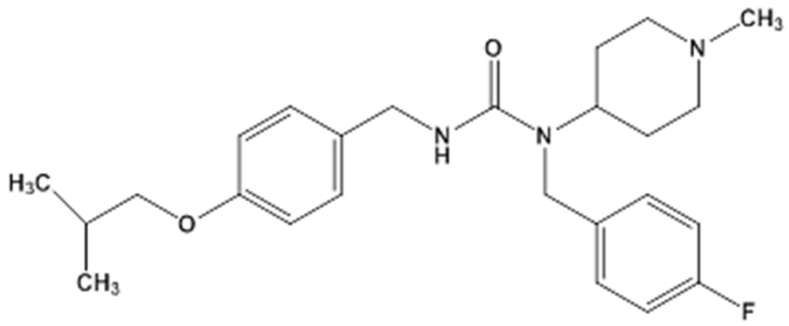


NUPLAZID™ (pimavanserin)

ACADIA Pharmaceuticals Inc.
March 29, 2016

Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration

NUPLAZID (pimavanserin) for the Treatment of Parkinson's Disease Psychosis

Michael Monahan

Director, Regulatory Affairs
ACADIA Pharmaceuticals Inc.

NUPLAZID (pimavanserin) Proposed Indication and Usage

NUPLAZID is indicated for the treatment of psychosis associated with Parkinson's disease

Parkinson's disease psychosis (PDP) is characterized by hallucinations and/or delusions that develop after diagnosis of Parkinson's disease and cannot be attributed to other causes

Recommended dose: 34 mg pimavanserin

Pimavanserin
Novel Approach to Treating Psychosis

- Selective and potent 5-HT_{2A} inverse agonist
- No dopaminergic, histaminergic, adrenergic, or muscarinic activity
- First anti-psychotic without dopamine blockade
- No negative impact on motor symptoms

Pimavanserin Regulatory History

- Agreements with FDA
  - SAPS-H+D – early development psychosis measure
  - UPDRS Parts II+III – key safety assessment
  - Study 020 design – PD-specific SAPS scale
  - NDA submission – Study 020 with supportive data
- Breakthrough Therapy Designation
- Priority Review

Pimavanserin Development Program

- 25 clinical studies
- Four placebo-controlled studies PDP subjects
  - Initial Phase 2 proof-of-concept Study 006
  - Phase 2b/3 Studies 012 and 014
  - Phase 3 Study 020
- Two open-label extension studies
- Over 1200 pimavanserin subjects
  - 616 Parkinson's disease psychosis subjects
  - 498 subjects in long-term extension studies
    - 250 subjects treated for >1 year and 170 >2 years

Pimavanserin
Positive Risk/Benefit Profile

- Progressive, debilitating condition with serious consequences for patients and caregivers
  - No FDA-approved treatment
- Antipsychotic efficacy demonstrated
  - Consistent meaningful improvement across multiple measures and perspectives
- Safety and tolerability evaluated
  - Observed imbalance in SAEs and deaths
  - No unifying pathophysiologic process
  - Consistent with risk factors associated with PD psychosis and medical comorbidities
- Important advancement in treatment of PD psychosis

Agenda

Introduction	Michael Monahan Director, Regulatory Affairs ACADIA Pharmaceuticals Inc.
Burden of PD Psychosis and Need for Additional Treatment Options	Stuart Isaacson, MD Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL
Efficacy of Pimavanserin	Serge Stankovic, MD, MSPH Executive Vice President, R&D ACADIA Pharmaceuticals Inc.
Safety of Pimavanserin	George Demos, MD Executive Director, Drug Safety and Pharmacovigilance ACADIA Pharmaceuticals Inc.
Benefit/Risk Profile	Serge Stankovic, MD, MSPH Executive Vice President, R&D ACADIA Pharmaceuticals Inc.
Clinician Perspective	Clive Ballard, MB ChB, MRCPsych, MMedSci, MD Professor, Institute of Psychiatry King's College London, London, UK

Burden of PD Psychosis and Need for Additional Treatment Options

Stuart H. Isaacson, MD

Director, Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL

Parkinson's Disease: Second Most Common Neurodegenerative Disease of Aging

- **Cardinal motor symptoms reflect striatal-nigral dopaminergic degeneration[1-2]**
  - **Bradykinesia, rigidity, rest tremor, and balance**
- **Non-motor symptoms reflect widespread degeneration and neurotransmitter derangements[3-5]**
  - **Autonomic, enteric, sleep/wake, sensory, neuropsychiatric**
- **Progressive motor and nonmotor symptoms[5]**
  - **Impact QOL, ADL's, caregivers, morbidity, and mortality**

1. Langston JW. *Ann Neurol*. 2006;59:591-596. 2. Jankovic J. *J Neurol Neurosurg Psychiatry*. 2008;79:368-376. 3. Fernandez HH. *Cleve Clin J Med*. 2012;79 Suppl 2:S14-8. 4. Goldman JG, Holden S. *Curr Treat Options Neurol*. 2014;16(3):281. 5. Olanow CW, Stern MB, Sethi K. *Neurology*. 2009;72(Suppl 4):S1-S136.

PD Psychosis is Serious and Progressive

- **Increasing prevalence with disease progression, PD duration, and motor severity[1]**
  - **Estimated lifetime prevalence range of 25-60% of PD patients[1]**
- **Increases risk of morbidity and mortality[2-3]**
  - **Major reason for hospitalization and nursing placement[1]**
- **Probably reflects underlying serotonergic dysfunction[4]**
  - **Can persistent despite reducing dopaminergic therapy[5]**

1. Goldman JG, Holden S. *Curr Treat Options Neurol*. 2014;16(3):281. 2. Forsaa EB, et al. *Neurology* 2010; 75:1270-1276. 3. Weintraub D, et. al. *JAMA neurol.* 2016 (published online). 4. Ravina B, Marder K, Fernandez HH, et al. *Mov Disord.* 2007;22(8):1061-8. 5. Merims D, Shabtai H, Korczyn AD, Peretz C, Weizman N, Giladi N. J Neural Transm 2004;111: 1447–1453.

NIH 2005 Consensus Meeting

- **PD psychosis is a distinct indication[1,2]**
  - **Differs from psychosis in other disorders**
  - **Dopaminergic medications not sufficient, unclear if necessary**
- **Diagnostic Criteria for PD psychosis[1,2]**
  - **Hallucinations, delusions, illusions, false sense of presence**
  - **Psychotic symptoms >1 month and begin after PD diagnosis**
- **Suggested Rating Scales for PD psychosis[3,4]**
  - **SAPS, BPRS, NPI, PANSS; CGI as secondary outcome**
  - **Recommended development of new scale**

1. Ravina B, Marder K, Fernandez HH, et al. *Mov Disord.* 2007;22(8):1061-8. 2. Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. *Arch Neurol*. 2006 May;63(5):713-6. 3. Fernandez HH, et. al. *Mov Disord.* 2008;23(4):484-500. 4. Goetz CG. *Parkinsonism Relat Disord*. 2009;15 Suppl 3:S38-41.

Hallmark Symptoms of PD Psychosis

- **Hallucinations**
  - Visual (most common)
  - Auditory
  - Tactile
- **Delusions**
  - Paranoia
  - Jealousy
  - Reference
- **Illusions**
- **False sense of presence**

Ravina B, Marder K, Fernandez HH, et al. *Mov Disord.* 2007;22(8):1061-8.
Chou KL, Messing S, Oakes D, Feldman PD, Breier A, Friedman JH. *Clin Neuropharmacol*. 2005;28(5):215-9.

Frequency and Severity of PD Psychosis

- Loss of insight
- Frequency of symptoms
- Severity of symptoms
- Impact on caregivers
- Agitation, aggression

SAPS Global Rating of Severity of Hallucinations

Scale	Severity	Subject Response
0	None	No hallucinations
1	Questionable	Uncertain
2	Mild	Hallucinations definitely present, but occur infrequently; at times the subject may question their existence
3	Moderate	Hallucinations are vivid and occur occasionally; they may bother him to some extent
4	Marked	Hallucinations are quite vivid, occur frequently, and pervade his/her life
5	Severe	Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling

Impact of PD Psychosis on Patients with PD

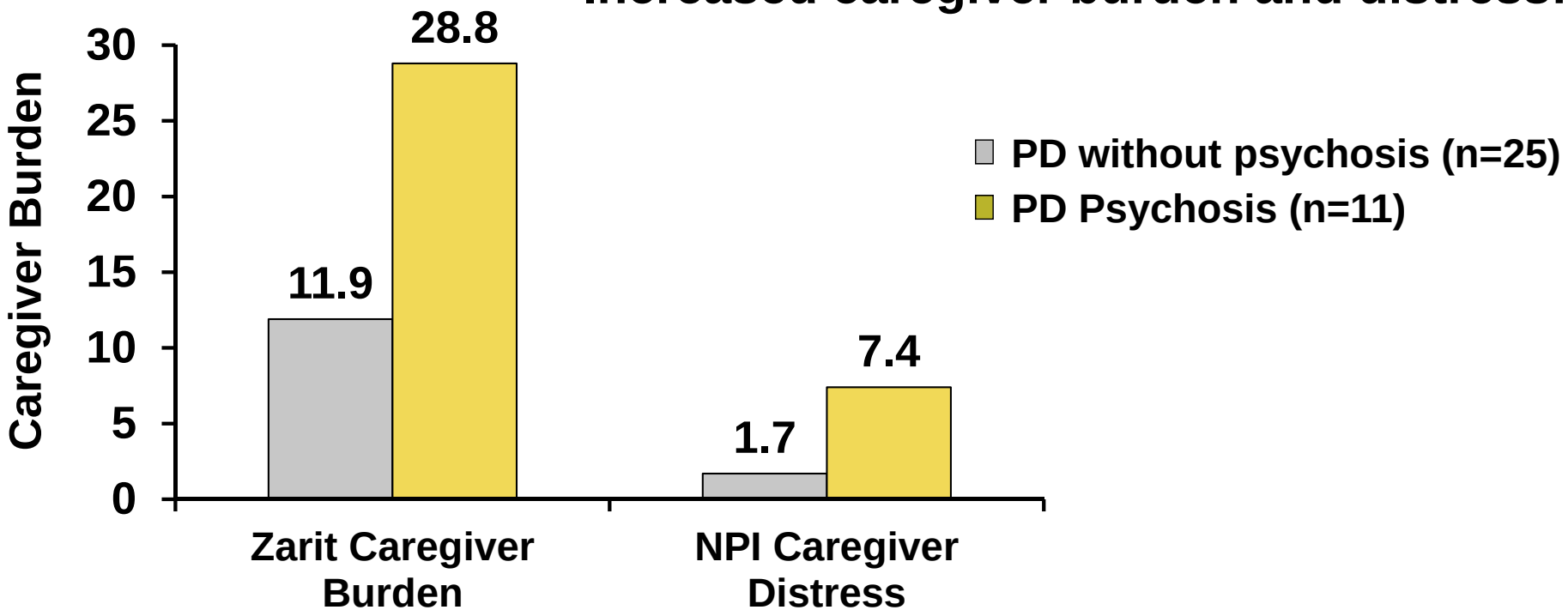
- **PD psychosis is a debilitating condition**
  - **Can overshadow PD motor symptoms**
- **Most common in advanced PD – a population with significant motor disability and complex comorbidity**
  - **Mobility, gait, and balance further impaired due to reduced PD medications or D2-antagonist antipsychotics**
- **Disrupts patient, caregiver, and family life**
  - **Stigma, social isolation, and significant impact on QOL**

Goldman JG, Holden S. *Curr Treat Options Neurol*. 2014;16(3):281.

PD Psychosis Increases Caregiver Burden

- As PD progresses, patients need increasing assistance with medications, walking, dressing, bathing, other daily activities
- Physical, emotional, and social aspects of caregiver quality of life deteriorate as psychosis symptoms worsen[1]

Increased caregiver burden and distress:[2]



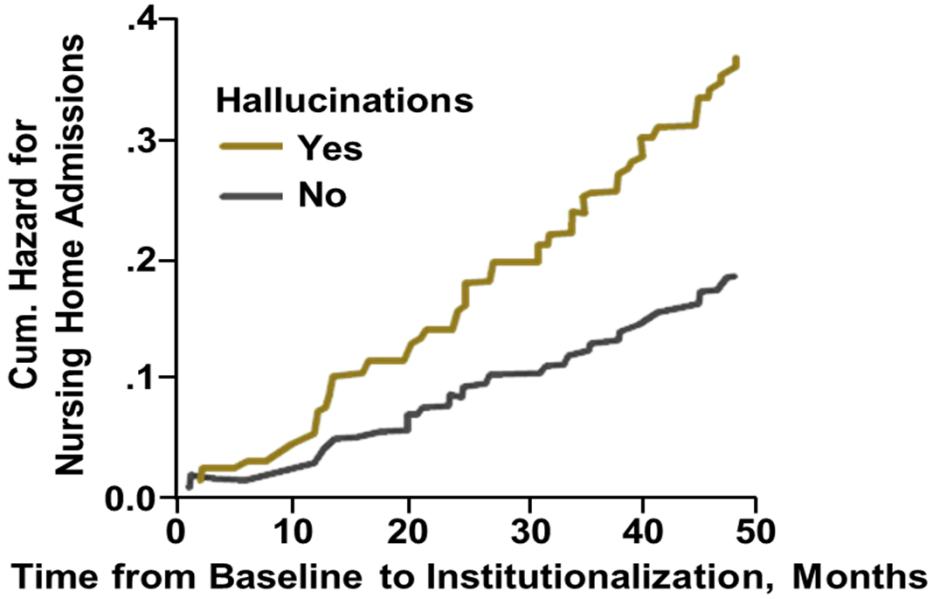
1. Schrag A, Hovris A, Morley D, Quinn N, Jahanshahi M. *Parkinsonism Relat Disord*. 2006;12(1):35-41.
2. Marsh L, Williams JR, Rocco M, et al. *Neurology*. 2004; 63(2):293-300.

PD Psychosis Increases Risk of Hospitalization and Nursing Home Placement

- **Precipitates and prolongs hospitalization[1]**
  - **24% of all hospitalizations of PD patients**
  - **29% of prolonged hospitalizations and repeat admissions**

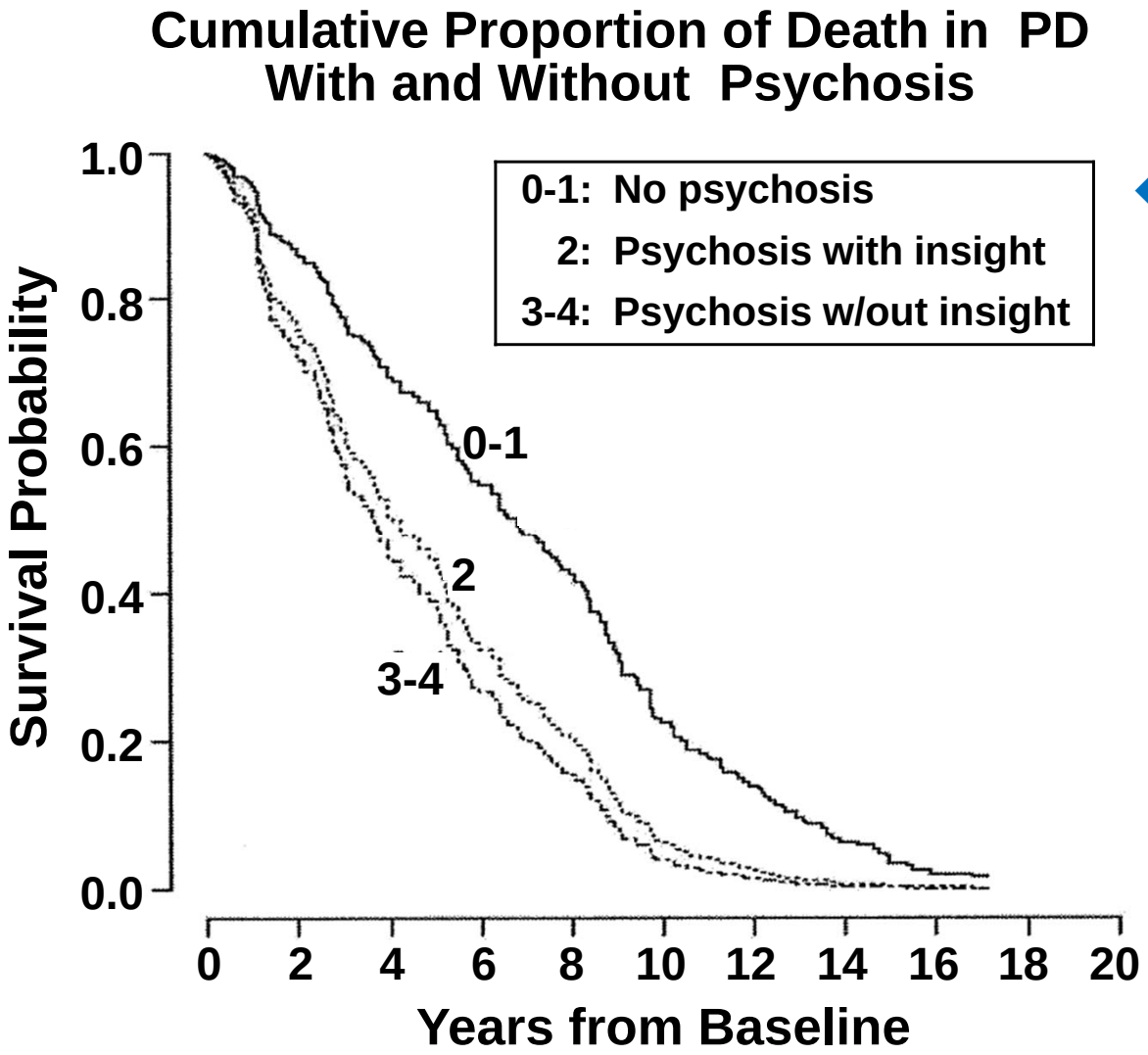
- **Strongest independent predictor of nursing home placement**
  - **Long term care placement is often permanent[2]**

4-year cumulative risk for nursing home admission for PD vs. PD psychosis[3]



1. Klein C, Prokhorov T, Miniovitz A, Dobronevsky E, Rabey JM. *J Neural Transm (Vienna).* 2009;116(11):1509-12.
2. Goetz CG, Stebbins GT. *Neurology*. 1993;43(11):2227-9. 3. Aarsland D et al. *J Am Geriatr Soc*. 2000; 48:938-942.

