period	
		Pimavanserin N=105	Placebo N=112
Age (years), mean	75	74	75
Female, %	58%	59%	62%
White, %	97%	98%	98%
ADP Subgroup, %	66%	64%	63%
SAPS-H+D, mean	24.4	5.0	5.2
MMSE, mean	16.7	18.3	17.9

Study 045: Improvement in Psychosis Symptoms During Open-Label Period



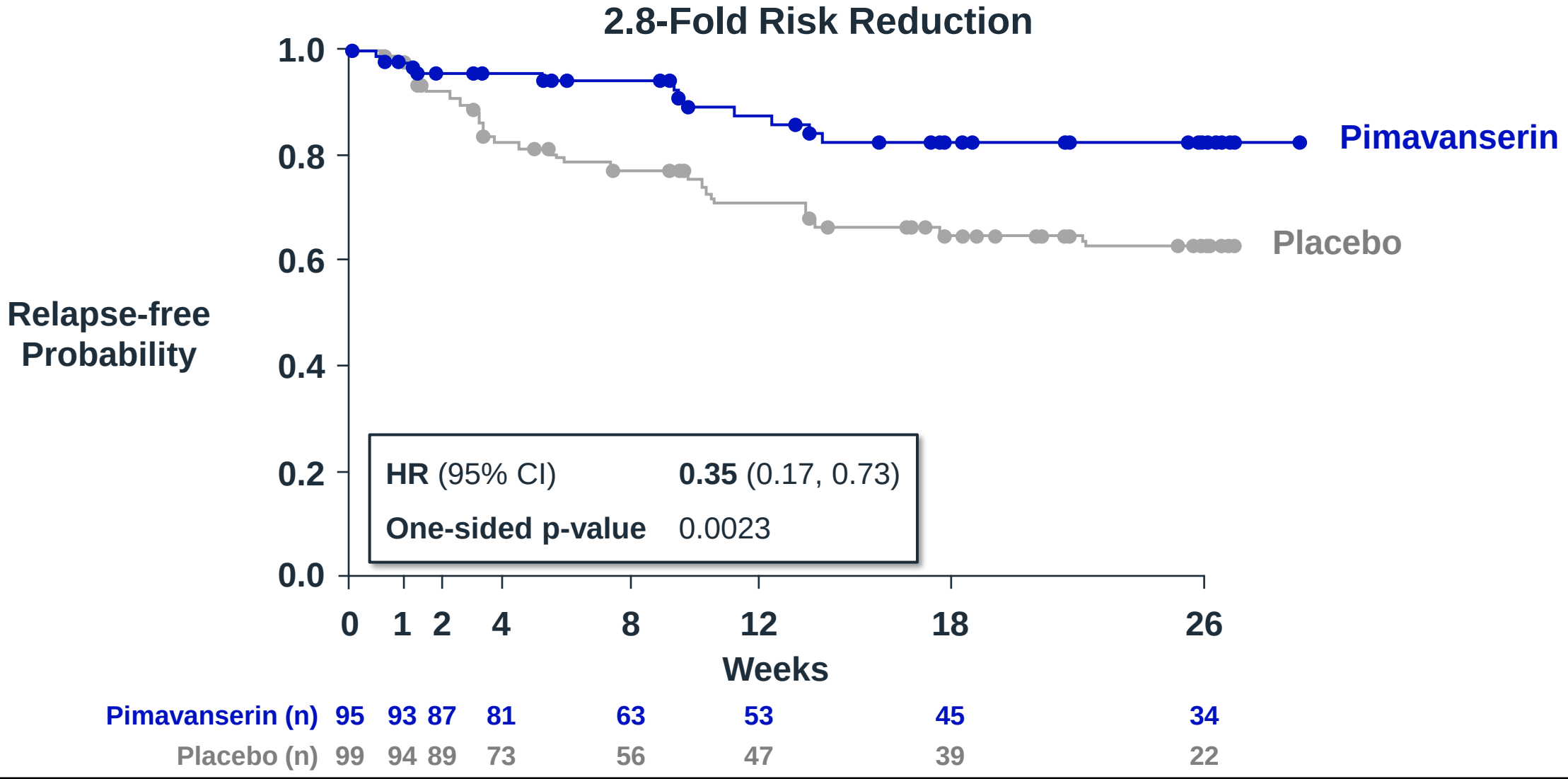
	OL Period Sustained Response Rate at Weeks 8 and 12	
	%	n / N
DRP	62%	217 / 351
PDD	71%	42 / 59
ADP	60%	137 / 229

At week 12:
21% (DRP) / 27% (PDD) / 19% (ADP) complete response to pimavanserin

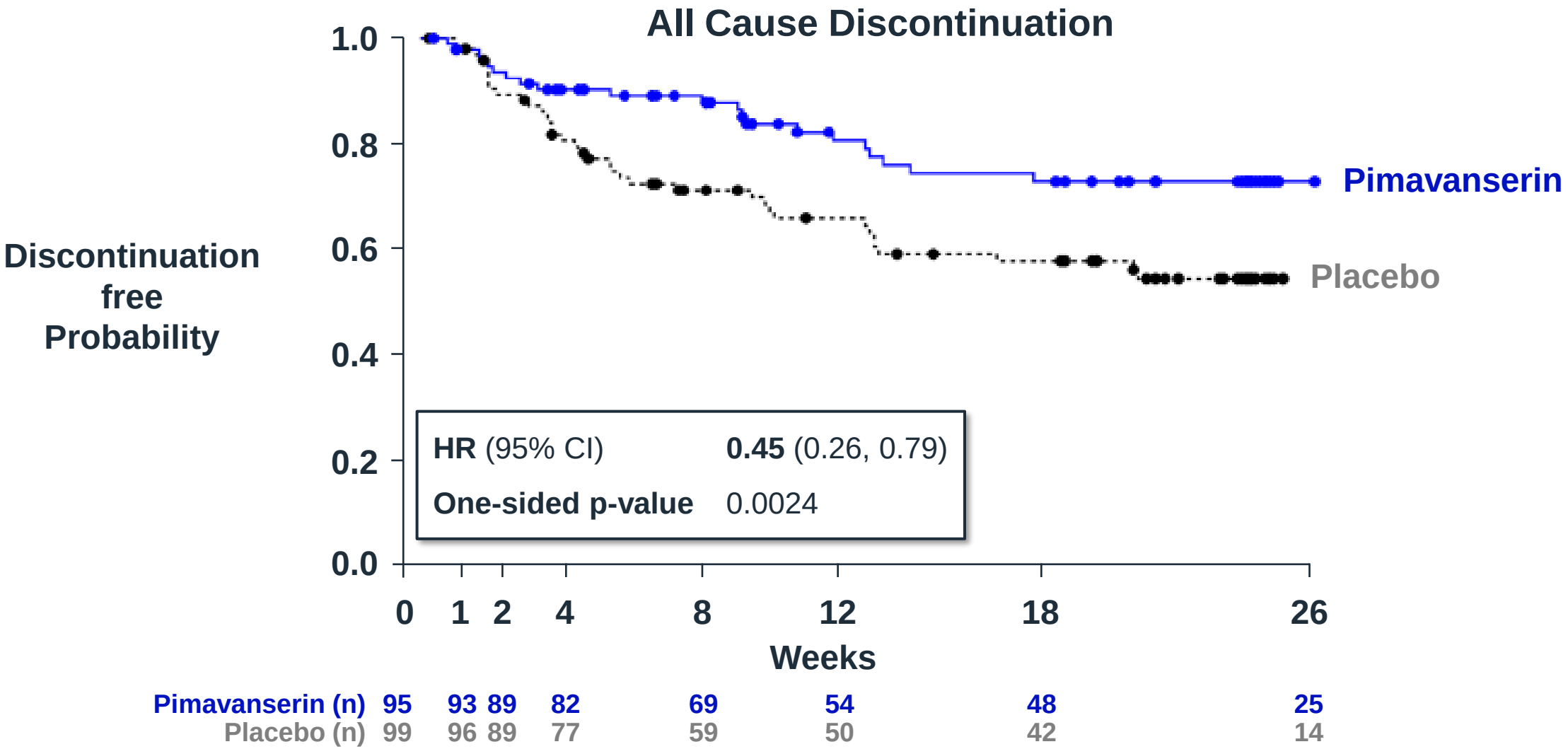
SAPS-H+D: Scale for the Assessment of Positive Symptoms-hallucinations and delusions subscales