PD Psychosis Increases Mortality in PD



- **Cumulative proportion of death in PD patients with psychosis at baseline or who developed psychosis:**
  - **1-year: ~7%**
  - **2-year: ~24%**
  - **3-year: ~40%**

Note: Cox regression adjusts baseline age to 75.

Forsaa EB, et al. *Neurology* 2010; 75:1270-1276.

Current Management of PD Psychosis Suboptimal Reflecting Critical Unmet Need

- **Identify triggers of PD psychosis**
  - **Minimize polypharmacy**
  - **Treat co-morbid illnesses (e.g., infections)**
- **Utilize psycho-social interventions**
- **Reduce, stop, or not increase dopaminergic therapy**
  - **Leads to increased motor symptoms**
  - **Psychosis often persists / recurs despite dose reduction**
- **No FDA-approved medication for PD psychosis**
  - **Most often treated by lowering PD medication**
  - **Empiric use of off-label antipsychotics is common**

Goldman JG, Vaughan CL, Goetz CG. *Expert Opin Pharmacother*. 2011;12(13):2009-24.
Goldman JG, Holden S. *Curr Treat Options Neurol*. 2014;16(3):281.

Off-label Antipsychotic Use in PD Psychosis Despite Significant Safety Concerns

- **Dopamine D2 receptor antagonists worsen PD mobility[1]**
- **Increased mortality risk in PD[2]**
- **Adverse effects especially problematic in PD patients[1,2]**
  - **Somnolence (histaminergic H1 antagonism)**
  - **Orthostatic hypotension (adrenergic alpha-1 antagonism)**
  - **Constipation, dry mouth (muscarinic antagonism)**
  - **Drooling, dysphagia, cognitive impairment**
  - **Neuroleptic sensitivity / neuroleptic malignant syndrome**
  - **Metabolic syndrome, cerebrovascular events, seizures**
  - **Leukopenia, neutropenia, agranulocytosis**

1. Goldman JG, Holden S. *Curr Treat Options Neurol*. 2014;16(3):281.
2. Weintraub D, et. al. *JAMA Neurol.* 2016 (published online).

Off-label Antipsychotic Use is Common in PD Psychosis

Antipsychotic Prescribed	FY 2008[1] N=2597 n (%)	FY 1999-2010[2] N=7877 n (%)
Any antipsychotic use	1298 (50.0)	7877 (100.0)
Any typical (high potency)	192 (14.8)	422 (5.4)
Quetiapine	856 (65.9)	5270 (66.9)
Risperidone	224 (17.3)	1155 (14.7)
Olanzapine	149 (11.5)	837 (10.6)
Other	206 (15.9)	193 (2.5)*
Clozapine	23 (1.8)	(<2.5)*

*(Clozapine was not reported separately)

Adapted from 1. Weintraub D, Chen P, Ignacio RV, Mamikonyan E, Kales HC. *Arch Neurol*. 2011;68(7):899-904. 2. Weintraub D, et. al. *JAMA Neurol.* 2016 (published online).

Reported Efficacy in Double-blind, Randomized, Controlled Trials in PD Psychosis

Drug	Study	N	Duration/ # Sites	Scale	% Improvement	
					Placebo	Active
Olanzapine	Ondo et al., 2002	30	9 wk 1 US site	Baylor-H	27%	20%
	Breier et al., 2002	160	4 wk 37 US and Europe sites	BPRS+	23% (US) 35% (EUR)	25% (US) 31% (EUR)
	Nichols et al., 2013	23	4 wk 1 US site	BPRS	0%	-9%
Quetiapine	Ondo et al., 2005	31	12 wk 1 US site	BPRS	17%	0%
	Rabey et al., 2007	58	12 wk 1 Israeli site	BPRS	11%	-1%
	Fernandez et al., 2009	16	4 wk 1 US site	BPRS	1%	-3%
	Shotbolt et al., 2009[c]	24	12 wk 1 UK site	BPRS	6%	11%
Clozapine	US PSG, 1999	60	4 wk 6 US sites	SAPS	17%	56%*
	Pollak et al., 2004	60	4 wk 13 French sites	PANSS+	5%	31%**

(*p=.01, **p<.0001)

Burden of PD Psychosis and Need for Additional Treatment Options

- **PD psychosis is debilitating, progressive, and can overshadow advancing motor symptoms**
- **Significant challenge to clinical management, with serious consequences for patients and caregivers**
- **Current antipsychotics worsen motor symptoms, have limiting side effects, and/or significant risks**
- **Major unmet need for an effective and safe therapy that does not worsen motoric function**

Goldman JG, Holden S. *Curr Treat Options Neurol*. 2014;16(3):281.

Agenda

Introduction	Michael Monahan Director, Regulatory Affairs ACADIA Pharmaceuticals Inc.
Burden of PD Psychosis and Need for Additional Treatment Options	Stuart Isaacson, MD Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL
Efficacy of Pimavanserin	**Serge Stankovic, MD, MSPH** **Executive Vice President, R&D** **ACADIA Pharmaceuticals Inc.**
Safety of Pimavanserin	**George Demos, MD** **Executive Director, Drug Safety and Pharmacovigilance** **ACADIA Pharmaceuticals Inc.**
Benefit/Risk Profile	**Serge Stankovic, MD, MSPH** **Executive Vice President, R&D** **ACADIA Pharmaceuticals Inc.**
Clinician Perspective	**Clive Ballard, MB ChB, MRCPsych, MMedSci, MD** **Professor, Institute of Psychiatry** **King's College London, London, UK**

Efficacy of Pimavanserin in Parkinson's Disease Psychosis

Serge Stankovic, MD, MSPH

Executive Vice President, Research and Development
ACADIA Pharmaceuticals Inc.

High Selectivity for 5-HT_{2A} Receptor

Receptor	Side Effects	Pimavanserin	Clozapine	Olanzapine	Quetiapine	Risperidone
5-HT_{2A}		0.4	7	2.5	250	0.2
5-HT_{2B}		--	40	80	1100	12
5-HT_{2C}		16	40	80	--	100
5-HT_{1A}		--	--	--	--	--
H1	Sedation	--	0.5	4	5	60
M1	Sialorrhea Urinary retention	--	16	60	250	--
M2		--	--	150	ND	--
M3		--	6	250	200	--
M4		--	--	40	150	--
M5		--	30	60	ND	--
D1		--	250	100	ND	60
D2	EPS+Prolactinemia	--	50	4	30	0.5
D3		--	200	25	9	13
Alpha 1A	Orthostatic Hypotension	--	8	100	ND	3
Alpha 1D		--	150	--	--	50
Alpha 2A		--	300	--	--	20
Alpha 2B		--	50	--	--	50
Alpha 2C		--	40	--	--	13

Data are Ki values in nM derived from functional antagonist R-SAT™ assays. "–" denotes no response.
ND = Not Done. Derived from Hacksell et al., 2014; data on file.

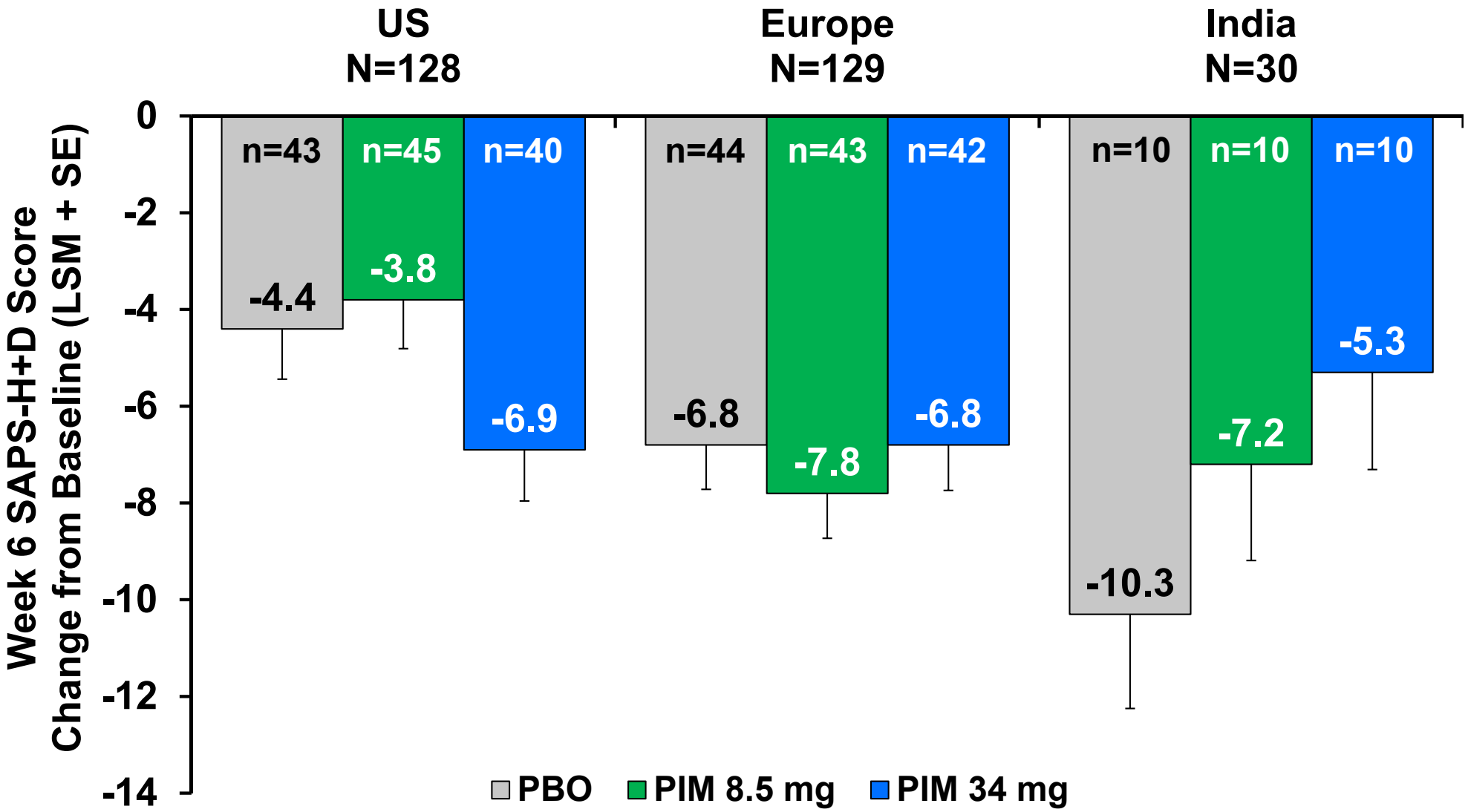
Pimavanserin Phase 2 and Phase 3 Studies

Study Type	Study #	Subjects, N	Duration/ Primary Endpoint	Dose(s)
Concept Phase 2	006	60	4 weeks/ UPDRS Parts II+III	17, 34, 51 mg, PBO flexible dose
Phase 2b/3	012	298	6 weeks/ SAPS-H+D	8.5, 34 mg, PBO
	014	123		8.5, 17 mg, PBO
Pivotal Phase 3	020	199	6 weeks/ SAPS-PD	34 mg, PBO
Open-label Extension Studies	010	498	Ongoing (10+ years)/ Safety Assessments	17, 34, 51 mg flexible dose
	015			34 mg

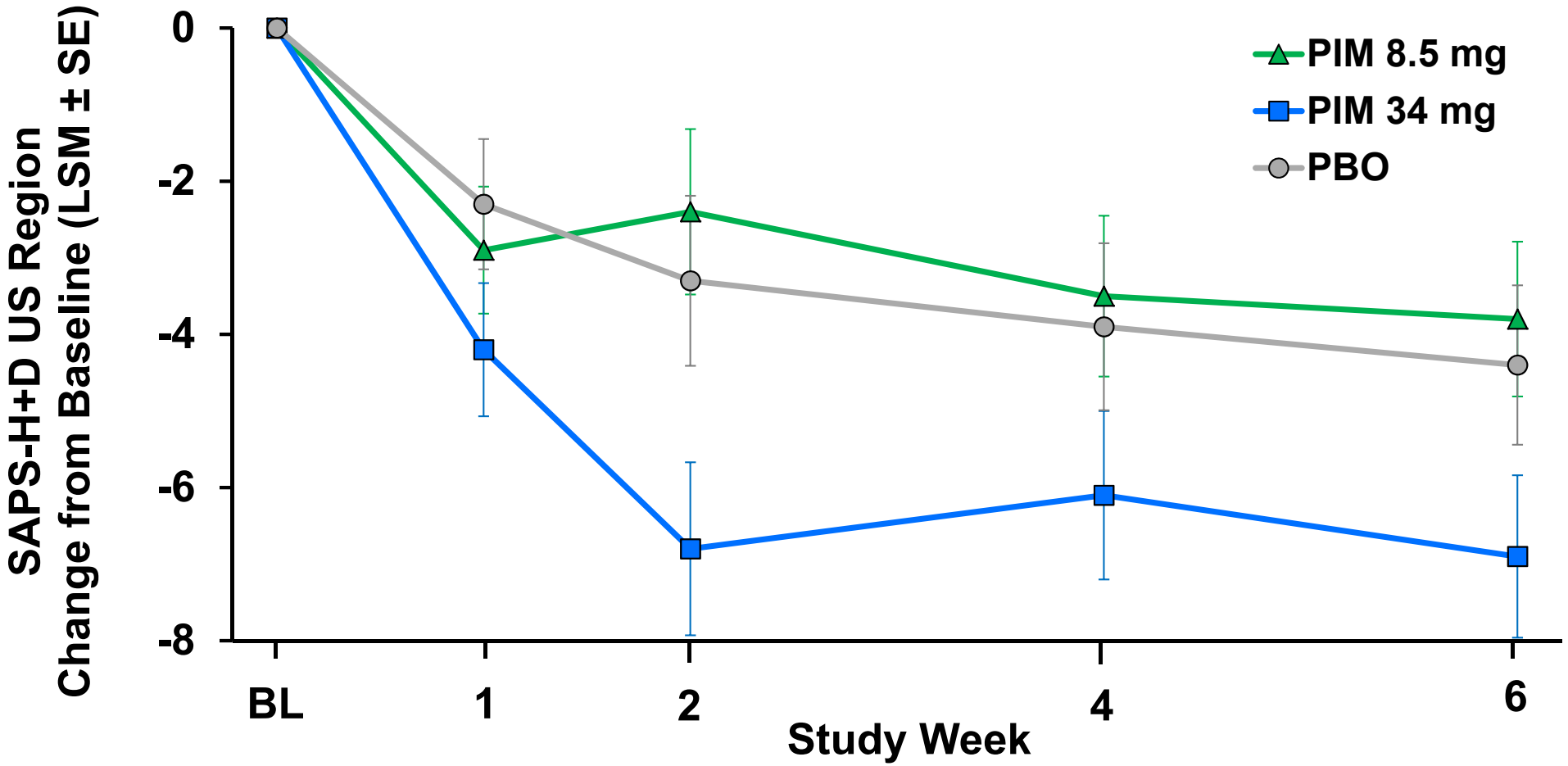
Phase 2b/3 Study 012

- Six-week, randomized, double-blind, placebo-controlled, dose-ranging study
- Two pimavanserin doses (8.5 mg and 34 mg)
- Enrolled mild to moderate PDP patients
- Primary endpoint SAPS-H+D
- Global study (US, Europe, and India)
  - Centralized rating in the US
  - Local site raters used in Europe and India
- Pimavanserin failed to separate from placebo on primary endpoint
  - High placebo response in regions without centralized rating

Study 012: Primary Endpoint Results by Region (mITT, LOCF, N=287)



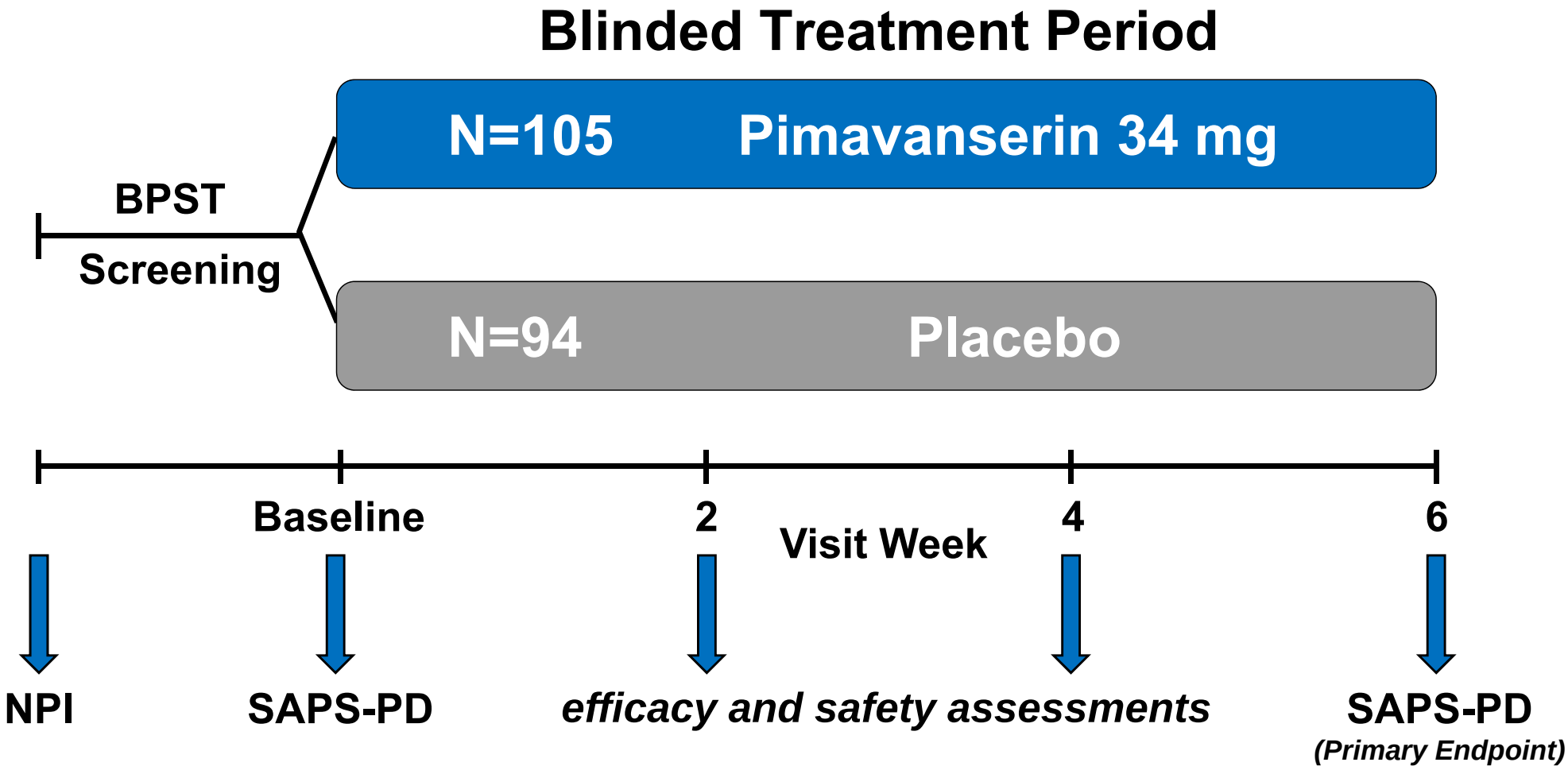
Study 012: US Region (Centralized Raters) (mITT, LOCF, N=128)