PDD = Parkinson's Disease Dementia

Study 045: Positive Results on Primary Endpoint in DRP

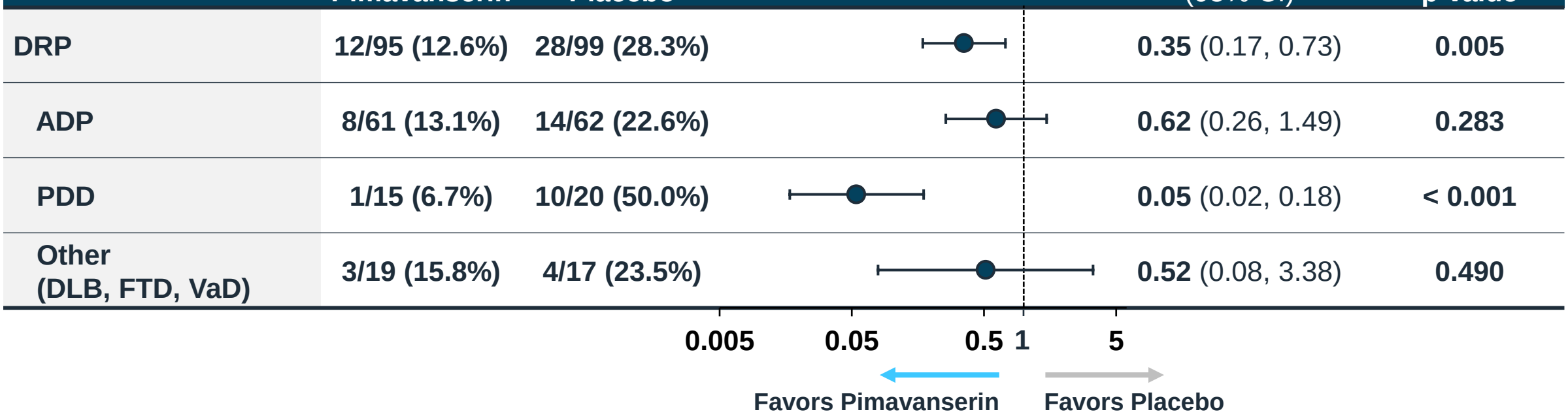


Study 045: Positive Results on Key Secondary Endpoint in DRP

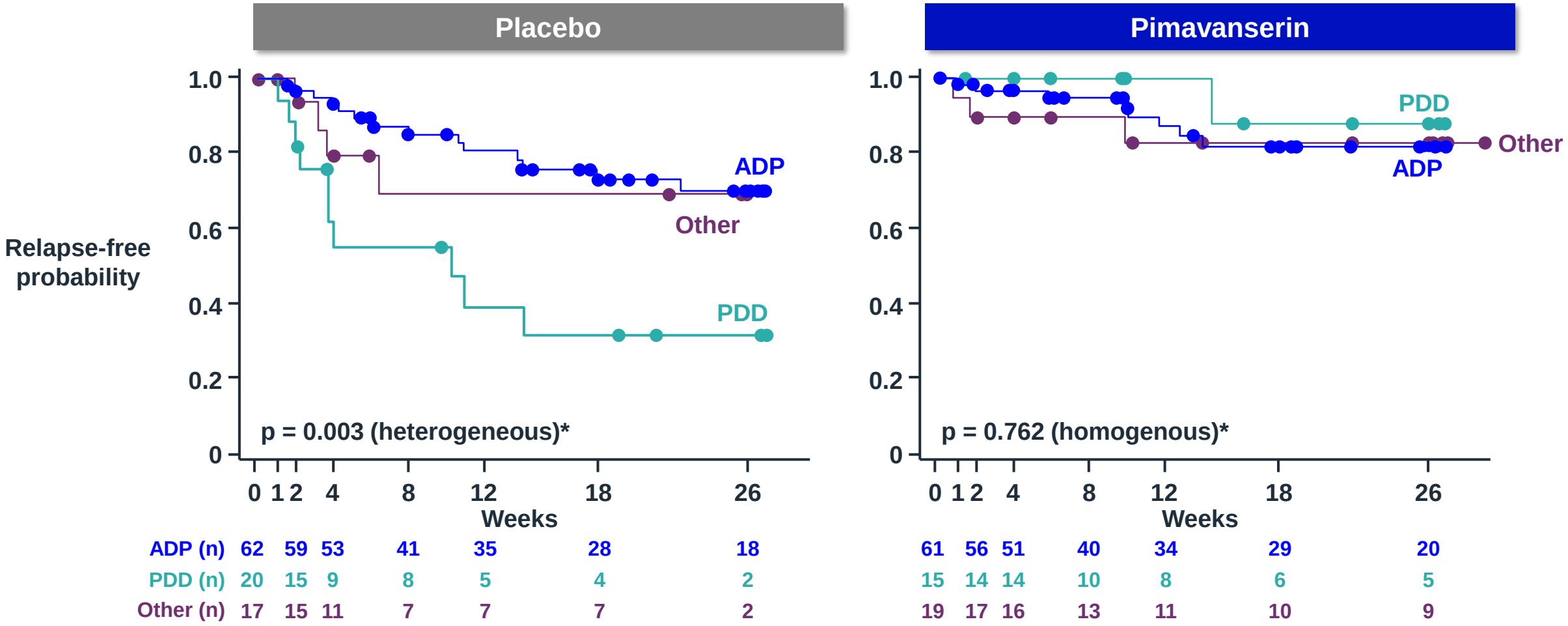


Study 045: Exploratory Efficacy by Dementia Subgroup in Double-Blind Period

	Events, n/N (%)		HR (95% CI)	Two-sided p-value
	Pimavanserin	Placebo		
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%)	**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**



Study 045: Faster Relapse in Placebo Group After Withdrawal of Pimavanserin for PDD



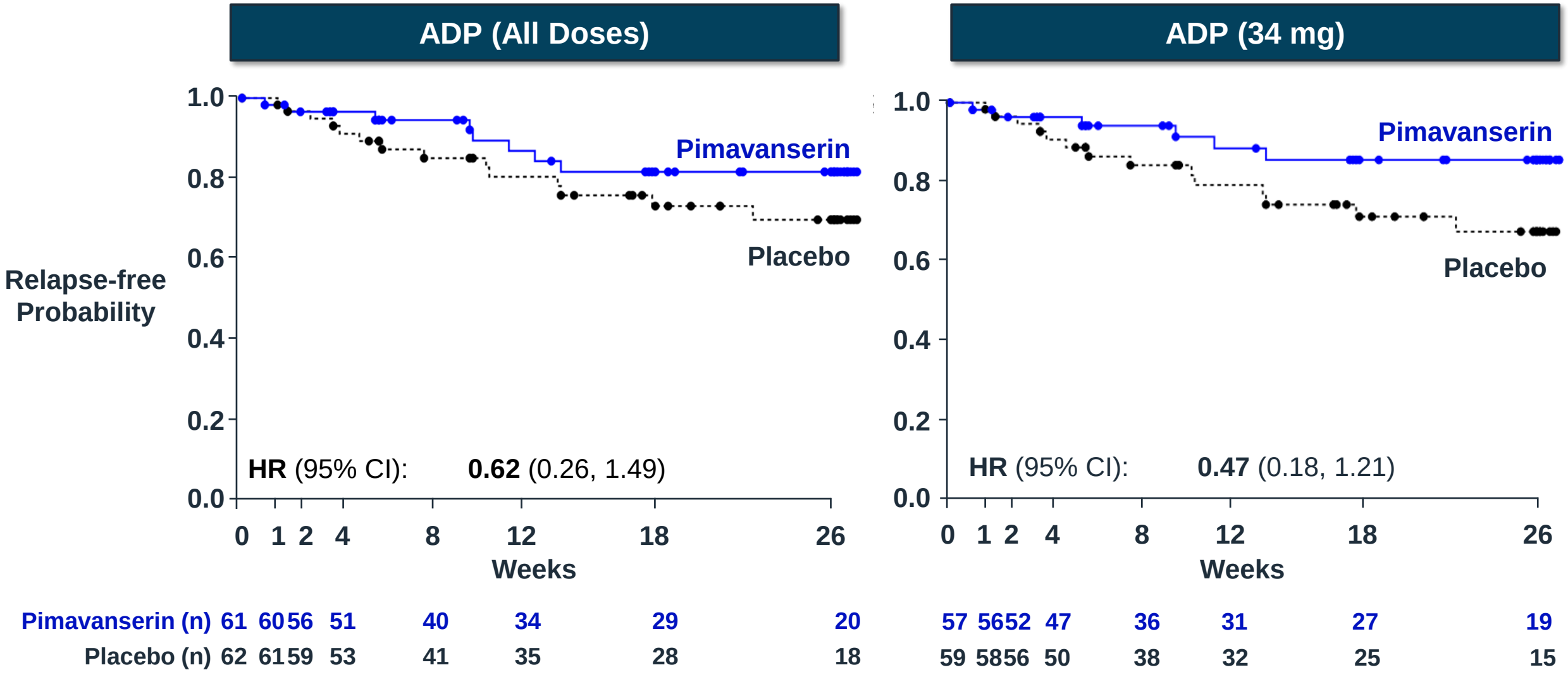
*Test of homogeneity of relapse-free survival curves; Other = DLB, FTD, and VaD combined subgroup