Key Learnings from Previous Studies

- Pimavanserin 34 mg appropriate dose
- Brief Psycho-Social Therapy (BPST) lead-in
- Reduced frequency of visits and treatment arms
- Central independent rating of primary efficacy outcome

Study 020: Design



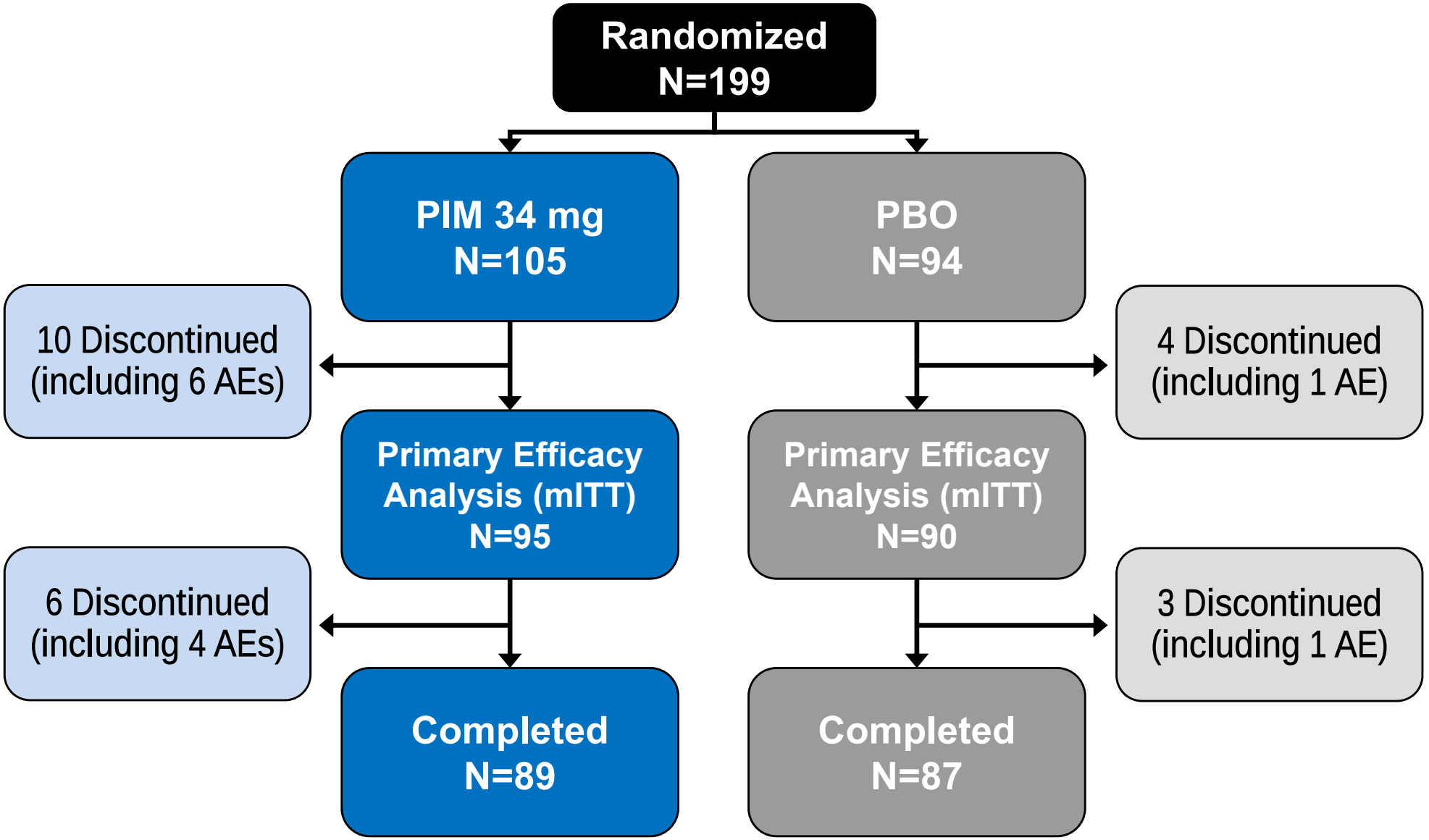
Study 020: Inclusion and Exclusion Criteria

- **Key Inclusion Criteria**
  - PD ≥1 year
  - Psychosis ≥1 month
  - Severe enough to require Rx treatment:
    - NPI criterion at screening
    - SAPS-PD criterion at randomization
  - Stable PD medication
- **Key Exclusion Criteria**
  - Psychosis attributable to another disease
  - Other antipsychotic medication
  - MMSE score <21

Study 020: Efficacy Measures from Multiple Perspectives

	Measure	Rater
Primary	SAPS-PD	Central Independent
Secondary	CGI-I	Investigator
	CGI-S	Investigator
Exploratory	Zarit Caregiver Burden	Caregiver
	SCOPA-Night	Subject
	SCOPA-Night Global	Subject
	SCOPA-Day	Subject
Additional	SAPS-H+D	Central Independent
	SAPS-H	Central Independent
	SAPS-D	Central Independent

Study 020: Subject Enrollment and Disposition



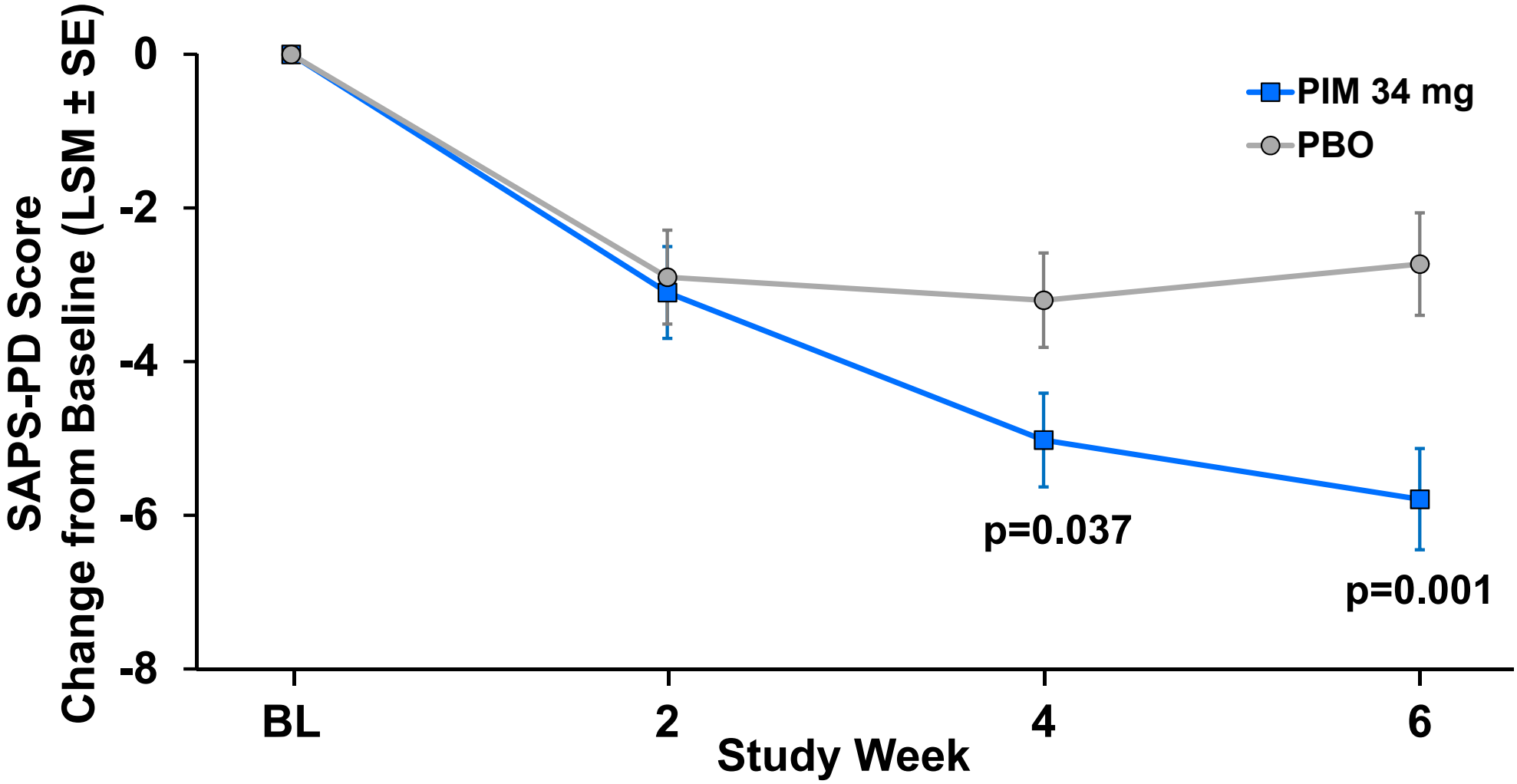
Study 020: Baseline Demographics (mITT)

Demographics	PIM 34 mg N=95	PBO N=90
Age (years)		
Mean (SD)	72.4 (6.55)	72.4 (7.92)
Median (min, max)	72.0 (56, 85)	72.0 (53, 90)
Age Group, n (%)		
<65 yrs	11 (11.6)	11 (12.2)
65-75 yrs	53 (55.8)	50 (55.6)
>75 yrs	31 (32.6)	29 (32.2)
Sex, n (%)		
Male	64 (67.4)	52 (57.8)

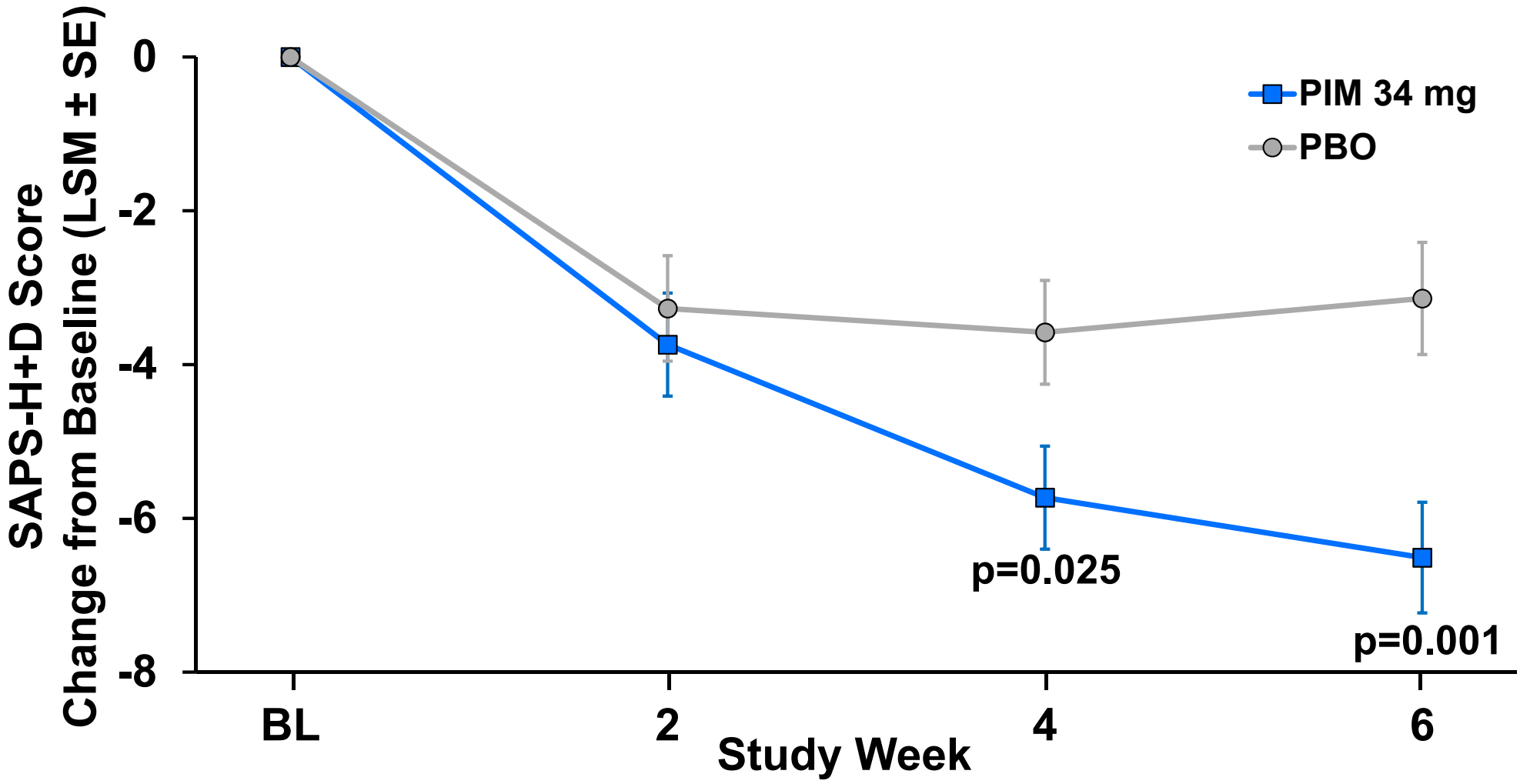
Study 020: Disease Characteristics (mITT)

Characteristic (mean)	PIM 34 mg N=95	PBO N=90
SAPS-PD	15.9	14.7
SAPS-H+D	17.5	15.8
NPI-H+D	11.8	12.2
CGI-Severity	4.3	4.3
MMSE	26.0	26.6
UPDRS II+III	51.5	52.6
Caregiver Burden Scale	28.7	30.7
Using PD (motor) medications, %	99%	99%
Duration of PD (months)	116	128
Duration of PDP (months)	31	36

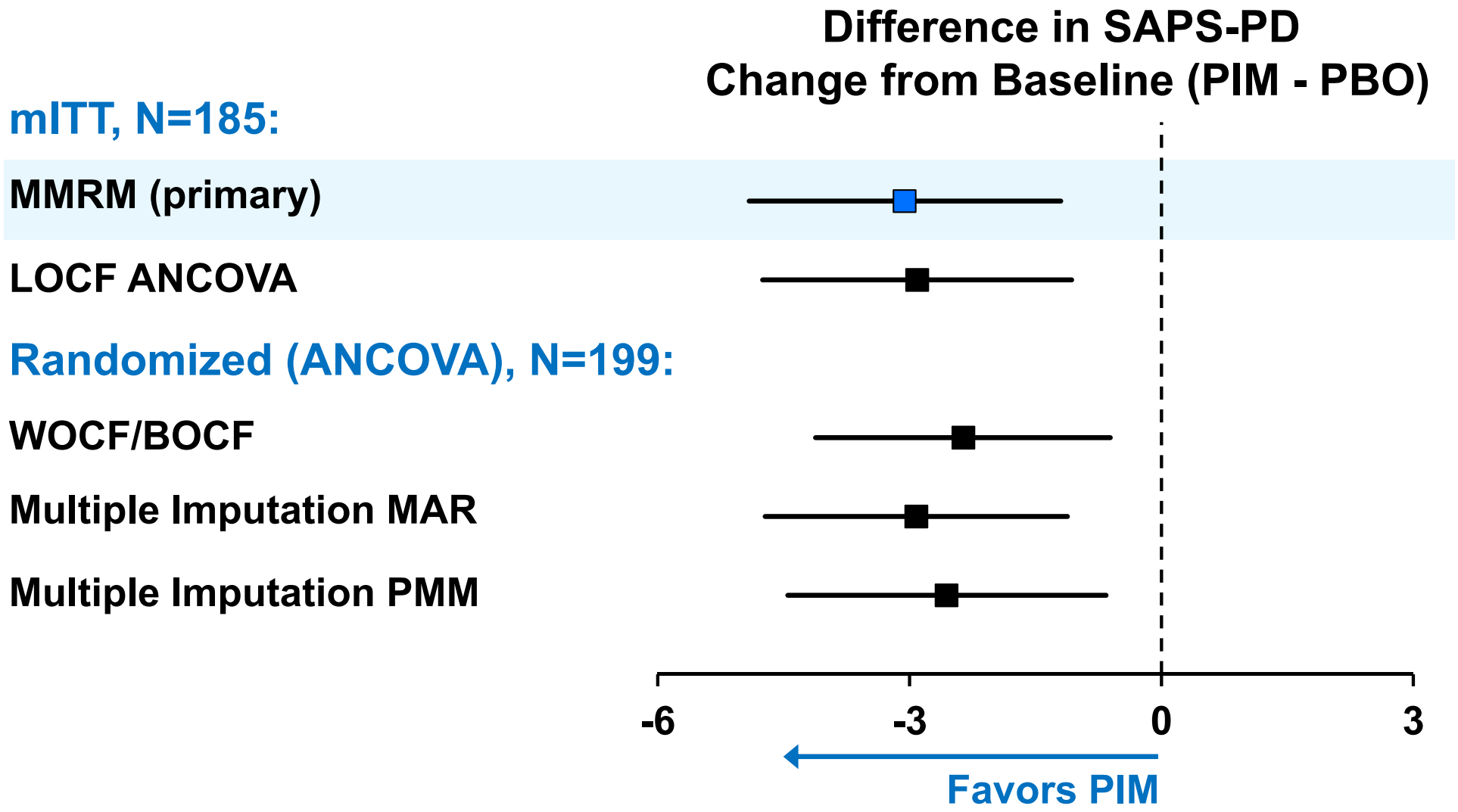
Study 020: Primary Endpoint
SAPS-PD Score (mITT, MMRM, N=185)



Study 020:
SAPS-H+D Score (mITT, MMRM, N=185)