Study 045: Additional Analyses Supporting Efficacy in ADP

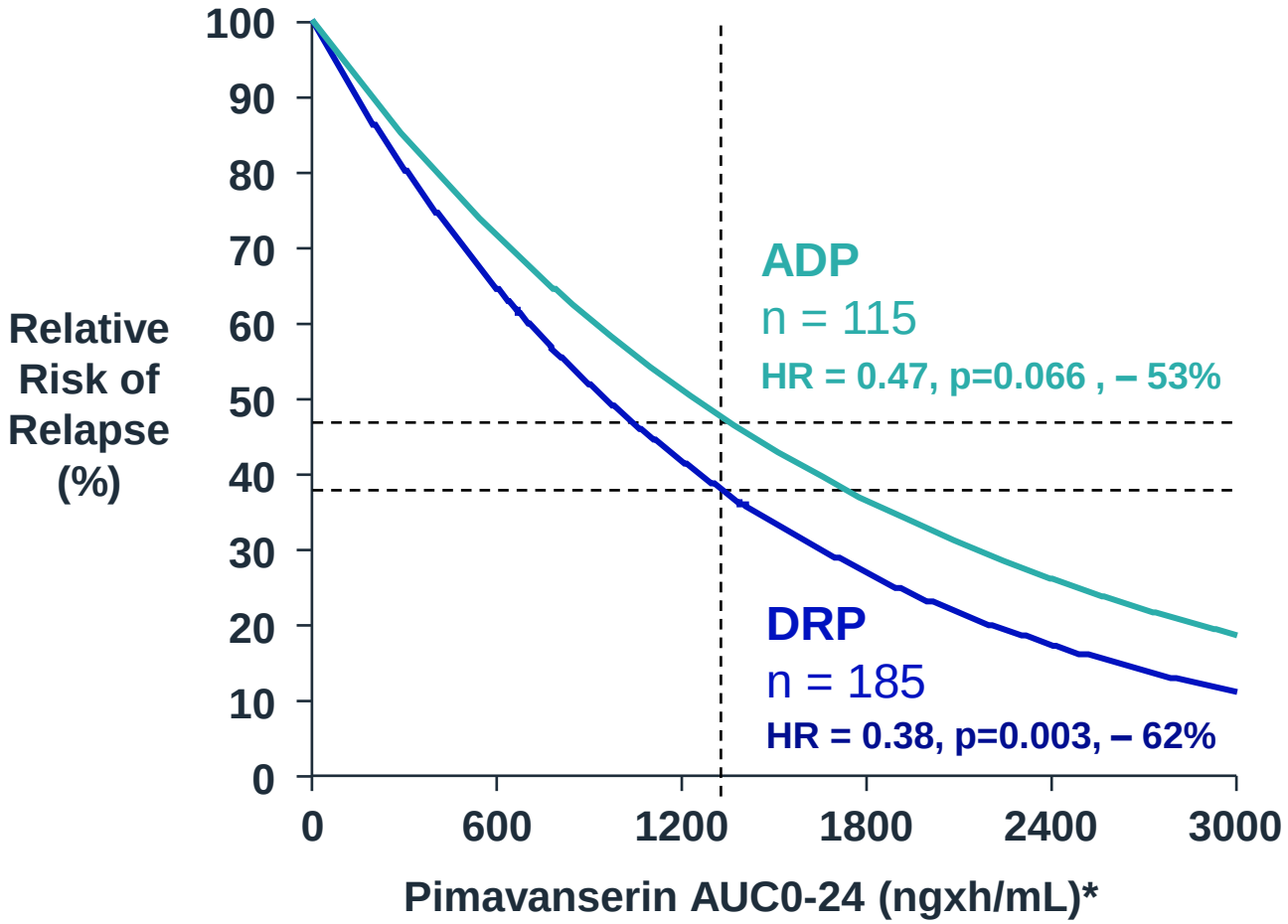
Pimavanserin 34 mg Recommended Dose for Patients with ADP

- Studies 019, 020 assessed only 34 mg
- 34 mg approved dose for PDP
- Study 045
  - During open-label period, 94% of stabilized patients received 34 mg
  - During double-blind period, patients randomized to continue stabilized dose (e.g., 34 mg) or matching placebo

Study 045: Patients with ADP Showed Clinically Meaningful Reduction in Risk of Relapse