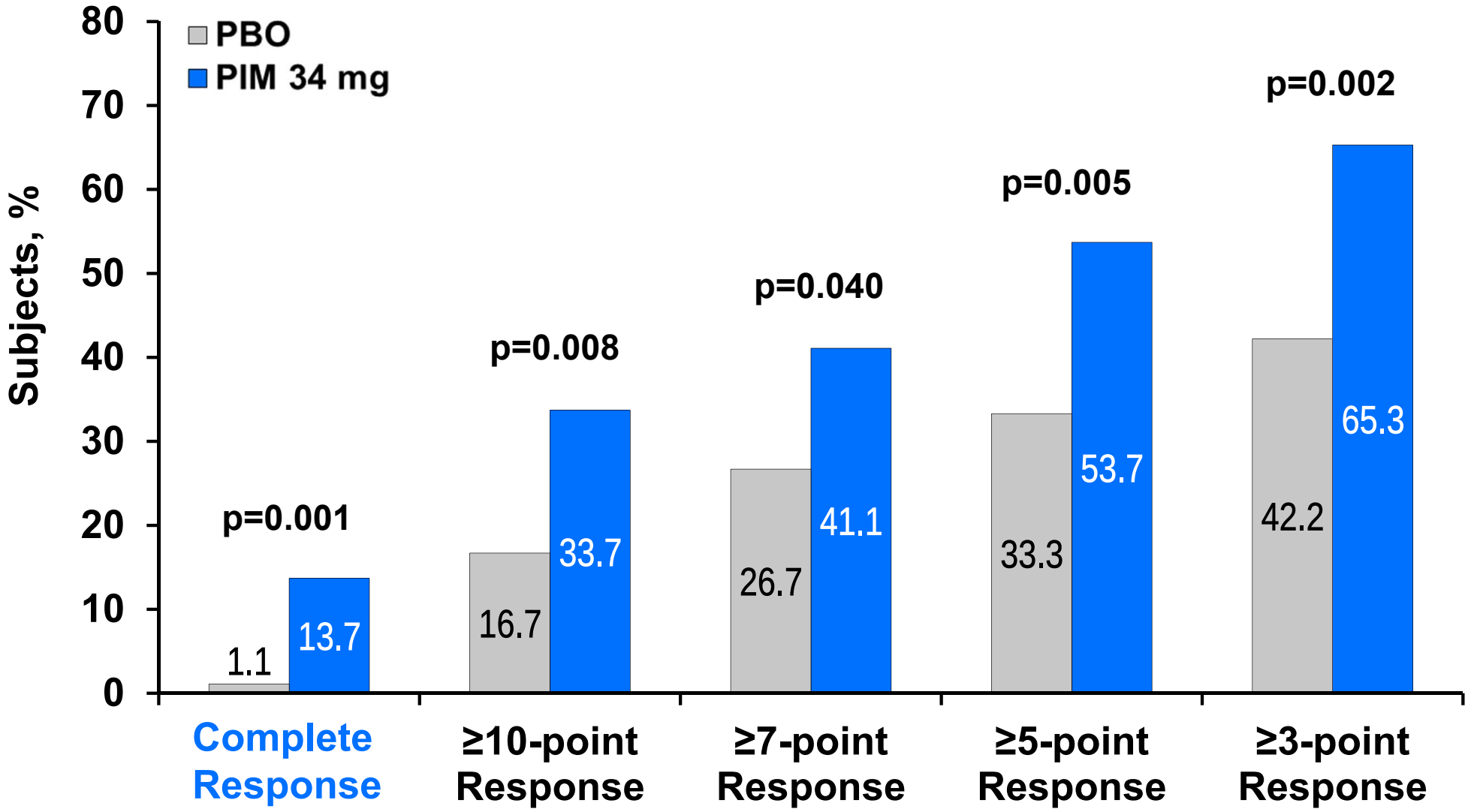


Study 020: Multiple Sensitivity Analyses



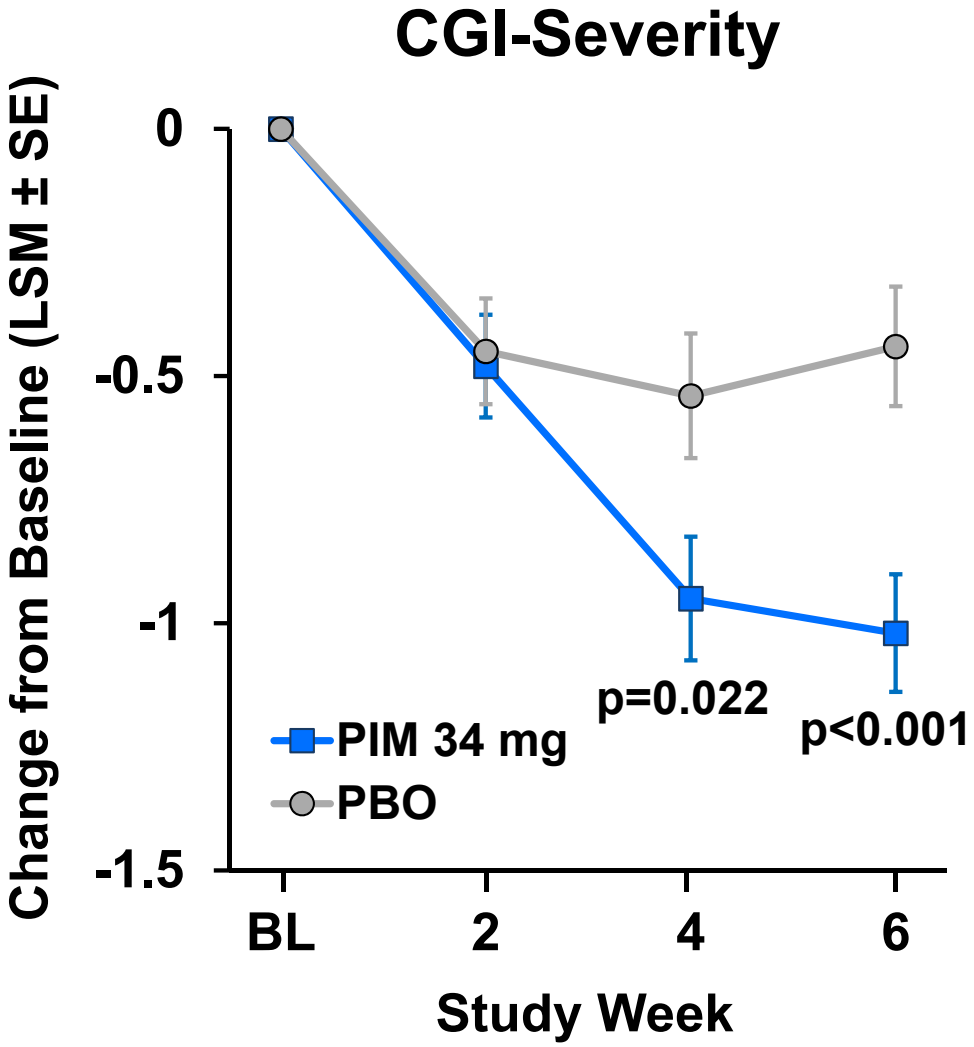
MMRM = Mixed model repeated measures; MAR = Missing at random; PMM = Pattern mixture model.

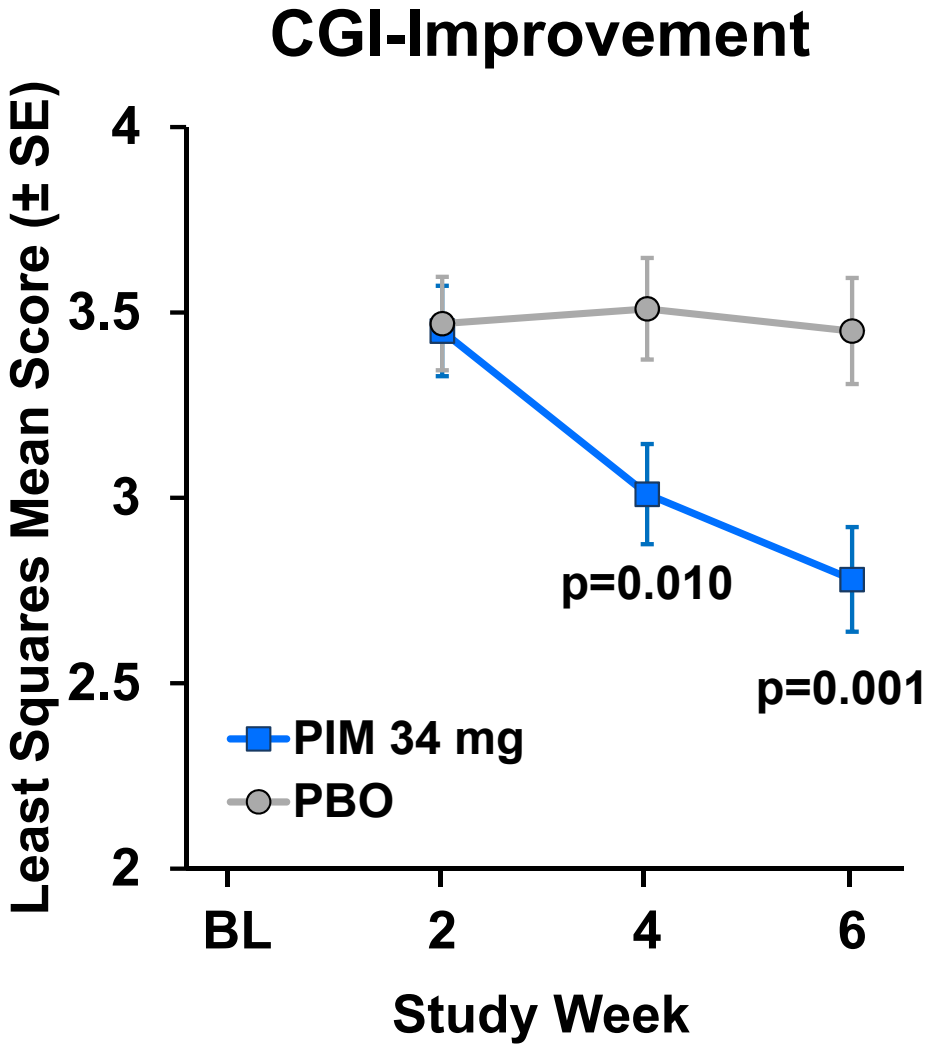
Study 020: SAPS-PD Score Improvement (mITT, N=185)



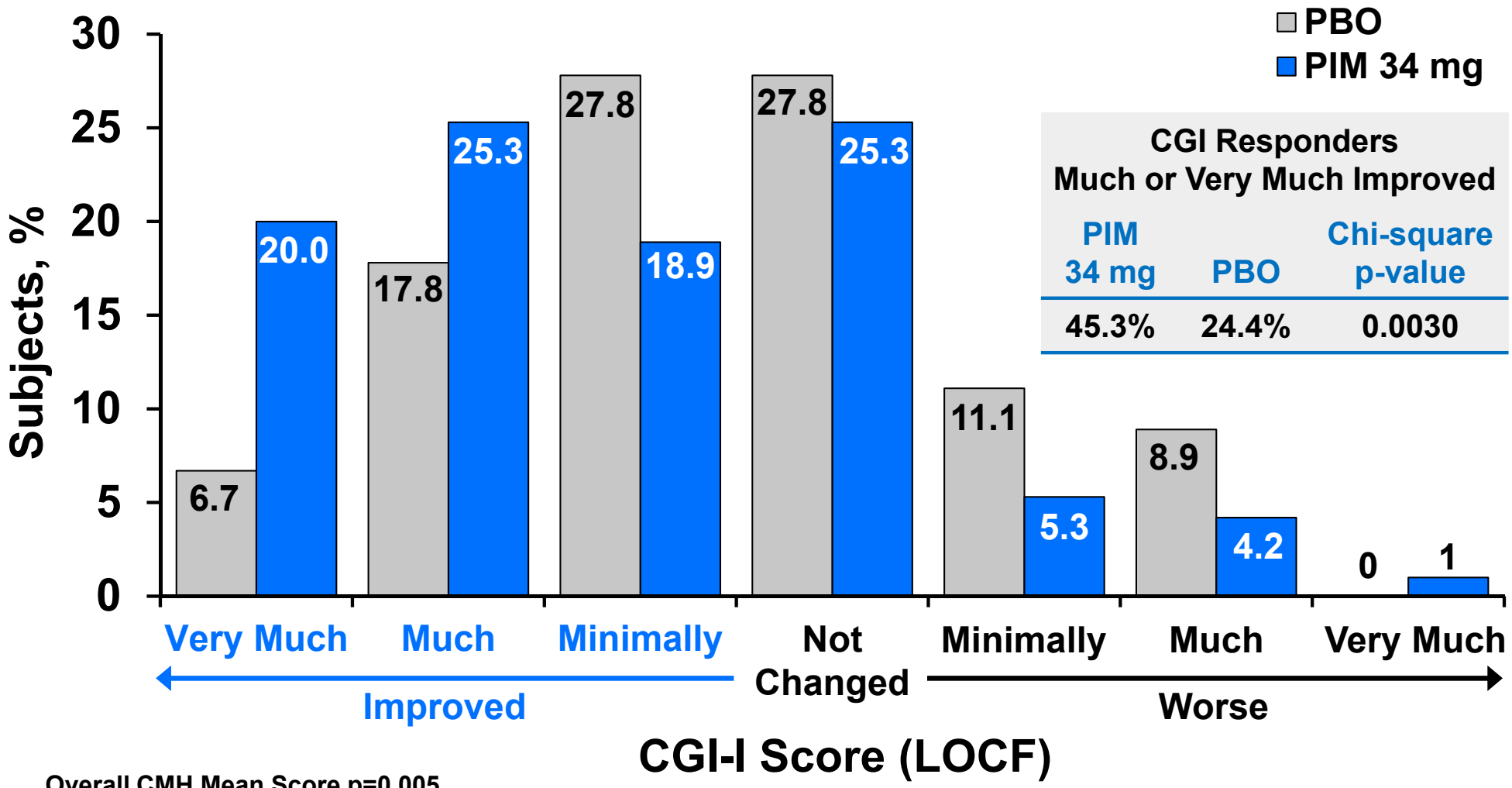
p-values from Mantel-Haenszel Chi-Square test

Study 020: CGI-S and CGI-I Scores (mITT, MMRM, N=185)





CGI-I Response (mITT, N=185)



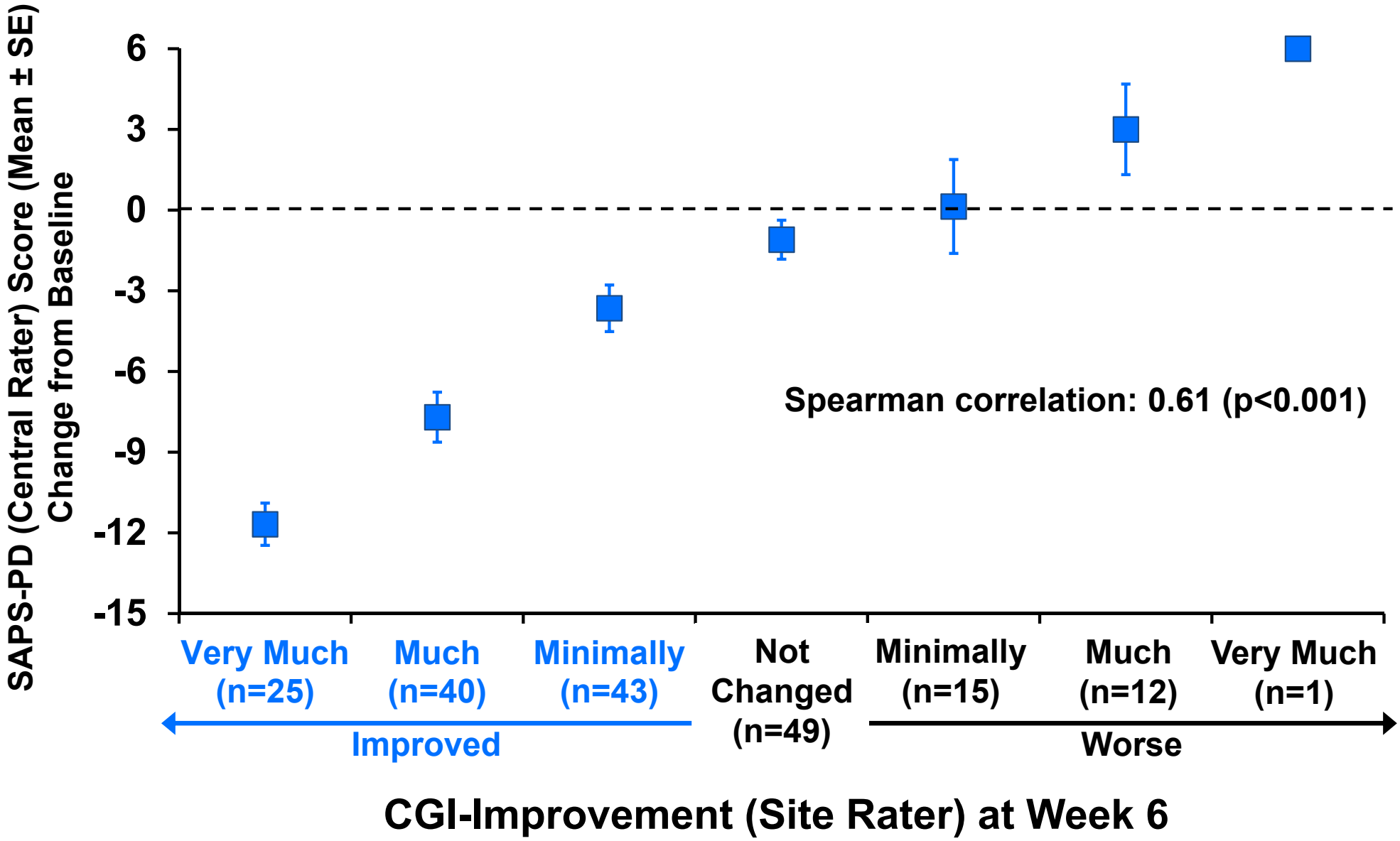
CGI Responders
Much or Very Much Improved

PIM 34 mg	PBO	Chi-square p-value
45.3%	24.4%	0.0030

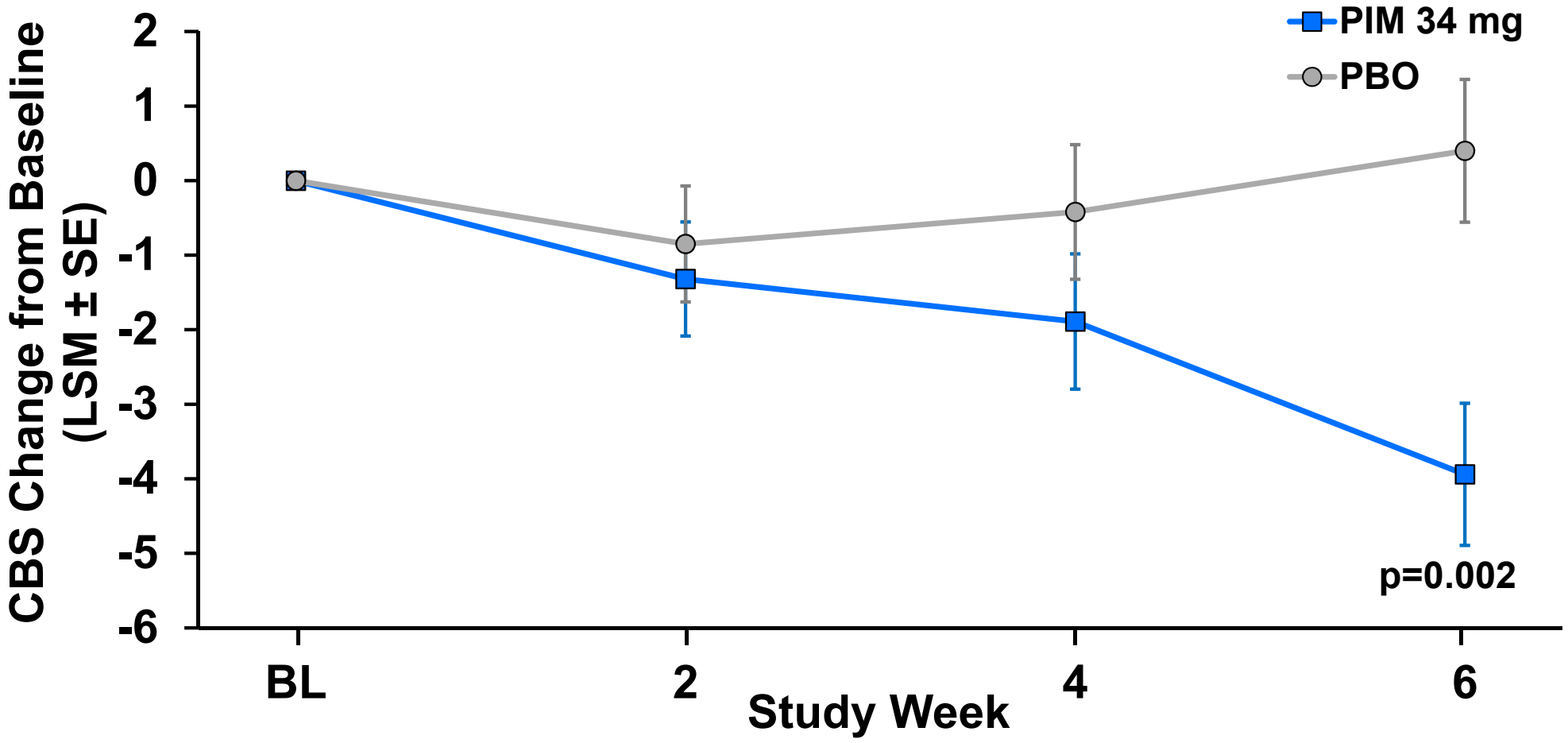
Overall CMH Mean Score p=0.005

PBO	n=	6	16	25	25	10	8	0
PIM 34 mg	n=	19	24	18	24	5	4	1

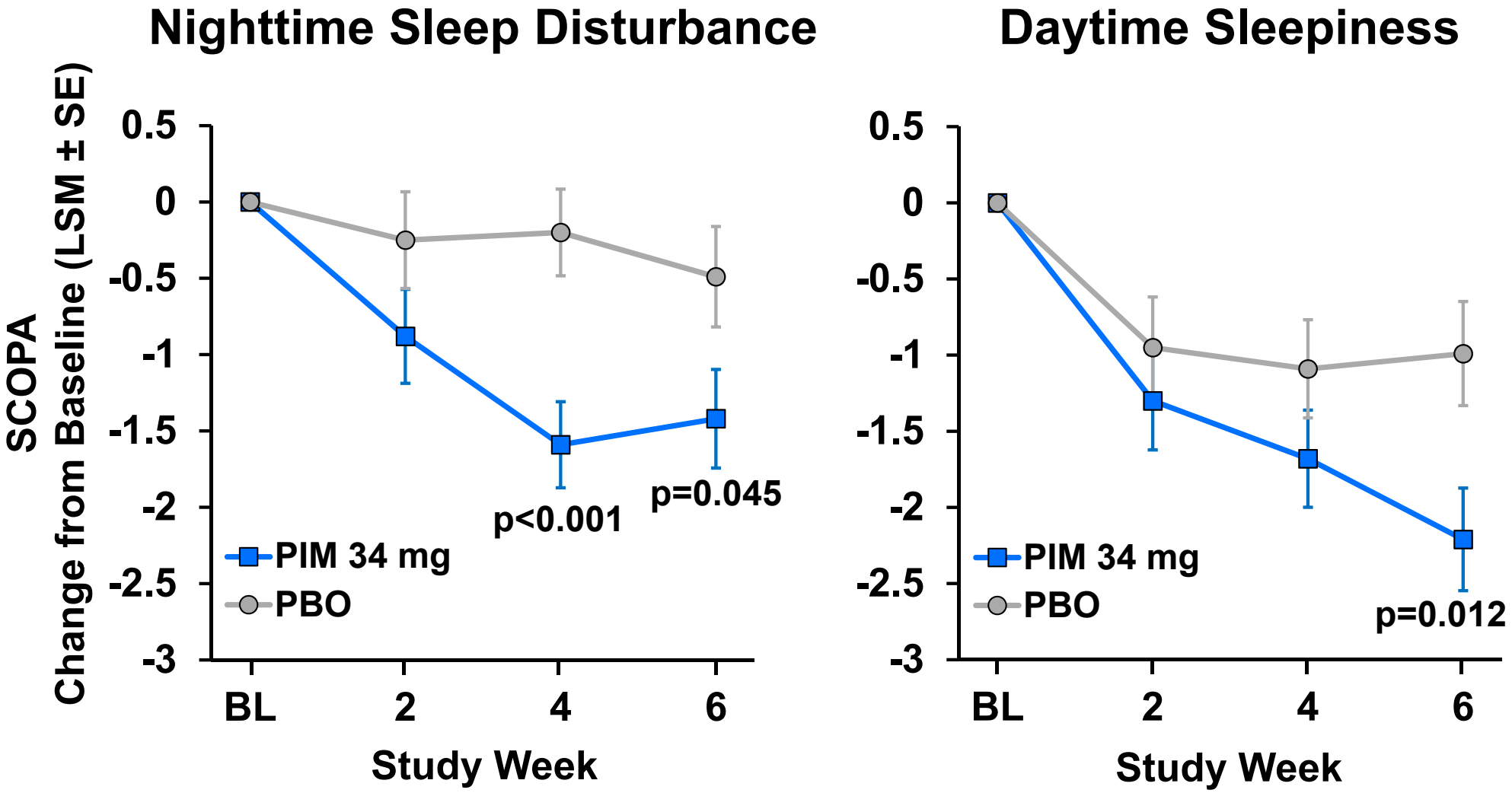
Study 020: Correlation Between SAPS-PD and CGI (mITT, LOCF, PIM & PBO Combined)



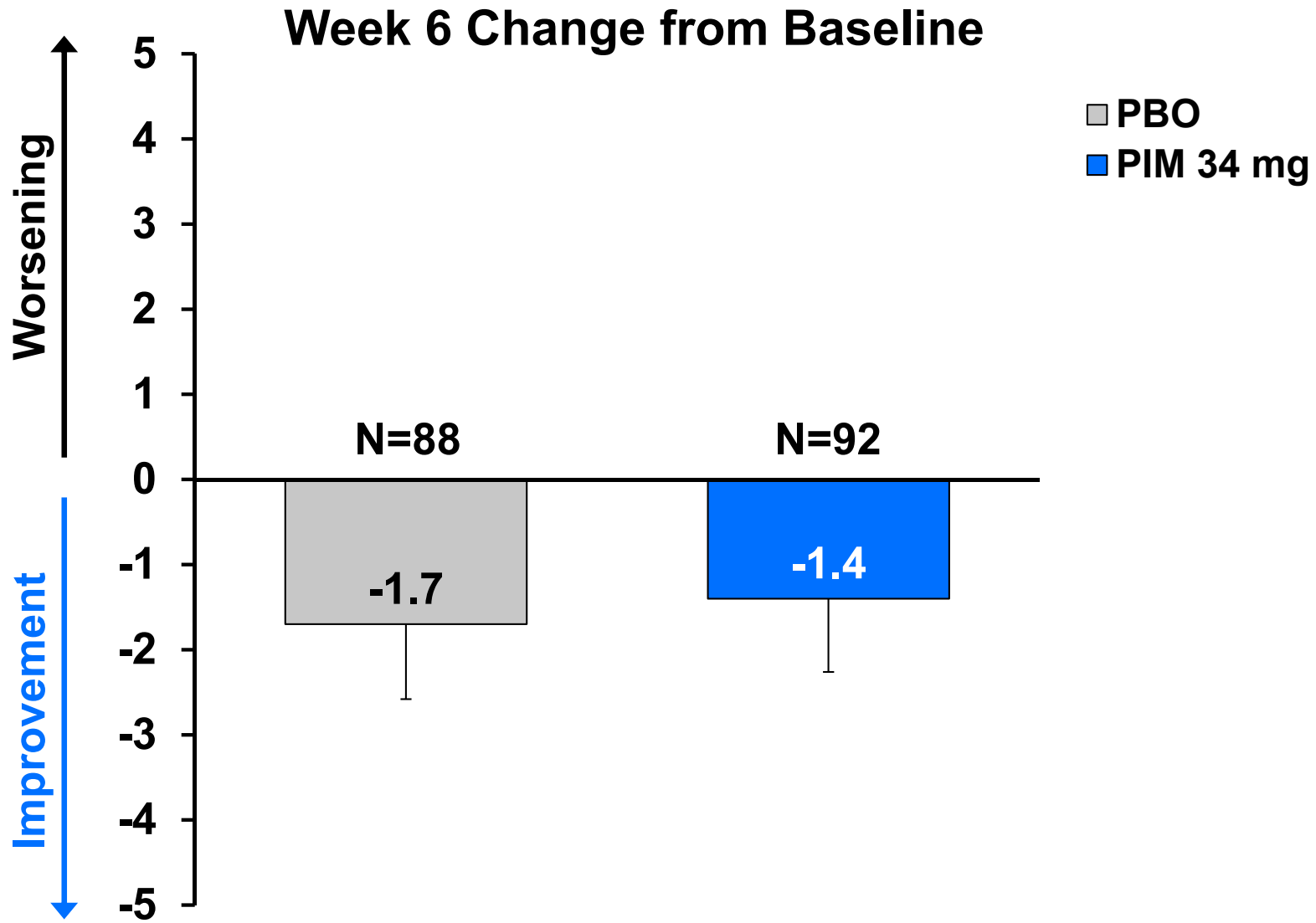
Study 020: Zarit Caregiver Burden Scale (mITT, MMRM, N=185)



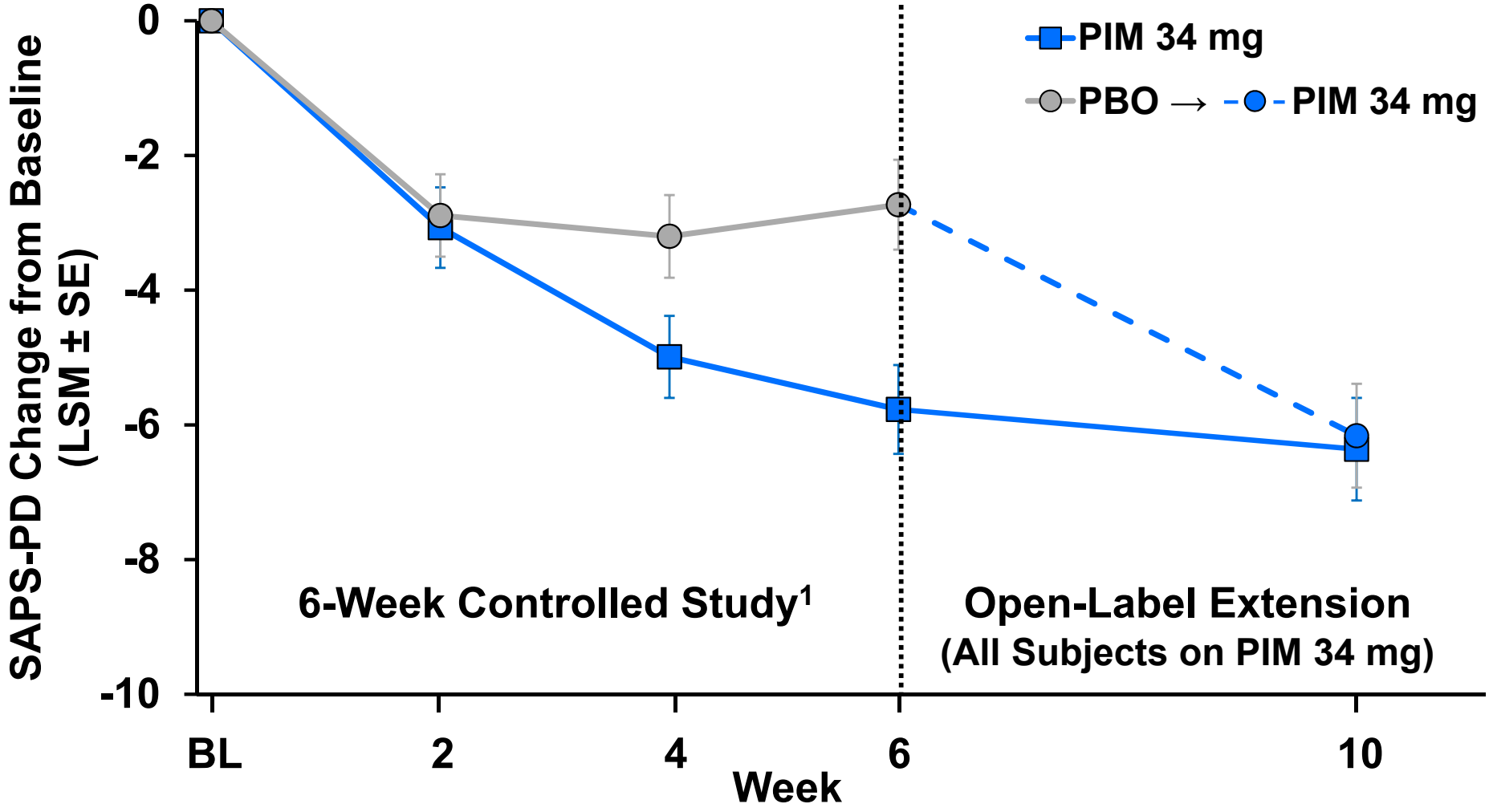
Study 020: SCOPA Sleep
(mITT, MMRM, N=185)



Study 020: UPDRS Parts II+III (mITT, LOCF, N=185)

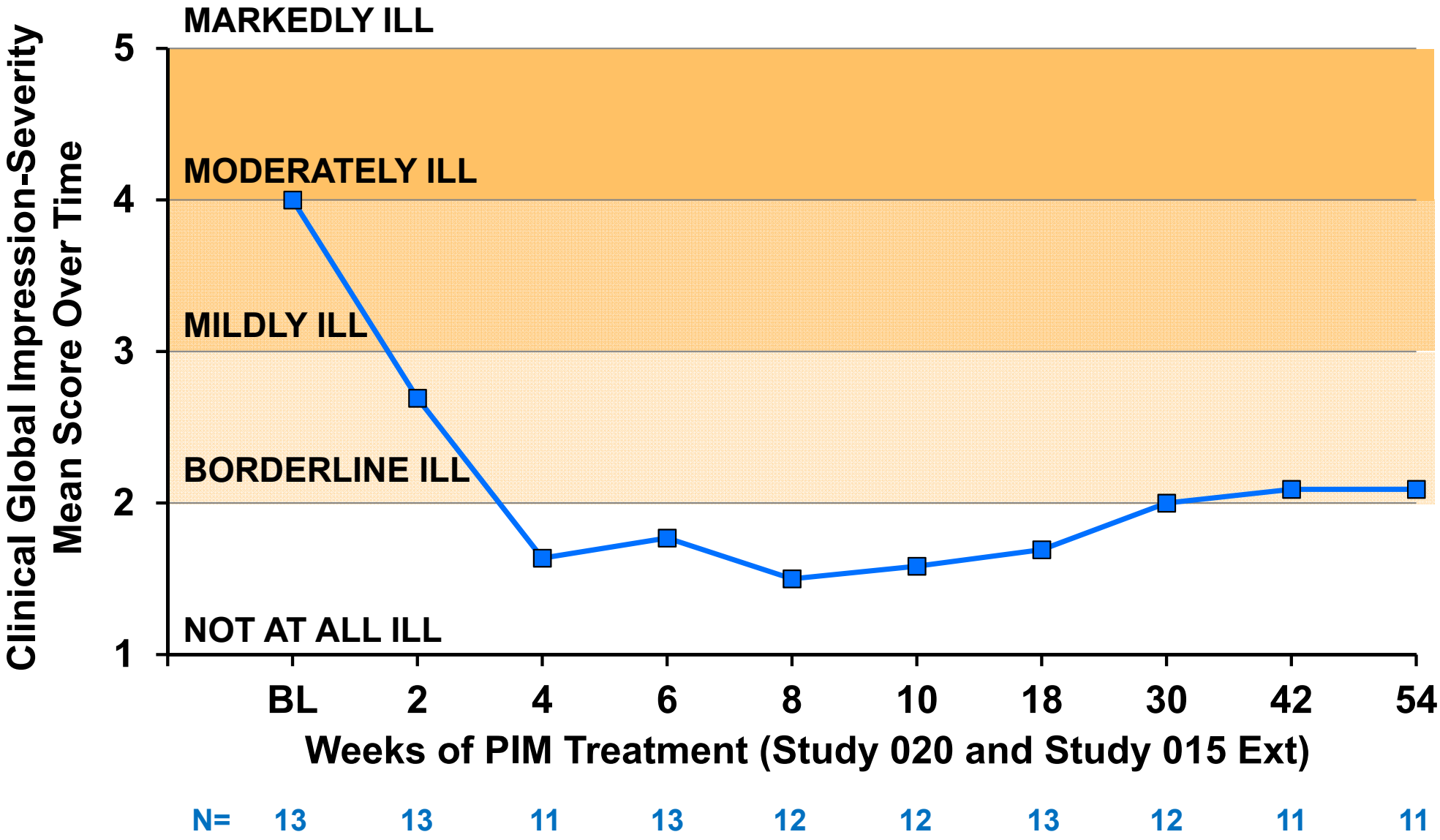


Study 015: Switching from Double-blind to Open-label



1. mITT subjects from Study 020.