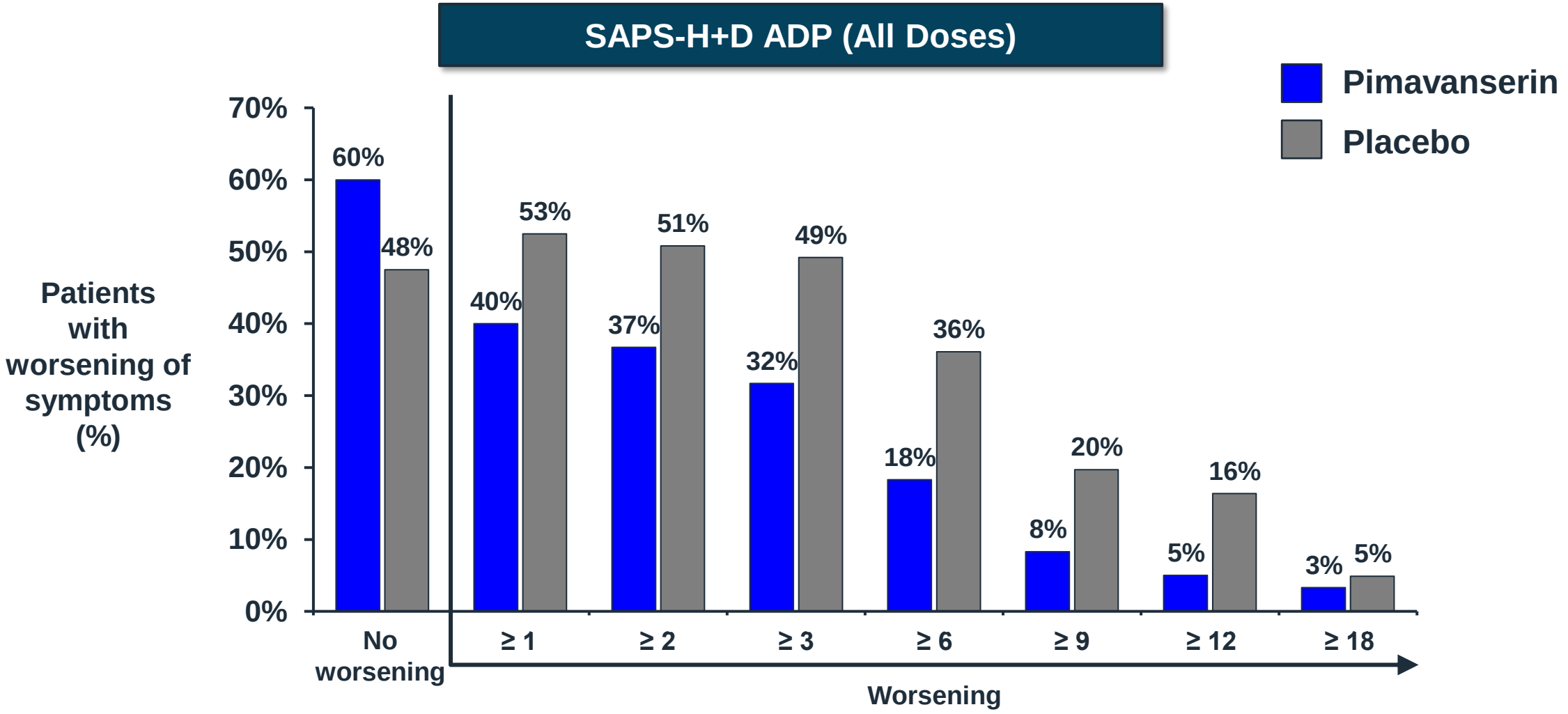


Study 045: Exposure-Response for ADP

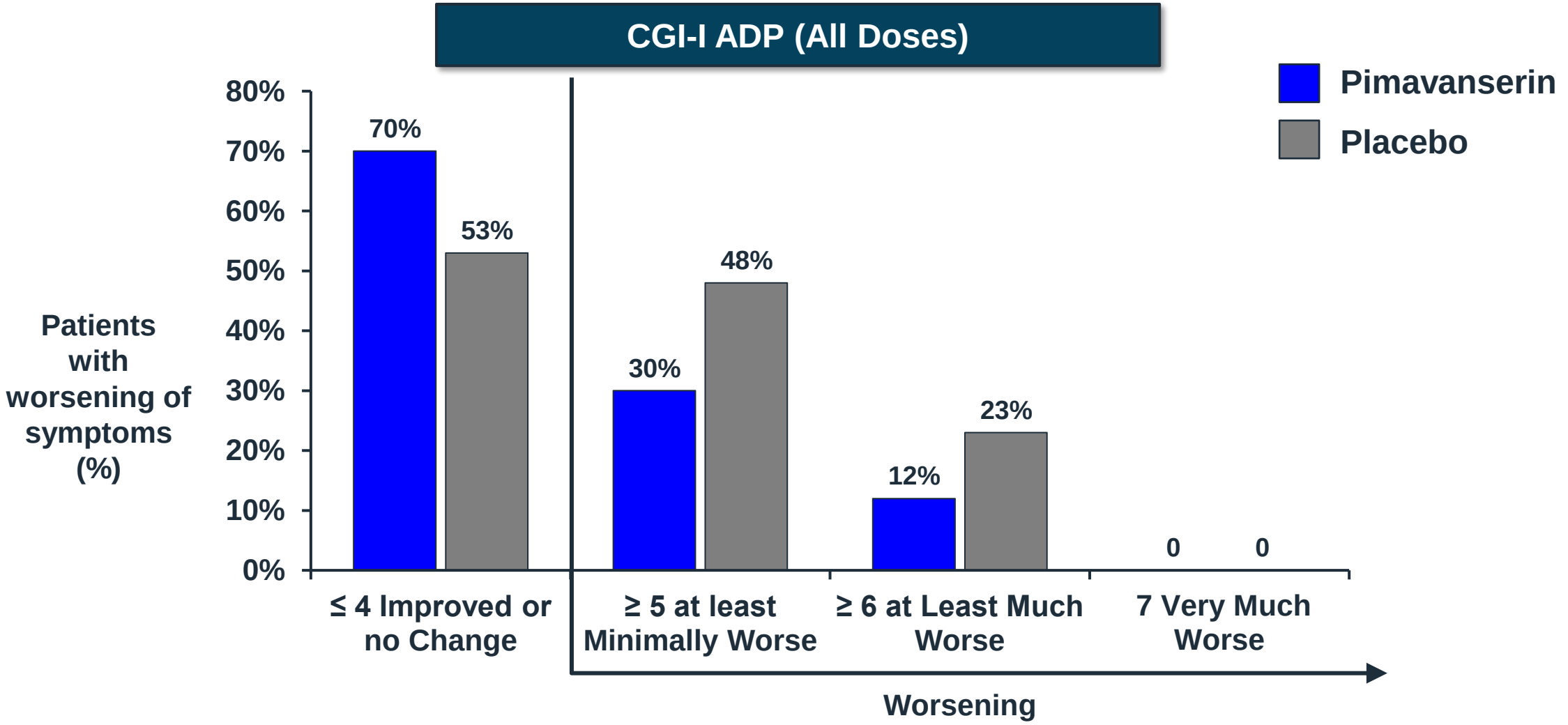


* AUC_{0-24} based on sparse PK samples and Bayesian estimates

Study 045: Pimavanserin Reduces Symptom Recurrence Compared to Placebo Following Randomization

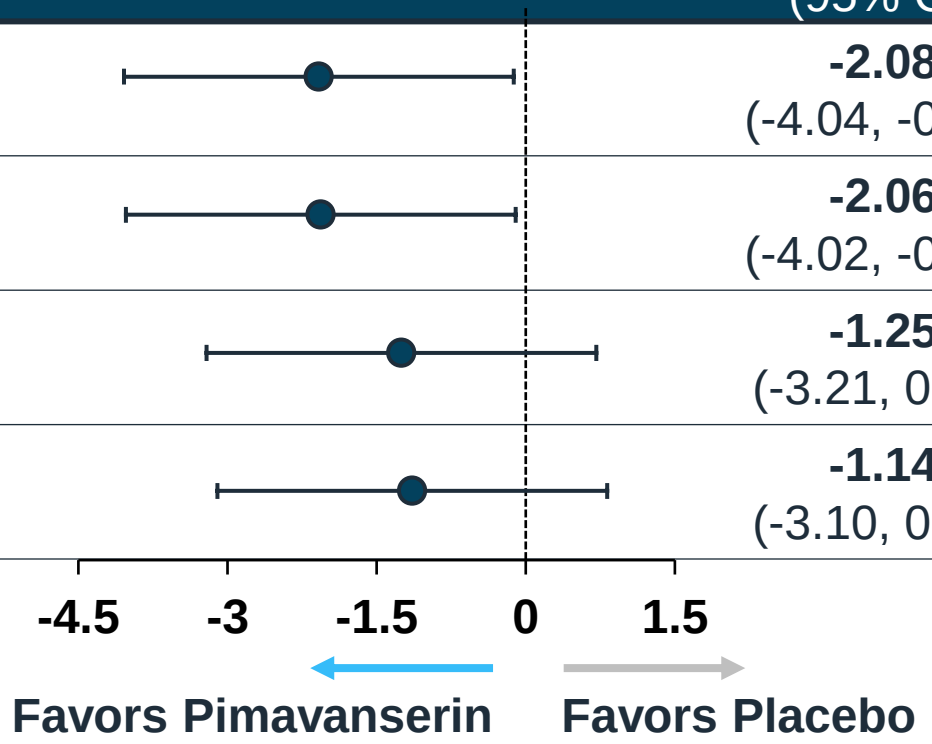


Study 045: Pimavanserin Reduces Symptom Recurrence Compared to Placebo Following Randomization



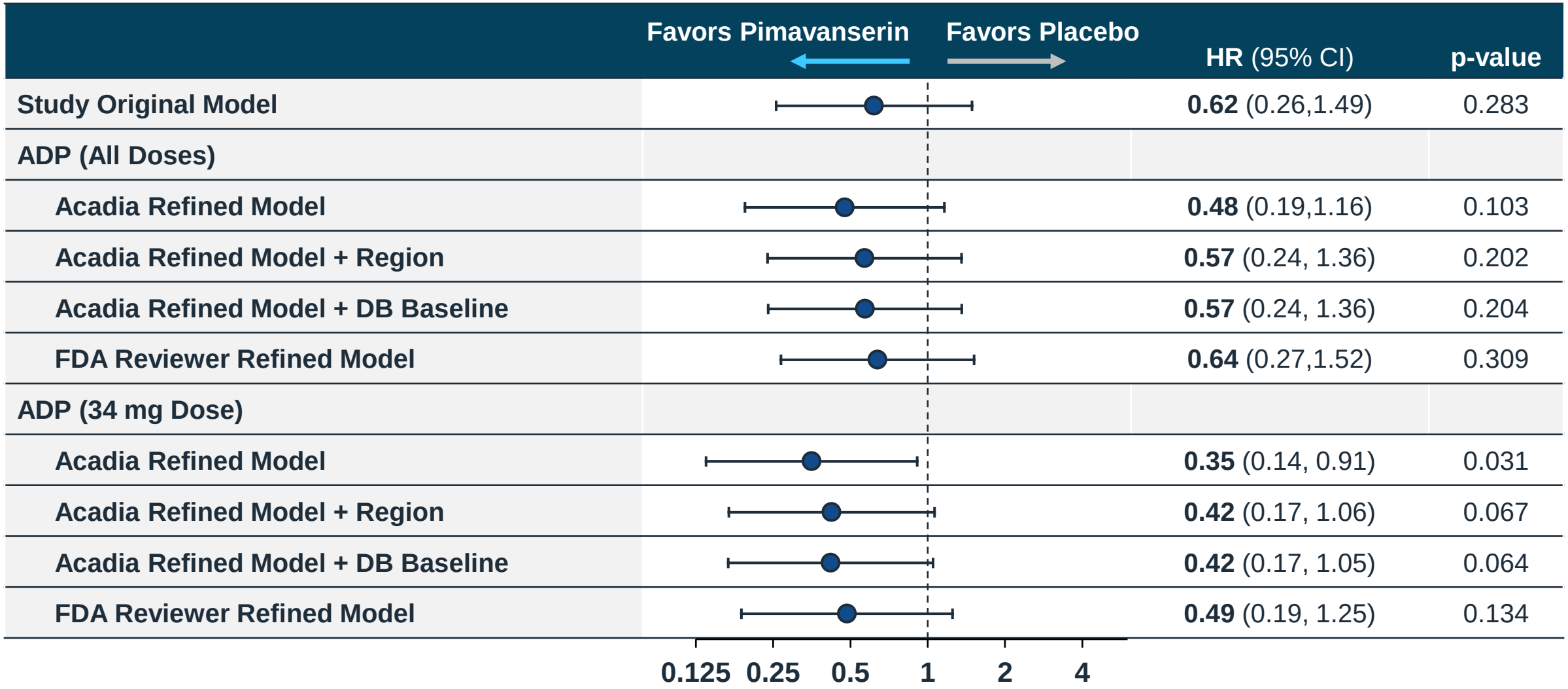
Study 045: Consistent Benefits Across Additional Efficacy Measures in ADP

ADP (All Doses)	N: Pimavanserin	N: Placebo	z-score (95% CI)	p-value
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



ZBI = Zarit Burden Inventory; EQ-5D-5L = QoL measure

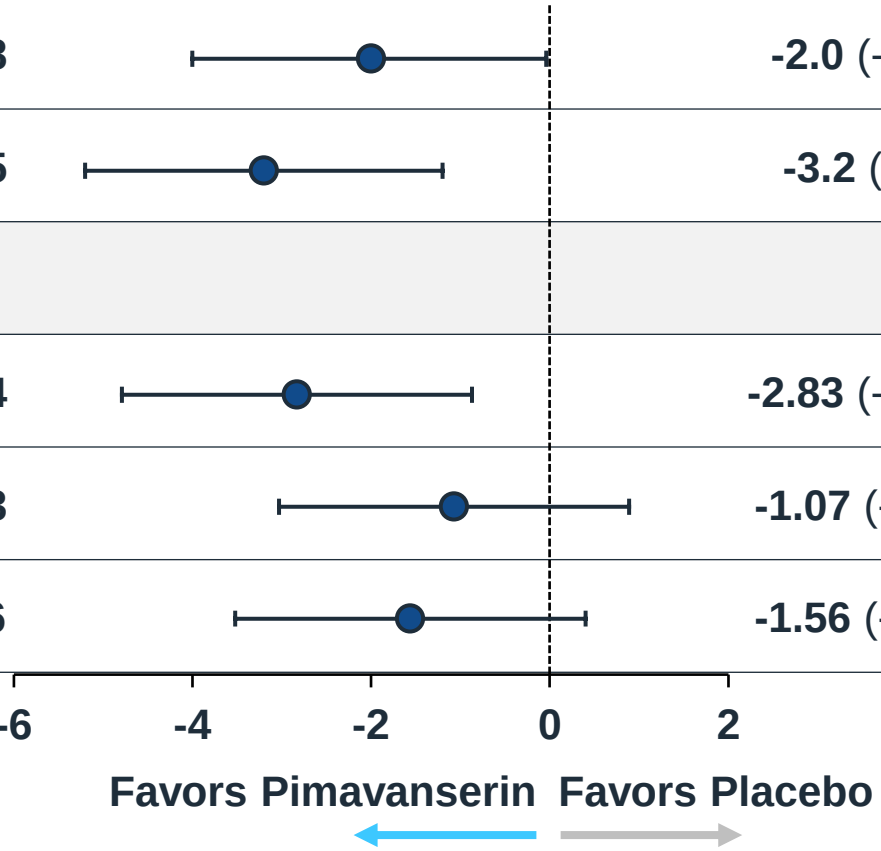
Study 045: Covariate Adjusted Cox Models for ADP Subgroup



	HR (95% CI)	p-value
Study Original Model	**0.62** (0.26,1.49)	0.283
ADP (All Doses)		
Acadia Refined Model	**0.48** (0.19,1.16)	0.103
Acadia Refined Model + Region	**0.57** (0.24, 1.36)	0.202
Acadia Refined Model + DB Baseline	**0.57** (0.24, 1.36)	0.204
FDA Reviewer Refined Model	**0.64** (0.27,1.52)	0.309
ADP (34 mg Dose)		
Acadia Refined Model	**0.35** (0.14, 0.91)	0.031
Acadia Refined Model + Region	**0.42** (0.17, 1.06)	0.067
Acadia Refined Model + DB Baseline	**0.42** (0.17, 1.05)	0.064
FDA Reviewer Refined Model	**0.49** (0.19, 1.25)	0.134

Consistent Evidence of Efficacy Across Studies

	n	z-score (95% CI)	p-value	Estimate (95% CI)
Study 019 ADP NPI-NH PS	**178**	**-2.0** (-4.0, -0.04)	**0.045**	-1.84 (-3.64, -0.04)
Study 020 PDP SAPS-PD	**185**	**-3.2** (-5.2, -1.2)	**0.001**	-3.06 (-4.91, -1.20)
Study 045 Time to Relapse				
DRP	**194**	**-2.83** (-4.79, -0.87)	**0.005**	0.35 (0.17, 0.73)
ADP (All Doses)	**123**	**-1.07** (-3.03, 0.89)	**0.283**	0.62 (0.26, 1.49)
ADP (34 mg)	**116**	**-1.56** (-3.52, 0.40)	**0.118**	0.47 (0.18, 1.21)



Estimates and p-values are from the primary analysis models in each study.

Safety Profile: Key Aspects

Mary Ellen Turner, MD, MPH

Senior Vice President, Pharmacovigilance and Corporate Safety Officer

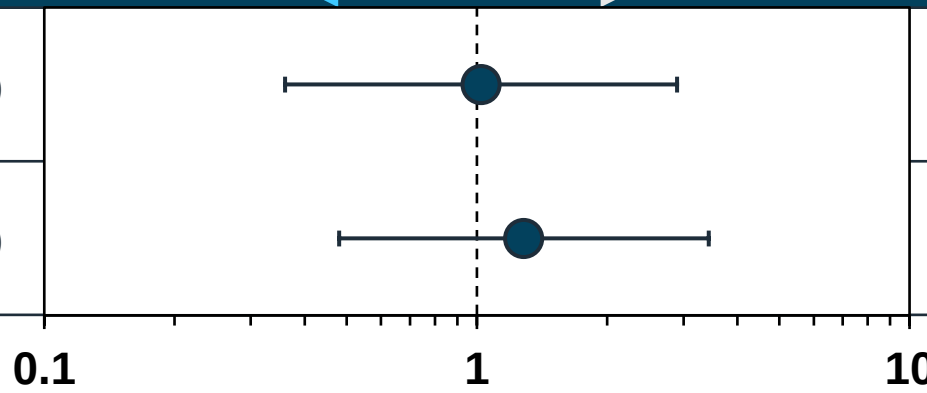
Acadia

Pimavanserin Has a Well-Characterized, Favorable Safety Profile (N=3,579)

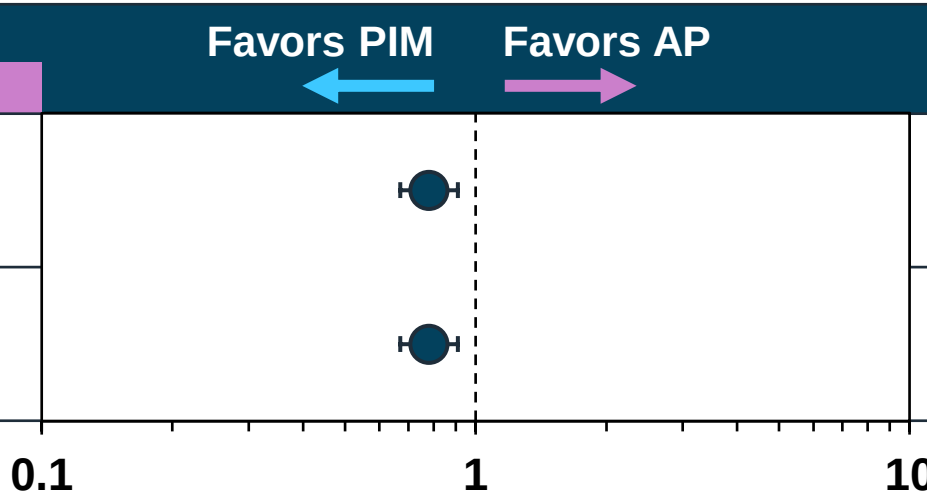
- Largest clinical program in patients with neurodegenerative disease (NDD) (N=1,502)
- > 6 years post-marketing experience (> 44,000 PDP patients)
- AD safety profile consistent with known safety profile
- Key safety and tolerability features differentiate pimavanserin from current standard of care
  - Reassuring mortality data
  - No negative impact on cognitive function
  - No negative impact on motor function

Mortality Data Across Placebo Controlled Trials and Real-World Evidence vs. Antipsychotics

NDD Pool	Events, % (n/N) PIM 34 mg	Events, % (n/N) Placebo	IRR (95% CI)
Deaths within 30 days of last treatment received	**1.2%** (7/580)	**1.1%** (7/649)	**1.02** (0.36, 2.90)
Deaths within study intended treatment period + 30 days	**1.6%** (9/580)	**1.2%** (8/649)	**1.28** (0.48, 3.43)



PDP	PIM	AP	HR (95% CI)
Mosholder, 2020[1]	N=3,227	N=3,251	**0.78** (0.67, 0.91)
Layton, 2022[2]	N=2,892	N=19,083	**0.78** (0.67, 0.91)

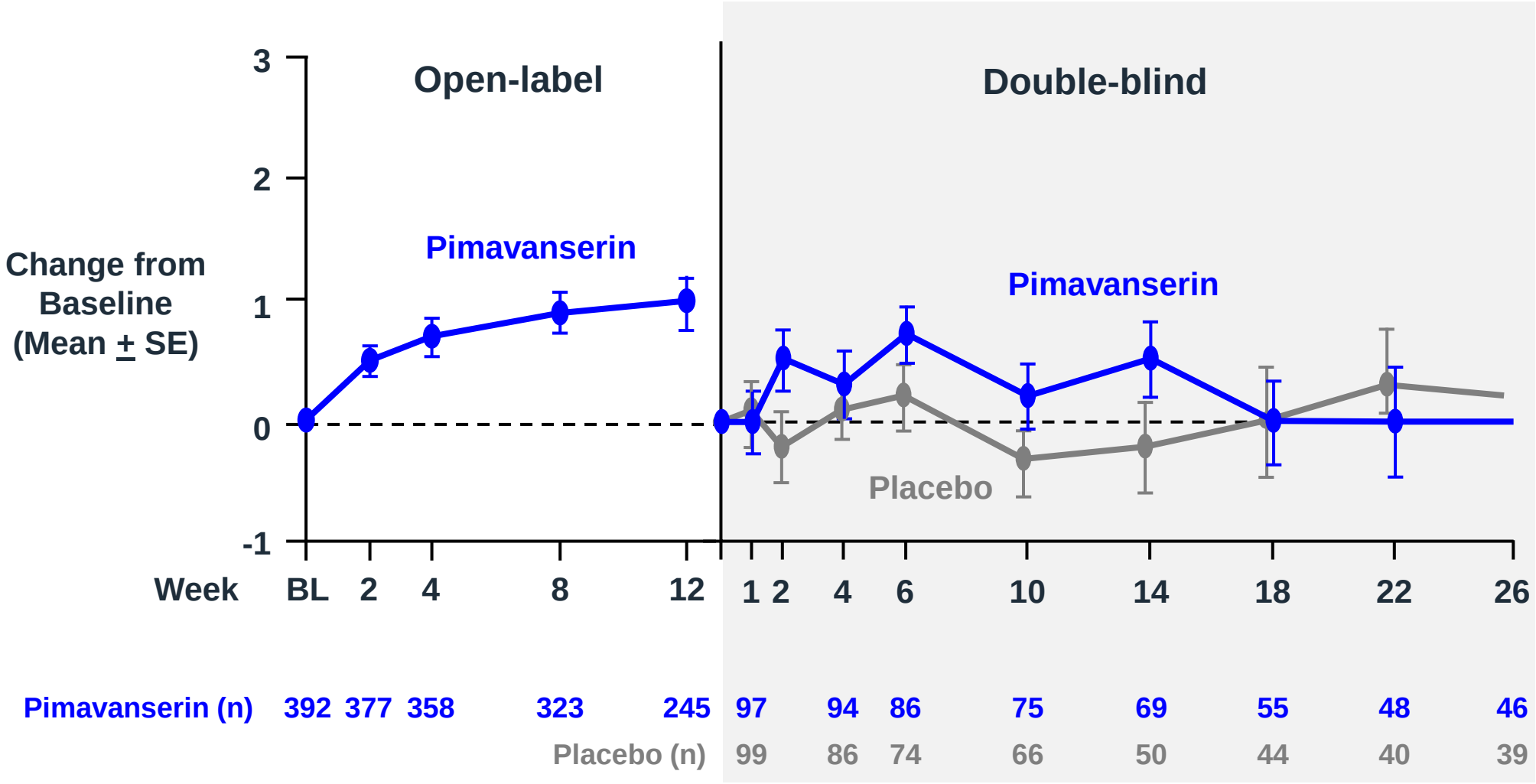


AP = Antipsychotics

1. Mosholder et al, Mov Disord. 2020;35(suppl S1):S469.
2. Layton et al, Presentation at ASCP, 2022 and submitted to FDA by Acadia.