Study 020: SAPS-PD Complete Responders One Year Follow-up



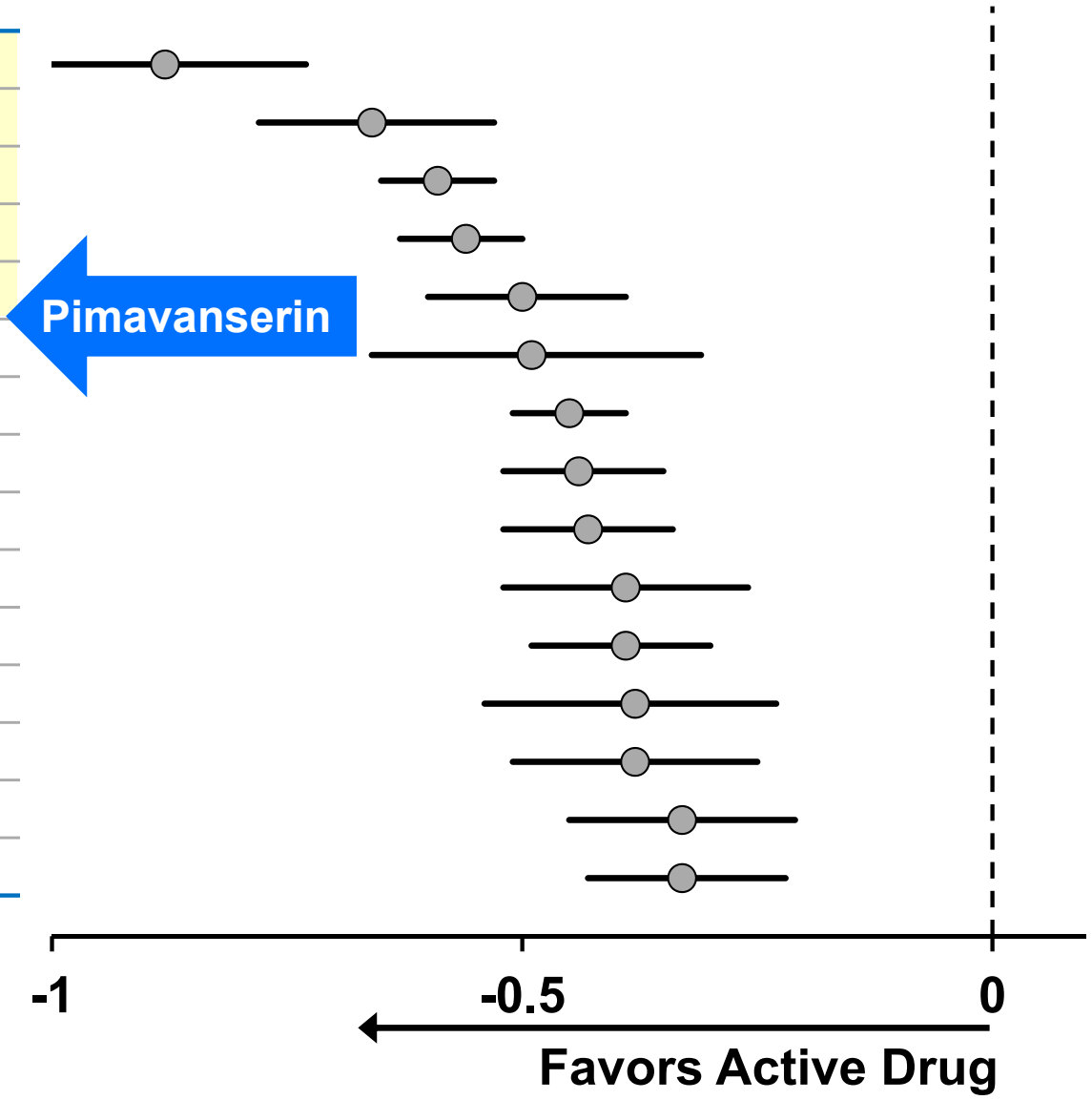
Study 020: Consistent Efficacy Across All Measures and Perspectives

	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*

Antipsychotic Effect Size in Schizophrenia

Antipsychotic	SMD	(95% CrI)
Clozapine	-0.88	(-1.03, -0.73)
Amisulpride	-0.66	(-0.78, -0.53)
Olanzapine	-0.59	(-0.65, -0.53)
Risperidone	-0.56	(-0.63, -0.50)
Paliperidone	-0.50	(-0.60, -0.39)
Zotepine	-0.49	(-0.66, -0.31)
Haloperidol	-0.45	(-0.51, -0.39)
Quetiapine	-0.44	(-0.52, -0.35)
Aripiprazole	-0.43	(-0.52, -0.34)
Sertindole	-0.39	(-0.52, -0.26)
Ziprasidone	-0.39	(-0.49, -0.30)
Chlorpromazine	-0.38	(-0.54, -0.23)
Asenapine	-0.38	(-0.51, -0.25)
Lurasidone	-0.33	(-0.45, -0.21)
Iloperidone	-0.33	(-0.43, -0.22)



SMD=Standardized mean difference.
CrI=Credible interval.
Leucht S. *Lancet*. 2013; 382:951-962.

Numbers Needed to Treat by Response (mITT, N=185)

Responder Definition	NNT
SAPS-PD Response:	
≥3 point response	5
≥5 point response	5
≥7 point response	7
≥10 point response	6
Complete response	8
CGI-I Response:	
Much or Very Much Improved	5

Efficacy Conclusions

- Clinically meaningful and convincing efficacy
  - Pimavanserin patients
    - 45% achieved “much improved” or “very much improved” response
    - 14% achieved a complete response
  - Improvement on primary endpoint (SAPS-PD) consistent with clinician assessment (CGI)
  - Persuasive statistical evidence
  - Substantial effect sizes and low NNTs
  - Confirmatory sensitivity analyses
- Antipsychotic efficacy achieved without worsening motor function

Agenda

Introduction	Michael Monahan Director, Regulatory Affairs ACADIA Pharmaceuticals Inc.
Burden of PD Psychosis and Need for Additional Treatment Options	Stuart Isaacson, MD Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL
Efficacy of Pimavanserin	Serge Stankovic, MD, MSPH Executive Vice President, R&D ACADIA Pharmaceuticals Inc.
Safety of Pimavanserin	**George Demos, MD** **Executive Director, Drug Safety and Pharmacovigilance** **ACADIA Pharmaceuticals Inc.**
Benefit/Risk Profile	**Serge Stankovic, MD, MSPH** **Executive Vice President, R&D** **ACADIA Pharmaceuticals Inc.**
Clinician Perspective	**Clive Ballard, MB ChB, MRCPsych, MMedSci, MD** **Professor, Institute of Psychiatry** **King's College London, London, UK**

Pimavanserin Safety Profile

George Demos, MD

Executive Director
Drug Safety and Pharmacovigilance
ACADIA Pharmaceuticals Inc.

Safety Topics

- PDP6 Population – 6-Week Phase 3 Studies
  - Adverse events
  - Deaths
  - Serious adverse events
  - Discontinuations
- Open-label Safety
- Adverse Events of Special Interest
- Summary

PDP6: Demographics and Disease Characteristics

Demographics and Medical History	PDP6 Population N=614
Age (years):	
Mean	71.0
>75 years, (%)	31.3
Male sex, (%)	63.7
Duration of PD (months)	109
Duration of PDP (months)	26
Baseline UPDRS Parts II+III	52.0
Medical history/Concomitant medications, (%)	
with ≥2 CV-related risk factors	41
≥5 non-PD con-medications	50

Overview of Subjects Exposed

Subjects Exposed	N
PD non-Psychosis	9
PD Psychosis	616
Healthy Subjects	276
Healthy Subjects + Adjunctive Therapy	18
Schizophrenia	177
Controlled or Extension Studies	**1096**
Ongoing and Other Studies[1]	142
Total Treated with Pimavanserin	**1237**

764 of the 1096 subjects (70%) received 34 mg or higher

1. One subject who rolled over from NIH study is counted only once.

Summary: Adverse Events (PDP6 Population)

Adverse Event	Double-blind Treatment, n (%)				
	PIM 8.5 mg N=140	PIM 17 mg N=41	PIM 34 mg N=202	All PIM N=383	PBO N=231
Treatment emergent AEs	79 (56.4)	21 (51.2)	124 (61.4)	224 (58.5)	141 (61.0)
AEs leading to discontinuation	9 (6.4)	3 (7.3)	16 (7.9)	28 (7.3)	10 (4.3)
Serious AEs	8 (5.7)	1 (2.4)	16 (7.9)	25 (6.5)	8 (3.5)
Deaths	1 (0.7)	–	3 (1.5)	4 (1.0)	1 (0.4)

Common Treatment Emergent AEs ≥5% (PDP6 Population)

Preferred Term	Subjects, n (%) PIM 34 mg N=202	PBO N=231
Overall	124 (61.4)	141 (61.0)
Urinary tract infection	15 (7.4)	16 (6.9)
Nausea	14 (6.9)	10 (4.3)
Edema peripheral	14 (6.9)	5 (2.2)
Fall	13 (6.4)	21 (9.1)
Confusional state	12 (5.9)	6 (2.6)
Hallucination	10 (5.0)	7 (3.0)
Headache	5 (2.5)	12 (5.2)
Orthostatic hypotension	2 (1.0)	12 (5.2)

Studies 012 and 020 34 mg vs PBO.

Subjects with Fatal Outcome (PDP6 Population)

Age/Sex/ Dose	Event	Time on Drug (days)	Time to Death (days)
85 M Placebo	Cardio-respiratory arrest	27	36
61 M PIM 8.5 mg	Myocardial infarction	46	46
84 F PIM 34 mg	Respiratory distress	29	61
74 M PIM 34 mg	Sepsis	38	45
76 M PIM 34 mg	Septic shock	9	10

Other Serious Adverse Events Medical Review

Serious AE	PIM 34 mg	PBO
Event Occurred After Treatment Discontinuation	• Bronchitis (25 days post-treatment)	• None
Relevant Findings at Baseline	• Breast Cancer (Positive mammogram) • UTI (Day 2; Hx & leukocyturia pre-treatment) • UTI (Day 8-12; Hx & leukocyturia pre-treatment)[1] • UTI (Day 6; Hx & leukocyturia pre-treatment)	• None
Possible Alternative Etiologies	• Atrial Fibrillation (Pacemaker placement)[1] • Hemorrhoids (Abdominal pain)[1] • Parkinson's (Disability)[1] • Mental Status Changes (Dehydration)[1] • Mental Status Changes (Day 2 UTI)	• Mental Status Changes • UTI (Day 22) • GI Bleed[1] • Lumbar Fracture[1] • Decubitus Ulcer • Gastroenteritis/Delirium • Bronchitis
No Alternative Etiologies Identified	• Hallucination (Day 7) • Hallucination (Day 9) • Headache	• None

1. Subject remained on study drug.

AEs Leading to Discontinuation ≥1%: in Either Treatment Arm (PDP6 Population)

Preferred Term	Subjects, n (%) PIM 34 mg N=202	PBO N=231
Overall	16 (7.9)	10 (4.3)
Hallucination	4 (2.0)	1 (0.4)
Psychotic disorder	3 (1.5)	2 (0.9)
Urinary tract infection	2 (1.0)	1 (0.4)
Fatigue	2 (1.0)	–

NNH (Overall DC due to AEs) = 27

Studies 012 and 020 34 mg vs PBO.

Long-term, Open-label Treatment (PDPLT Population)

- Started in 2004 and ongoing
- 498 patients rolled over into long-term open-label studies
- Median time on treatment ~15 months
- >170 patients exceed 24 months
  - >900 total patient-years of exposure
  - Longest exposure 10+ years

No New Safety Risks Observed with Prolonged Treatment

- Most common adverse events – falls, UTIs, hallucinations, decreased weight, confusion, and constipation
- Most common serious adverse events – only pneumonia and UTI greater than 3%
- 62 reported deaths over 10 years of follow-up

Continued Risk Evaluation

- Diligent pharmacovigilance and follow up
- Ongoing clinical development program
- Epidemiological investigation
- Observational study
- Analyses of external healthcare databases

Topics and Events of Special Interest

- Drug Interactions
- QT prolongation
- Cerebrovascular accidents
- Orthostatic hypotension
- Sedation related events
- Metabolic disorders
- Blood dyscrasias
- Motor impairment

Drug-Drug Interaction Studies

- Co-administration of Sinemet
  - No effect on levodopa exposure
- CYP3A4 substrate drugs
  - No effect on midazolam
- 3-fold increase in exposure with potent CYP3A4 inhibitor
  - Dose reduction recommended

Cardiac Safety: QT Results

- Thorough QT Study
- Phase 3 Core lab ECG Analysis
- Pimavanserin 34 mg
  - Increase in QTc
    - Maximal Mean $\Delta\Delta$ 6.9 ms (upper 90% CI of 10 ms)
    - No meaningful outliers
      - QTc> 500ms
      - QTc increase from baseline >60ms

Topics and Events of Interest

- **Cerebrovascular accident**
  - No reports in controlled studies
  - 1.1/100 patient-years open-label

- **Orthostatic hypotension**

	Subjects, n (%)	
	PIM 34 mg	PBO
Orthostatic hypotension	2 (1.0)	12 (5.2)
Vital signs criteria	58 (29.6)	88 (38.4)

Topics and Events of Interest

- **Sedation**

	Subjects, n (%)	
	PIM 34 mg	PBO
Sedation related events	13 (6.4)	12 (5.2)
Sedation	–	–
Somnolence	5 (2.5)	6 (2.6)
Fatigue	5 (2.5)	5 (2.2)
Asthenia	3 (1.5)	1 (0.4)
Lethargy	2 (1.0)	–
Hypersomnia	–	–

Topics and Events of Interest

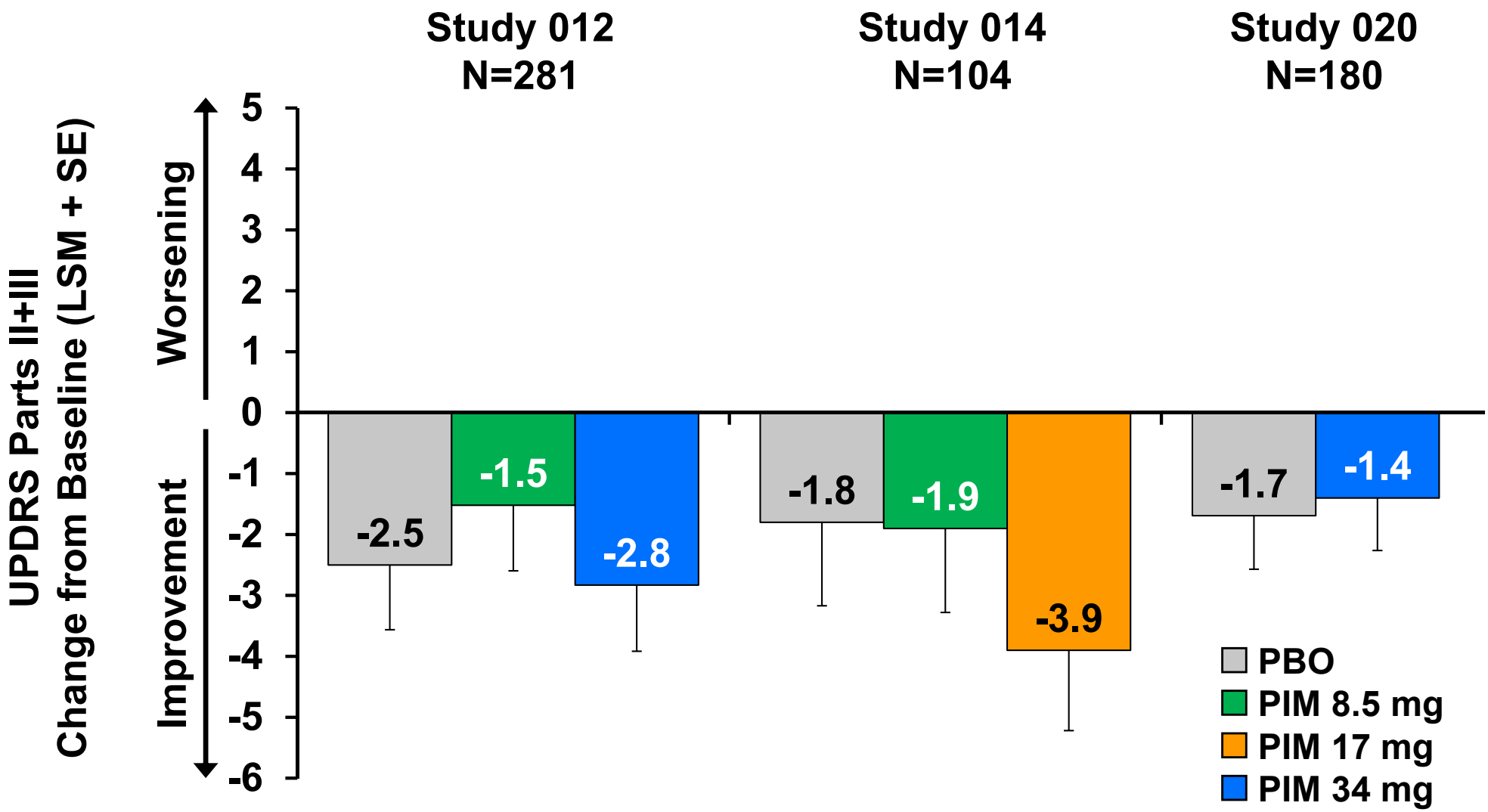
Metabolic disorders

	PIM 34 mg	PBO
Blood glucose increased (%)	–	–
Hyperglycemia (%)	–	1.0
Glucose (random), mmol/L (SD)	0.09 (1.671)	0.19 (1.694)
Weight mean change, kg (SD)	0.0 (2.60)	-0.2 (1.32)

Blood dyscrasia

	Subjects, n (%)	
	PIM 34 mg	PBO
ANC (<1.5 × 10^9/L)	1 (0.5)	6 (2.7)

UPDRS Parts II+III (Studies 012, 014, and 020)



Least squares means (LSM) and standard errors (SE) from ANCOVA model at Week 6 with treatment and region (Studies 012 and 014) as factors and baseline as a covariate (Studies 012, 014, and 020).