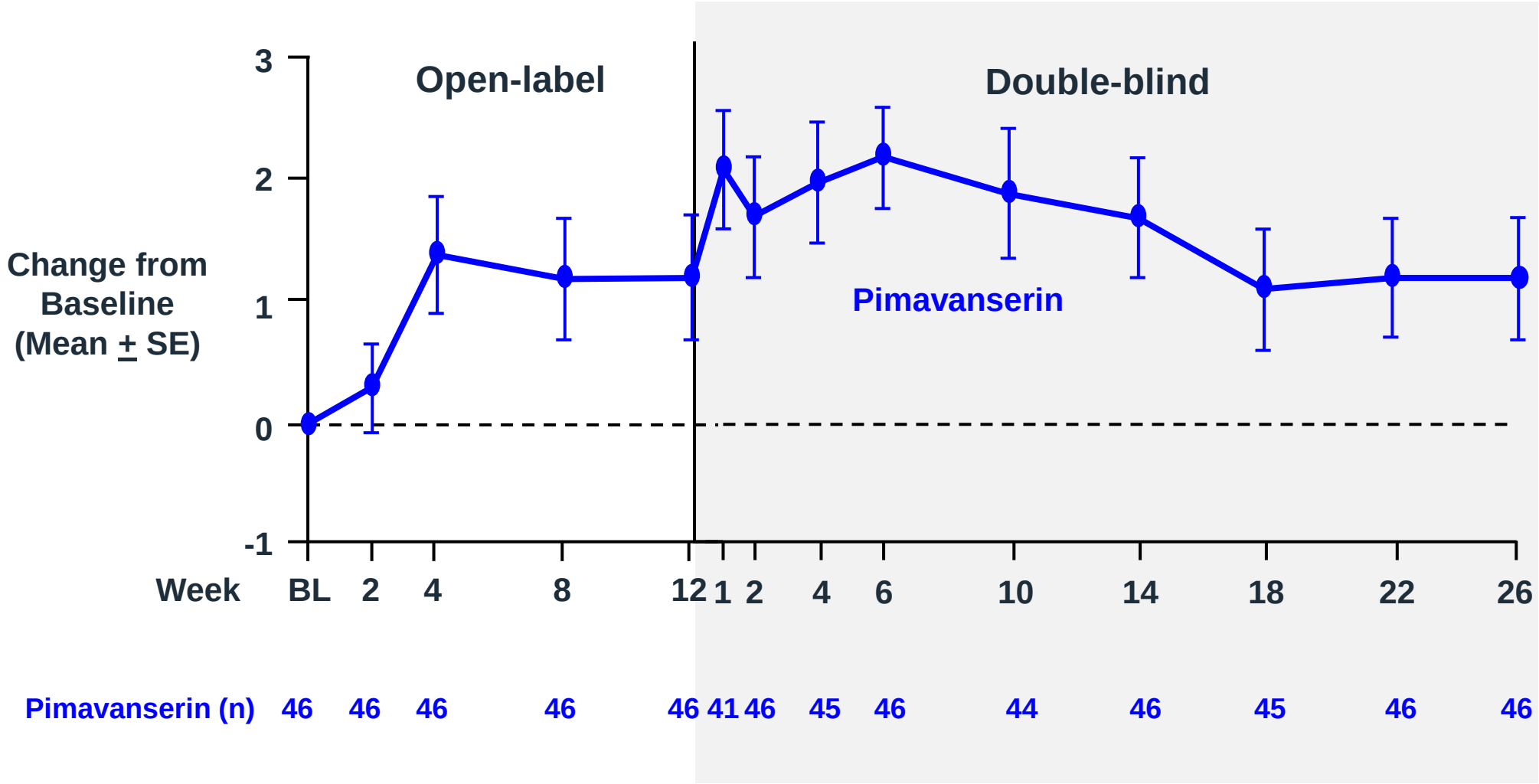
PIM = pimavanserin

Study 045: No Negative Impact on Cognitive Function Measured by MMSE



Patients with DRP

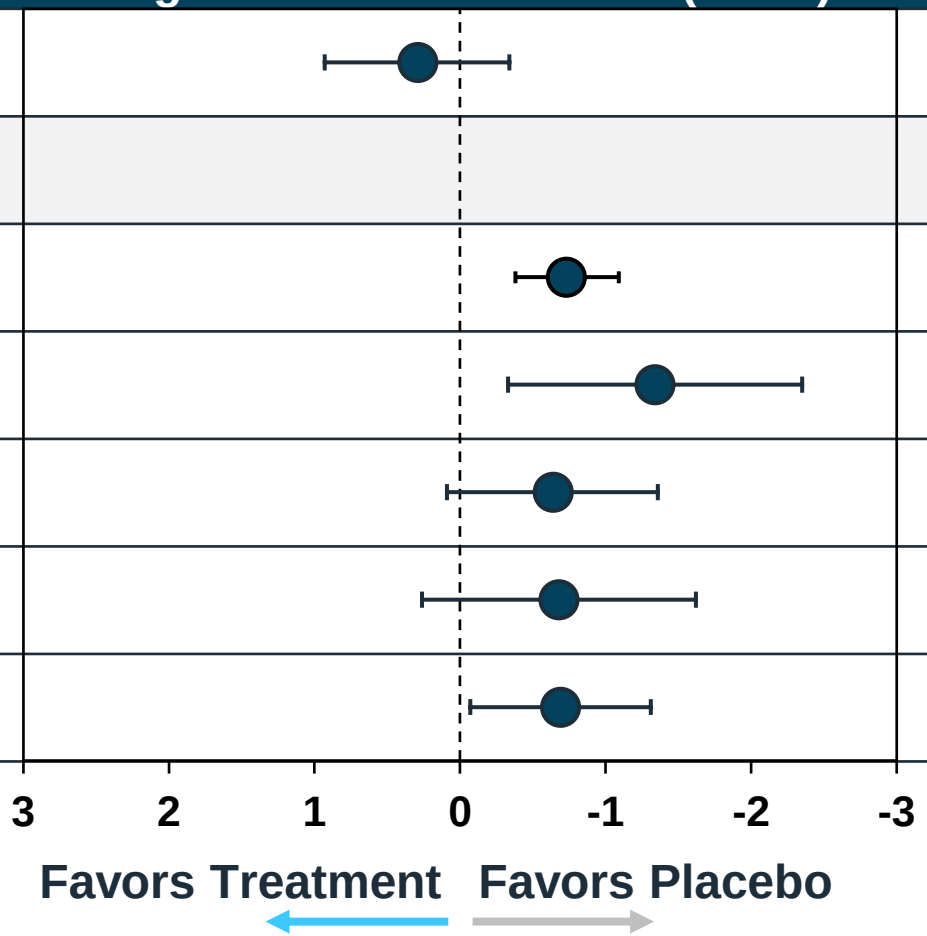
Study 045: No Negative Impact on Cognitive Function Measured by MMSE - Completers