Summary of Safety

- Well tolerated and overall AEs similar to placebo
- Observed imbalance in SAEs and deaths
  - No unifying pathophysiologic process
  - Consistent with risk factors associated with PD psychosis and medical comorbidities
- Modest QT prolongation addressed with labeling
- Important safety improvement in key liabilities of existing antipsychotics
- Safety profile adequately characterized and risks manageable

Agenda

Introduction	Michael Monahan Director, Regulatory Affairs ACADIA Pharmaceuticals Inc.
Burden of PD Psychosis and Need for Additional Treatment Options	Stuart Isaacson, MD Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL
Efficacy of Pimavanserin	Serge Stankovic, MD, MSPH Executive Vice President, R&D ACADIA Pharmaceuticals Inc.
Safety of Pimavanserin	George Demos, MD Executive Director, Drug Safety and Pharmacovigilance ACADIA Pharmaceuticals Inc.
Benefit/Risk Profile	**Serge Stankovic, MD, MSPH** **Executive Vice President, R&D** **ACADIA Pharmaceuticals Inc.**
Clinician Perspective	**Clive Ballard, MB ChB, MRCPsych, MMedSci, MD** **Professor, Institute of Psychiatry** **King's College London, London, UK**

Benefit / Risk Profile

Serge Stankovic, MD, MSPH

Executive Vice President, Research and Development
ACADIA Pharmaceuticals Inc.

Serious Unmet Medical Need

- Parkinson's psychosis is a progressive and debilitating condition
  - Dramatically increases the already existing burden in advanced PD patients
- No approved treatment options
- Treatments currently used "off-label" require critical compromises
  - Not effective
  - Worsen motor symptoms
  - Have serious safety concerns
  - Require extensive blood monitoring
- Left untreated, progressively severe consequences for patients, their families, and caregivers

Pimavanserin

- First anti-psychotic without dopamine blockade
- Benefits that matter to patients and caregivers
  - 37% average reduction in psychotic symptoms
  - 45% of patients “much improved” or “very much improved”
  - 14% of patients in complete remission
  - Significant reduction in caregiver burden
  - Improved sleep and daytime wakefulness

No “Off-target” Liabilities

- Worsening of motor symptoms
- Orthostatic hypotension
- Sedation-related events
- Metabolic changes
- Blood dyscrasias

Important Safety Observations

- SAEs and Deaths
  - No unifying pathophysiologic process
  - Consistent with risk factors associated with background disease and medical comorbidities
- QT Prolongation
  - Manageable through standard labeling
- CYP3A4 Inhibitors
  - Labeling recommendation for dose reduction

Positive Benefit/Risk Profile

- Breakthrough improvement
- Clinically meaningful benefit
- Manageable risks
- Significant unmet medical need
- Positive benefit/risk profile

Agenda

Introduction	Michael Monahan Director, Regulatory Affairs ACADIA Pharmaceuticals Inc.
Burden of PD Psychosis and Need for Additional Treatment Options	Stuart Isaacson, MD Parkinson's Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL
Efficacy of Pimavanserin	Serge Stankovic, MD, MSPH Executive Vice President, R&D ACADIA Pharmaceuticals Inc.
Safety of Pimavanserin	George Demos, MD Executive Director, Drug Safety and Pharmacovigilance ACADIA Pharmaceuticals Inc.
Benefit/Risk Profile	Serge Stankovic, MD, MSPH Executive Vice President, R&D ACADIA Pharmaceuticals Inc.
Clinician Perspective	**Clive Ballard, MB ChB, MRCPsych, MMedSci, MD** **Professor, Institute of Psychiatry** **King's College London, London, UK**

Clinician's Perspective

Clive Ballard, MB ChB, MRCPsych MMedSci MD

Professor of Age Related Diseases

Institute of Psychiatry

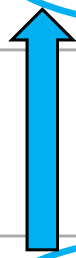
King's College London, London, UK

Example of Actual Trial Participant Achieving Mean Level of Benefit in Study 020

- 6 point improvement on SAPS-PD
  - Visual hallucinations improved from daily to occasional/weekly – 2 point improvement
  - Resolution of mild delusions – 2 point improvement
  - Improvement in auditory and somatic hallucinations – 1 point in each domain

SAPS Rating for Visual Hallucinations

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

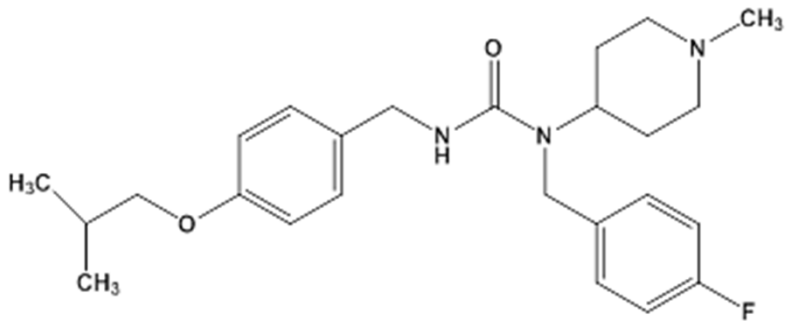


Example of Actual Trial Participant Achieving Complete Resolution of Symptoms

- Complete resolution of:
  - Almost daily persecutory delusions,
  - Almost daily visual hallucinations
  - Questionable auditory hallucinations
  - Questionable tactile hallucinations
  - Marked Global hallucination rating (4 of 5)
- Complete resolution reported in 14% of Study 020 participants

Antipsychotics in Parkinson's Disease Psychosis

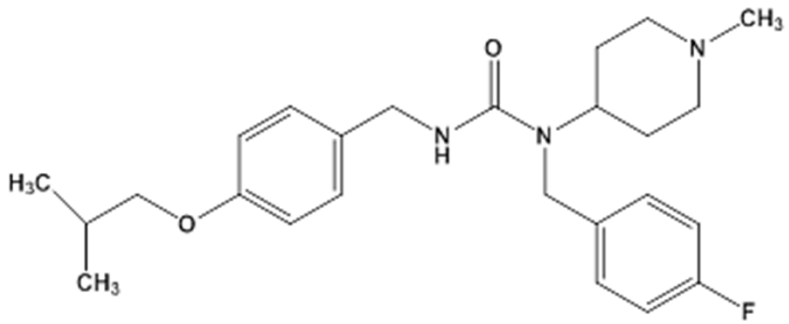
	Quetiapine	Olanzapine	Risperidone	Clozapine
Efficacy	-	-	-	+++
Mortality	+	+	+	+
Worsening of motor symptoms	+/-	++	++	+/-
Neuroleptic Malignant Syndrome	++	++	++	+
Cerebrovascular accident	++	++	++	+
Orthostatic hypotension	+	+	+	++
Falls	+	+	+	+
Somnolence/Fatigue	+++	++	++	++
Blood dyscrasias	+	+	+	+++
Other	Accelerated Cognitive Decline, Pulmonary Embolism, Tardive Dyskinesia, Seizures			



NUPLAZID™ (pimavanserin)

ACADIA Pharmaceuticals Inc.
March 29, 2016

Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration



NUPLAZID™ (pimavanserin)

ACADIA Pharmaceuticals Inc.
March 29, 2016

Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration

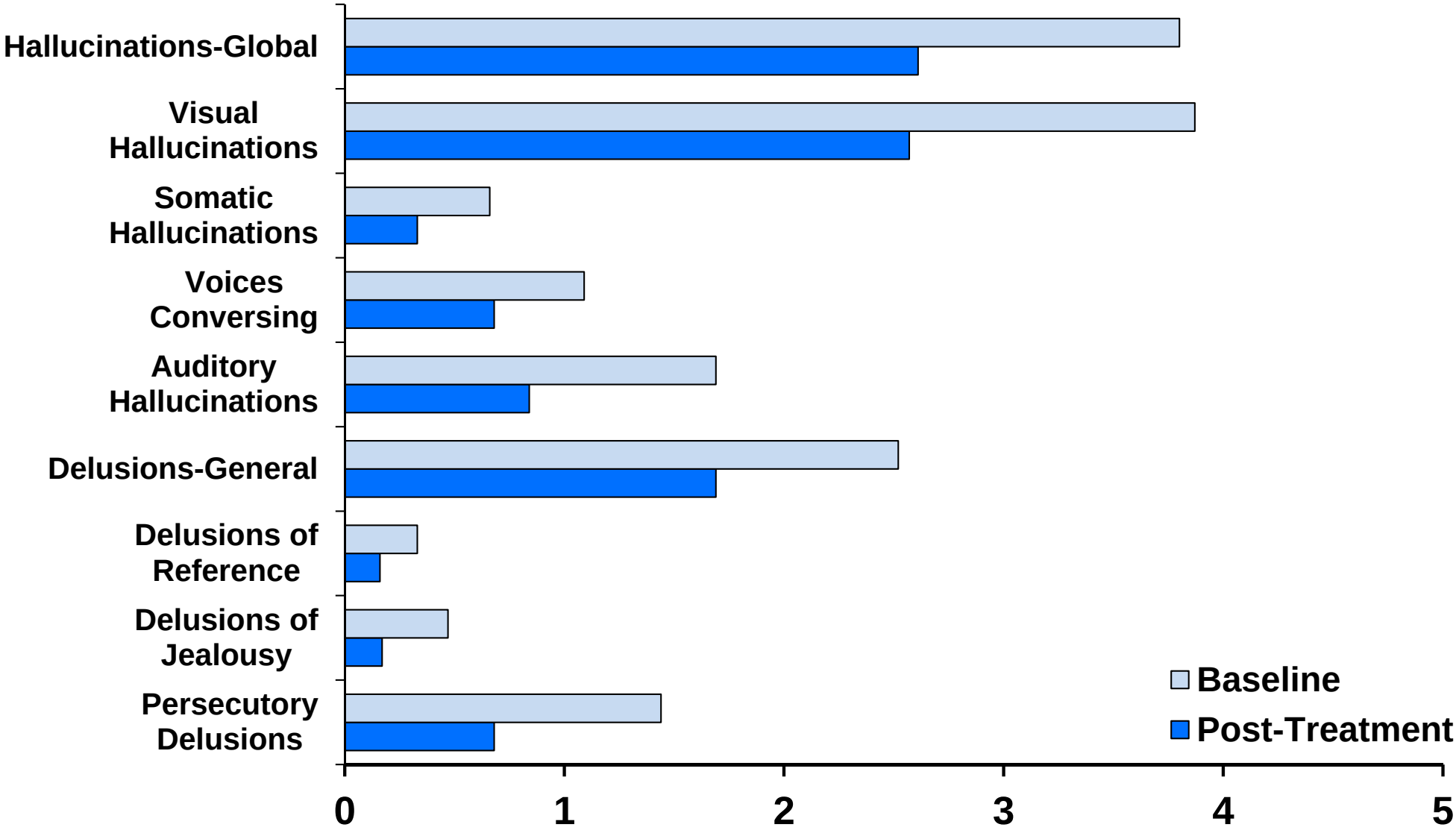
Acadia Pharmaceuticals

Supporting Slides

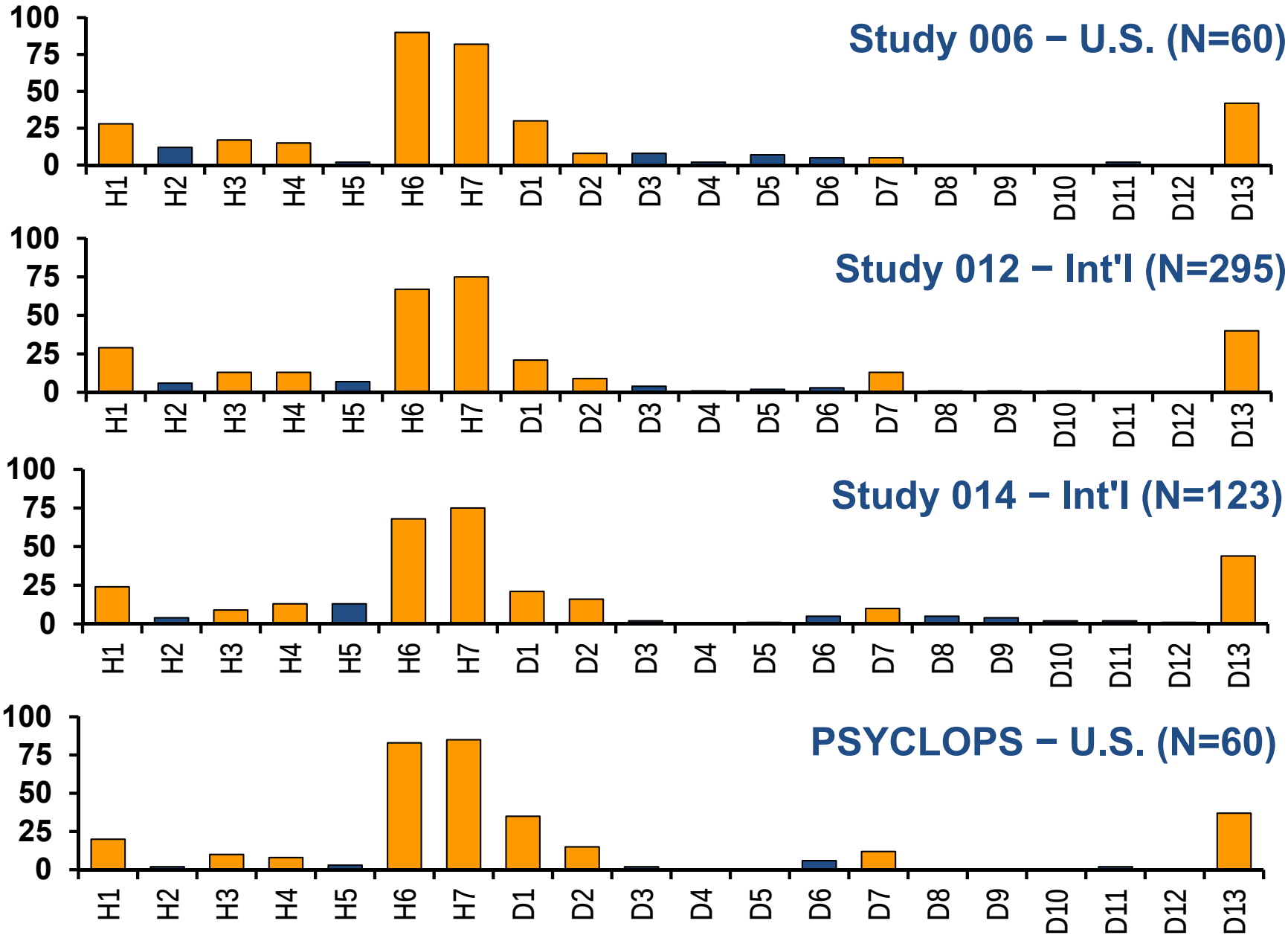
TEAEs: Overall Summary PDP Randomized Concomitant Selective Serotonin Reuptake Inhibitors

	With Drug		Without Drug	
Preferred Term, Events n (%)	34 mg N=40	PBO N=49	34 mg N=162	PBO N=182
Any TEAE	30 (75.0)	34 (69.4)	94 (58.0)	107 (58.8)
Any Serious TEAE	4 (10.0)	2 (4.1)	12 (7.4)	6 (3.3)
Any TEAE Leading to Treatment Discontinuation or Study Termination	4 (10.0)	1 (2.0)	12 (7.4)	9 (4.9)
Any TEAE Resulting in Death	–	–	3 (1.9)	1 (0.5)

Pimavanserin Control of Psychotic Symptoms in Parkinson's Patients



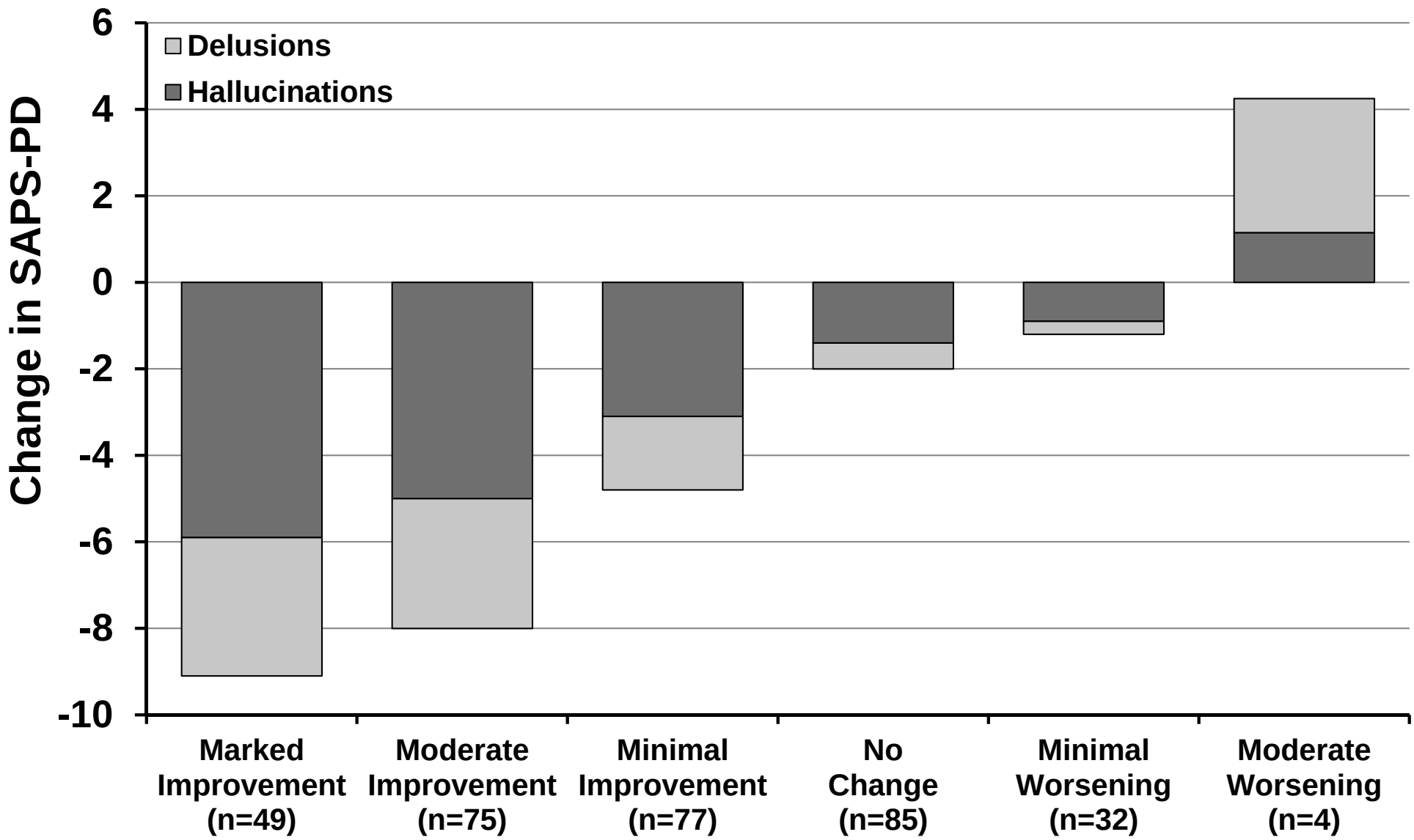
Baseline SAPS-H+D Scores (%) – Voss 2012