Patients with DRP

No Negative Impact on Cognitive Function Measured by MMSE Compared to Other APs

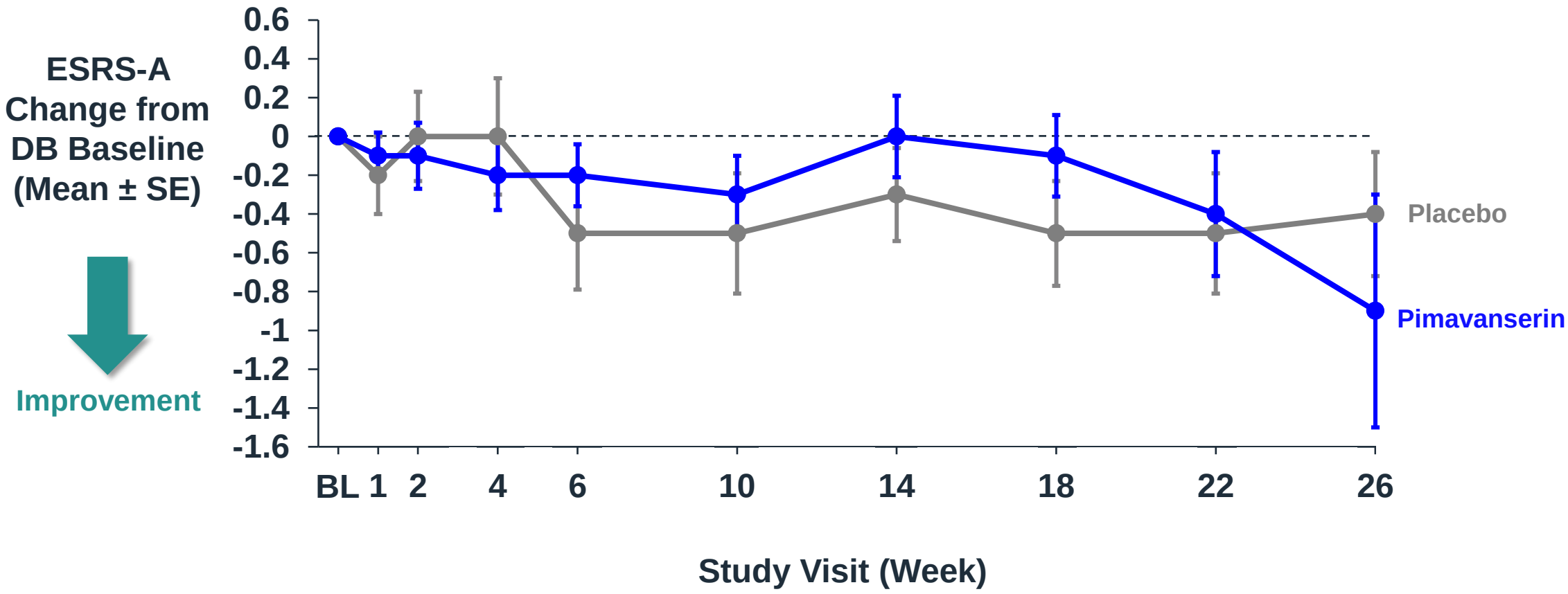
AD patients	Treatment (N)	Placebo (N)	WMD (95% CI)
Pimavanserin 34 mg	280	268	**0.29** (-0.34, 0.93)
Other antipsychotics[1]			
Total	950	614	**-0.73** (-1.09, -0.38)
Aripiprazole	87	82	**-1.34** (-2.35, -0.33)
Olanzapine	442	202	**-0.64** (-1.36, 0.09)
Quetiapine	124	125	**-0.68** (-1.62, 0.26)
Risperidone	297	205	**-0.69** (-1.31, -0.07)



APs = Antipsychotics

1. Schneider, 2006

Study 045: No Negative Impact on Motor Function Measured by ESRS-A



Pimavanserin (n)	104	93	93	91	84	74	70	56	47	44
Placebo (n)	112	96	104	84	74	66	51	44	39	38

ESRS-A = Extrapyramidal Symptom Rating Scale - Abbreviated

Conclusions

- Pimavanserin has well established, consistent, and favorable safety profile
- Profile is differentiated vs other antipsychotics
  - Reassuring mortality data
  - No negative impact on cognitive function
  - No negative impact on motor function

Benefit-Risk

Serge Stankovic, MD, MSPH

President

Acadia

ADP Presents Severe Unmet Medical Need

ADP has serious consequences

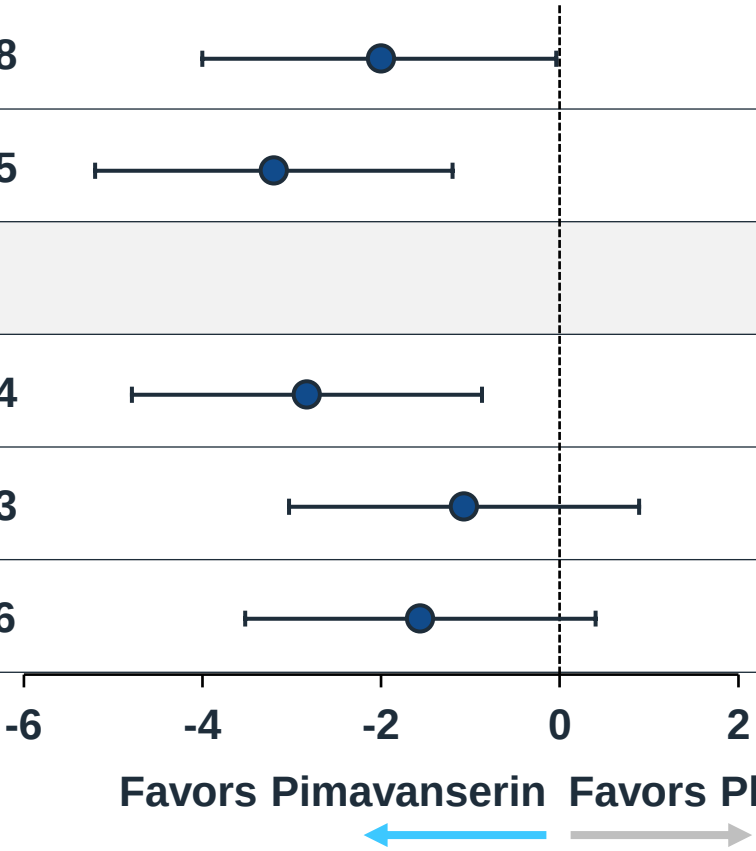
- Distress to patients and providers
- Acceleration of cognitive impairment
- Accelerated nursing home placement
- Increased morbidity and mortality

No approved treatment for ADP

- Off-label use of antipsychotics carry risks with little benefit
  - Marginal to no efficacy
  - Increased mortality
  - Cognitive worsening
  - Motor impairment

Significant and Meaningful Benefit Observed Across Multiple Studies

	n	z-score (95% CI)	p-value	Estimate (95% CI)
Study 019 ADP NPI-NH PS	**178**	**-2.0** (-4.0, -0.04)	**0.045**	-1.84 (-3.64, -0.04)
Study 020 PDP SAPS-PD	**185**	**-3.2** (-5.2, -1.2)	**0.001**	-3.06 (-4.91, -1.20)
Study 045 Time to Relapse				
DRP	**194**	**-2.83** (-4.79, -0.87)	**0.005**	0.35 (0.17, 0.73)
ADP All Doses	**123**	**-1.07** (-3.03, 0.89)	**0.283**	0.62 (0.26, 1.49)
ADP 34 mg	**116**	**-1.56** (-3.52, 0.40)	**0.118**	0.47 (0.18, 1.21)



Estimates and p-values are from the primary analysis models in each study.

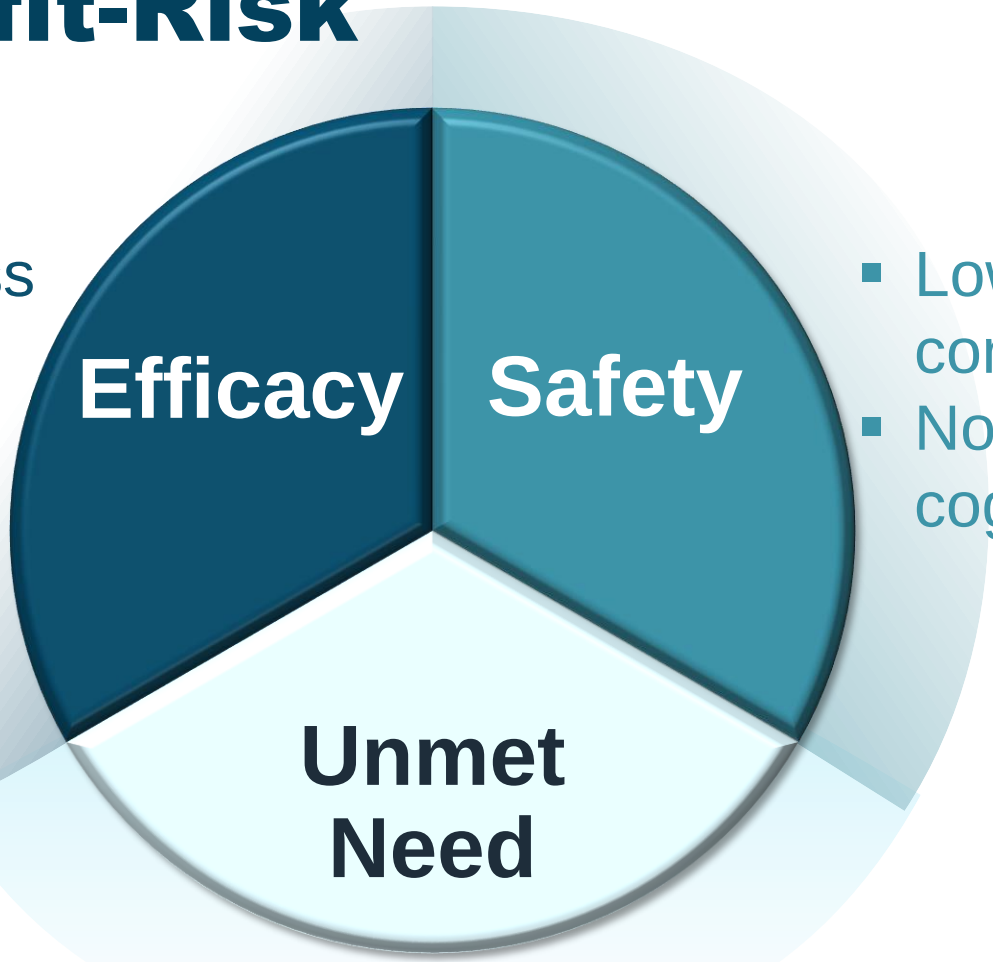
Evidence of Effectiveness of Pimavanserin in ADP

- FDA guidance[1]: “One adequate and well-controlled clinical investigation on a new indication for an approved drug, supported by existing adequate and well-controlled clinical investigation(s) that demonstrated the effectiveness of the drug for its other, closely related approved indication(s).”
- Positive Study 019 in target indication of ADP
  - Confirmatory evidence from positive Study 020 in closely related indication of PDP
  - Supportive data from positive Study 045 in closely related condition of DRP
    - Additional analyses in ADP subgroup consistent
- Pimavanserin meets standard for evidence of effectiveness in ADP

1. FDA Guidance 2019

Pimavanserin for Treatment of ADP: Positive Benefit-Risk

- Consistent results across studies and endpoints
- Clinically meaningful reduction of psychotic symptoms and prevention of relapse



- Lower mortality rates compared to off-label APs
- No negative effect on cognition or motor function

- Serious consequences of ADP
- No approved treatments
- Off-label use of antipsychotics carry risks

NUPLAZID® (pimavanserin) Treatment of Alzheimer's Disease Psychosis

Acadia Pharmaceuticals Inc. (Acadia)

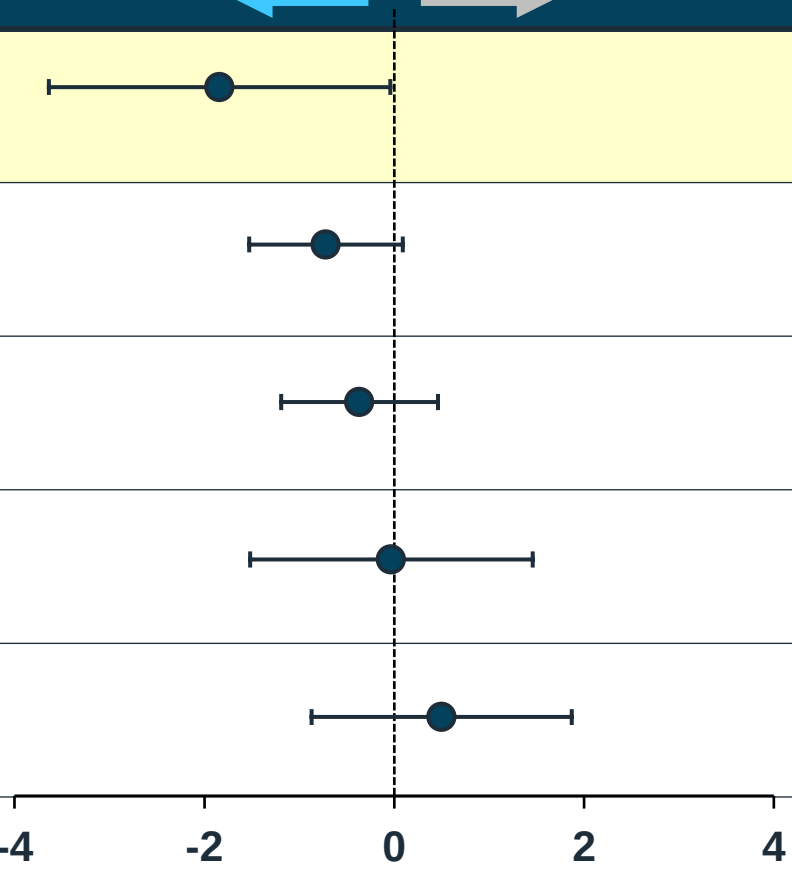
Psychopharmacologic Drugs Advisory Committee

17 June 2022

Q&A Slides Shown

Effect on Dementia Psychosis with Pimavanserin and Available APs (NPI Scales)

Drug Psychosis Scale	Drug N	PBO N	WMD (95% CI)	p-value	Effect size
Pimavanserin NPI-NH PS	**76**	**81**	**-1.84** (-3.64, -0.04)	**0.05**	**0.32**
Arpipiprazole[1] NPI Psy	**588**	**338**	**-0.72** (-1.53, 0.09)	**0.08**	**0.12**
Olanzapine[1] NPI Psy	**861**	**265**	**-0.37** (-1.19, 0.46)	**0.38**	**0.06**
Quetiapine[1] NPI Psy	**124**	**125**	**-0.03** (-1.52, 1.46)	**0.97**	**0.01**
Risperidone[1] NPI Psy	**190**	**91**	**0.50** (-0.87, 1.87)	**0.47**	**Negative**



Pimavanserin Study 019

1. Schneider, 2006

APs = Antipsychotics; WMD = Weighted Mean Difference

Study 020: Consistent Efficacy Across All Measures and Perspectives

	Measure	LSM Treatment Δ	Effect Size[1]	p-value
Primary	SAPS-PD	-3.06	0.50	0.001
Secondary	CGI-I	-0.67	0.51	0.001
	CGI-S	-0.58	0.52	<0.001
Exploratory	Zarit Caregiver Burden	-4.34	0.50	0.002
	SCOPA-Night	-0.93	0.31	0.045
	SCOPA-Night Global	-0.16	0.12	NS
	SCOPA-Day	-1.22	0.39	0.012
Additional	SAPS-H+D	-3.37	0.50	0.001
	SAPS-H	-2.08	0.45	0.003
	SAPS-D	-1.16	0.33	0.033

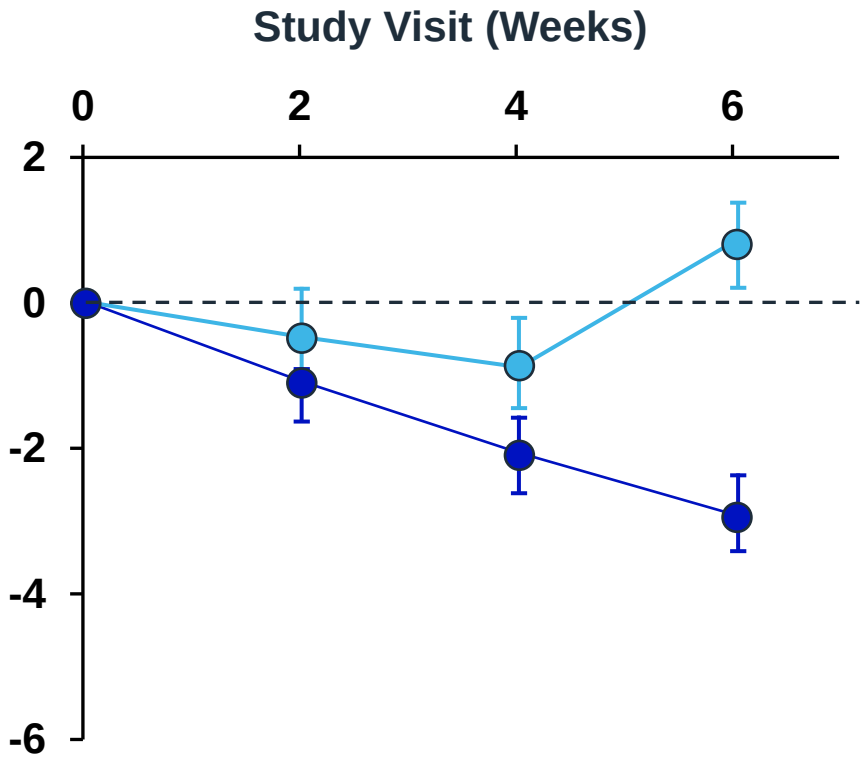
1. Cohen's *d*

Race / Ethnicity in AD in Double-Blind, Placebo-Controlled, Parallel-Group Studies

(ACP-103-019, -032, -046IA)

		All Pimavanserin N=322	Placebo N=279
Race	White	298 (92.5%)	261 (93.5%)
	Black or African American	6 (1.9%)	6 (2.2%)
	Asian	5 (1.6%)	- -
	American Indian or Alaska Native	- -	- -
	Native Hawaiian or Other Pacific Islander	- -	- -
	Other	13 (4.0%)	12 (4.3%)
Ethnicity	Hispanic or Latino	81 (25.2%)	64 (22.9%)
	Not Hispanic or Latino	241 (74.8%)	215 (77.1%)

Study 019: Changes in Agitation and Aggression Symptoms Among Psychosis Responders vs Non-responders



Psychosis Responders	44	43	44	44
Psychosis Non-responders	32	31	31	32

Ballard et al, 2020

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)

Study 019 Protocol Finalized Before Database Lock

- No changes to the primary outcome measure or timepoint
  - 2010: Protocol approved
  - 26 July 2013: Amendment 1
  - 24 Jan 2014: Amendment 2
  - 16 Nov 2015: Amendment 3
  - 5 July 2016: SAP Approved
  - 2 Dec 2016: Database lock
  - 5 Dec 2016: Data unblinded

Study 045 OL Period: Response at Week 2, 4, and 8 in Patients Not Randomized to DB