20-Item SAPS-H+D

- **Hallucinations**
  - ☑ Auditory Hallucinations
  - ☐ Voices Commenting
  - ☑ Voices Conversing
  - ☑ Somatic or Tactile Hallucinations
  - ☐ Olfactory Hallucinations
  - ☑ Visual Hallucinations
  - ☑ Global Rating of Severity of Hallucinations
- **Delusions**
  - ☑ Persecutory Delusions
  - ☑ Delusions of Jealousy
  - ☐ Delusions of Sin or Guilt
  - ☐ Grandiose Delusions
  - ☐ Religious Delusions
  - ☐ Somatic Delusions
  - ☑ Ideas of Delusions of Reference
  - ☐ Delusions of Being Controlled
  - ☐ Delusions of Mind Reading
  - ☐ Thought Broadcasting
  - ☐ Thought Insertion
  - ☐ Thought Withdrawal
  - ☑ Global Rating of Severity of Delusions

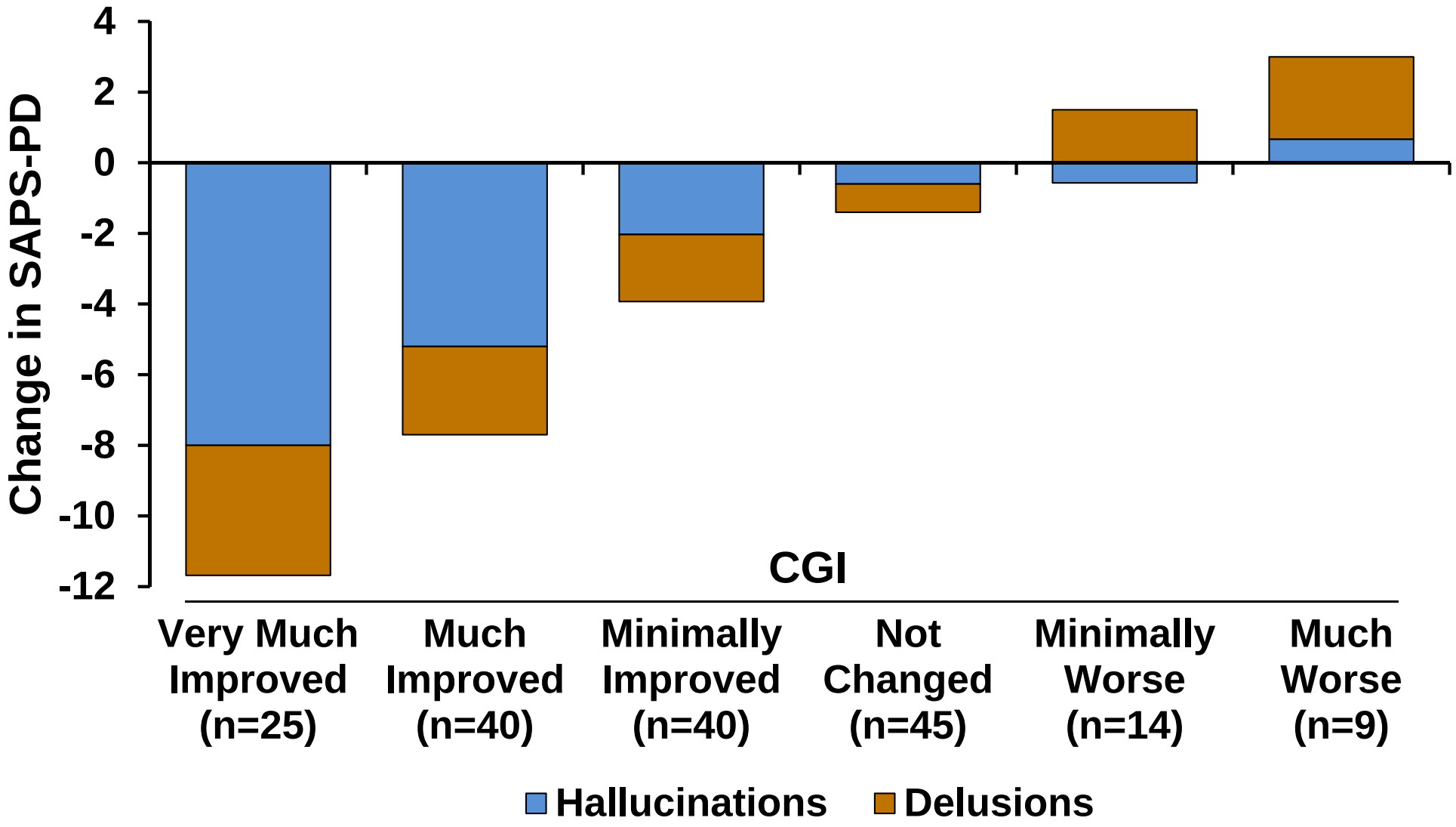
Sensitivity to Change of SAPS-PD Stratified by CGI-I (Voss 2012)



*Change is from baseline to final visit.

Adapted from *Voss et al., Parkinsonism and Related Disorders, 2012

Sensitivity to Change of SAPS-PD Stratified by CGI-I (Study 020)



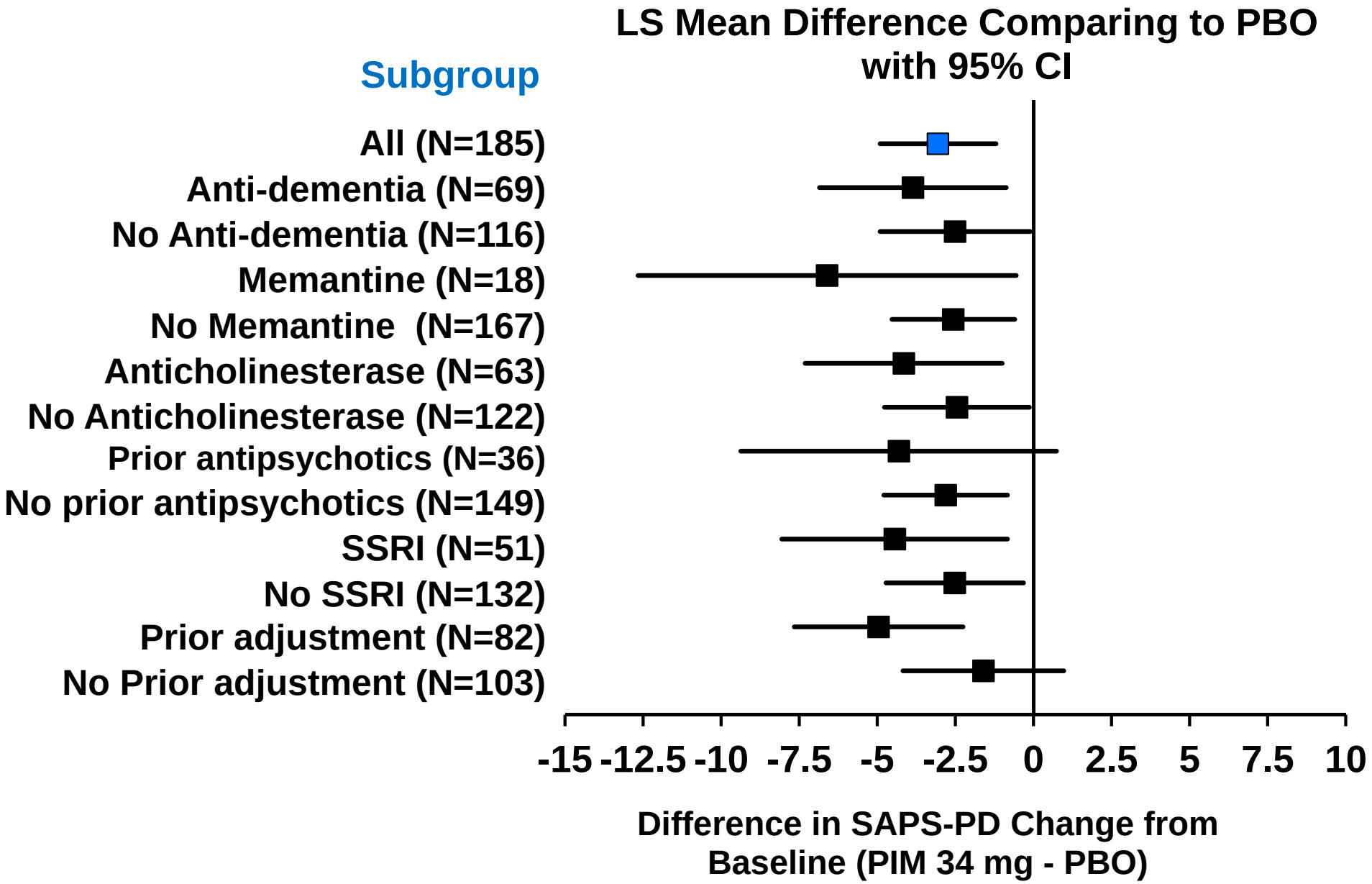
*Change is from Baseline to final visit.

Concomitant PD Medications
Study 020, Safety Population

	PIM 34 mg, n (%) n = 104	PBO, n (%) n = 94	Total, n (%) n = 198
Overall	103 (99.0)	93 (98.9)	196 (99.0)
Anticholinergic Agents , N04aa	1 (1.0)	-	1 (0.5)
Trihexyphenidyl Hydrochloride	1 (1.0)	-	1 (0.5)
Dopaminergic Agents , N04ba	98 (94.2)	90 (95.7)	188 (95.0)
Sinemet	89 (85.6)	81 (86.2)	170 (85.9)
Stalevo	14 (13.5)	14 (14.9)	28 (14.1)
Carbidopa	3 (2.9)	5 (5.3)	8 (4.0)
Levodopa	1 (1.0)	1 (1.1)	2 (1.0)
Dopaminergic Agents , N04bb	12 (11.5)	13 (13.8)	25 (12.6)
Amantadine	11 (10.6)	13 (13.8)	24 (12.1)
Amantadine Hydrochloride	1 (1.0)	-	1 (0.5)
Dopaminergic Agents , N04bc	44 (42.3)	44 (46.8)	88 (44.4)
Ropinirole	25 (24.0)	18 (19.2)	43 (21.7)
Pramipexole Dihydrochloride	15 (14.4)	19 (20.2)	34 (17.2)
Pramipexole	5 (4.8)	6 (6.4)	11 (5.6)
Rotigotine	-	1 (1.1)	1 (0.5)
Dopaminergic Agents , N04bd	34 (32.7)	29 (30.9)	63 (31.8)
Rasagiline Mesylate	29 (27.9)	20 (21.3)	49 (24.8)
Selegiline Hydrochloride	1 (1.0)	5 (5.3)	6 (3.0)
Selegiline	3 (2.9)	2 (2.1)	5 (2.5)
Rasagiline	1 (1.0)	2 (2.1)	3 (1.5)
Dopaminergic Agents , N04bx	11 (10.6)	15 (16.0)	26 (13.1)
Entacapone	10 (9.6)	15 (16.0)	25 (12.6)
Tolcapone	1 (1.0)	-	1 (0.51)

SAPS-PD Across Concomitant or Prior Medication Subgroups, PIM 34 mg vs.. PBO
Study 020; mITT; MMRM

EF-410



Psychiatric Disorder TEAEs (Population PDP6: Study 012 and 020)

MedDRA System Organ Class (SOC) Preferred Term	PIM 34 mg N=202	PBO N=231
Psychiatric Disorders	33 (16.3)	32 (13.9)
Confusional state	12 (5.9)	6 (2.6)
Hallucination	10 (5.0)	7 (3.0)
Insomnia	5 (2.5)	7 (3.0)
Psychotic disorder	3 (1.5)	5 (2.2)
Anxiety	2 (1.0)	3 (1.3)
Delusion	1 (0.5)	–
Hallucination, Visual	3 (1.5)	4 (1.7)
Agitation	1 (0.5)	1 (0.4)
Sleep Disorder	2 (1.0)	2 (0.9)
Delirium	2 (1.0)	1 (0.4)
Depression	2 (1.0)	1 (0.4)
Disorientation	–	2 (0.9)
Mental status changes	2 (1.0)	1 (0.4)
Somatic hallucination	1 (0.5)	-
Amnesia	1 (0.5)	–
Hypervigilance	1 (0.5)	–
Logorrhoea	1 (0.5)	–
Cognitive disorder		1 (0.4)
Hallucination, tactile		1 (0.4)
Psychiatric symptom		1 (0.4)

TEAEs Psychotic Related Events (Population PDP6: Study 012 and 020)

Preferred Term	Subjects, n (%) PIM 34 mg N=202	PBO N=231
Psychotic Related Events	17 (8.4)	17 (7.4)
Hallucination	10 (5.0)	7 (3.0)
Psychotic disorder	3 (1.5)	5 (2.2)
Delusion	1 (0.5)	-
Hallucination, Visual	3 (1.5)	4 (1.7)
Somatic hallucination	1 (0.5)	-
Hallucination, Tactile	-	1 (0.4)
Psychiatric symptoms	-	1 (0.4)

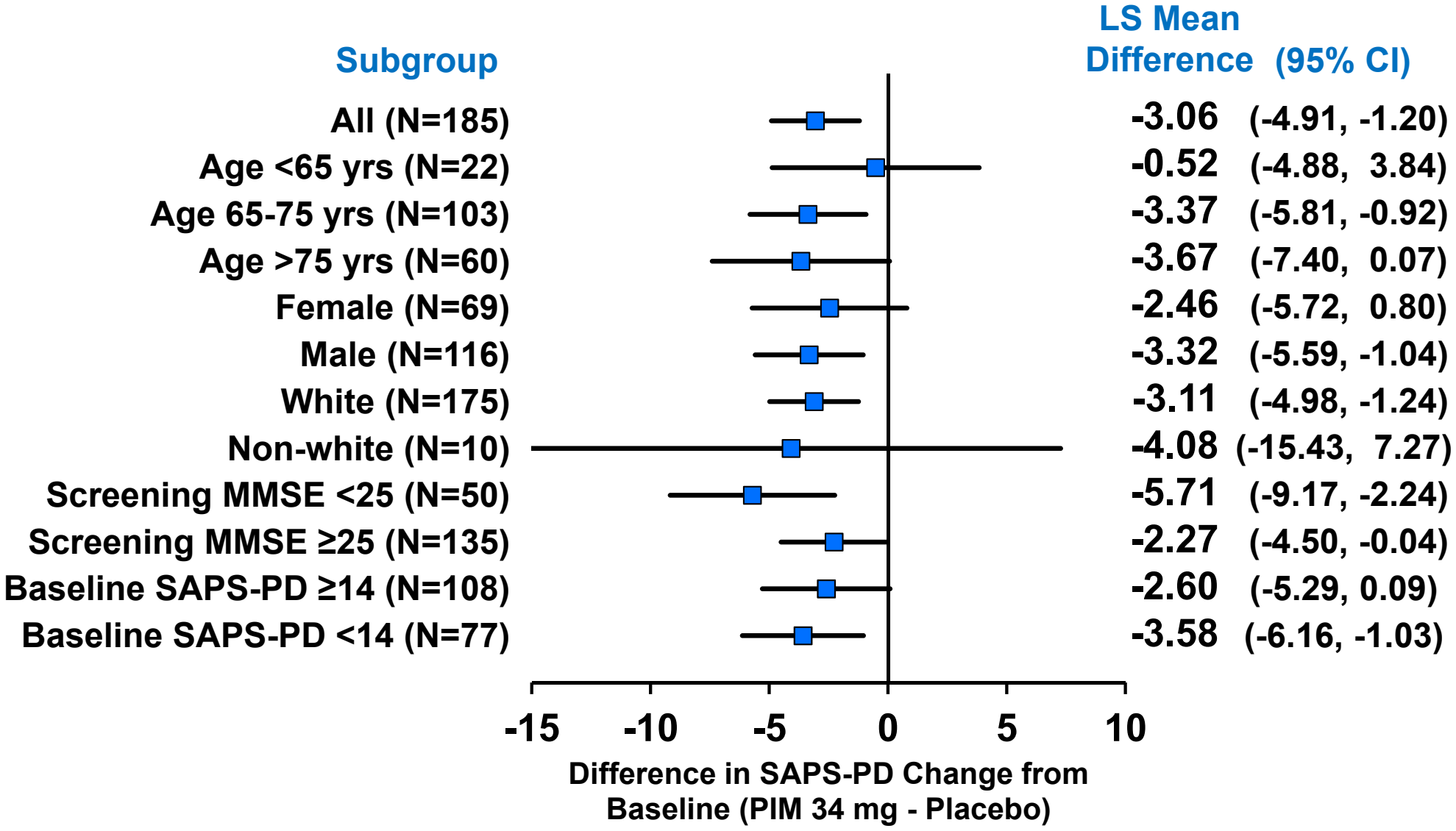
Study 020 Proportion of Responders Measured as SAPS-PD Percent Reduction from Baseline at Week 6 (mITT; N=185)

SAPS-PD Responders[1]	PIM 34 mg N=95 n (%)	PBO N=90 n (%)	Difference[2]	NNT[3]
20% response	60 (63.2)	42 (46.7)	16.5% (p=0.025)	7
30% response	47 (49.5)	32 (35.6)	13.9% (p=0.056)	8
50% response	35 (36.8)	25 (27.8)	9.1% (p=0.189)	12
75% response	22 (23.2)	8 (8.9)	14.3% (p=0.009)	8
Complete response	13 (13.7)	1 (1.1)	12.6% (p=0.001)	8

[1] Subjects with missing values were counted as non-responders.
[2] p-value from a Mantel-Haenszel Chi-Square test.
[3] Number Needed to Treat.

SAPS-PD Score Change from Baseline at Week 6 Across Subgroups
PIM 34 mg vs.. PBO, Study 020, mITT; MMRM

EF-400

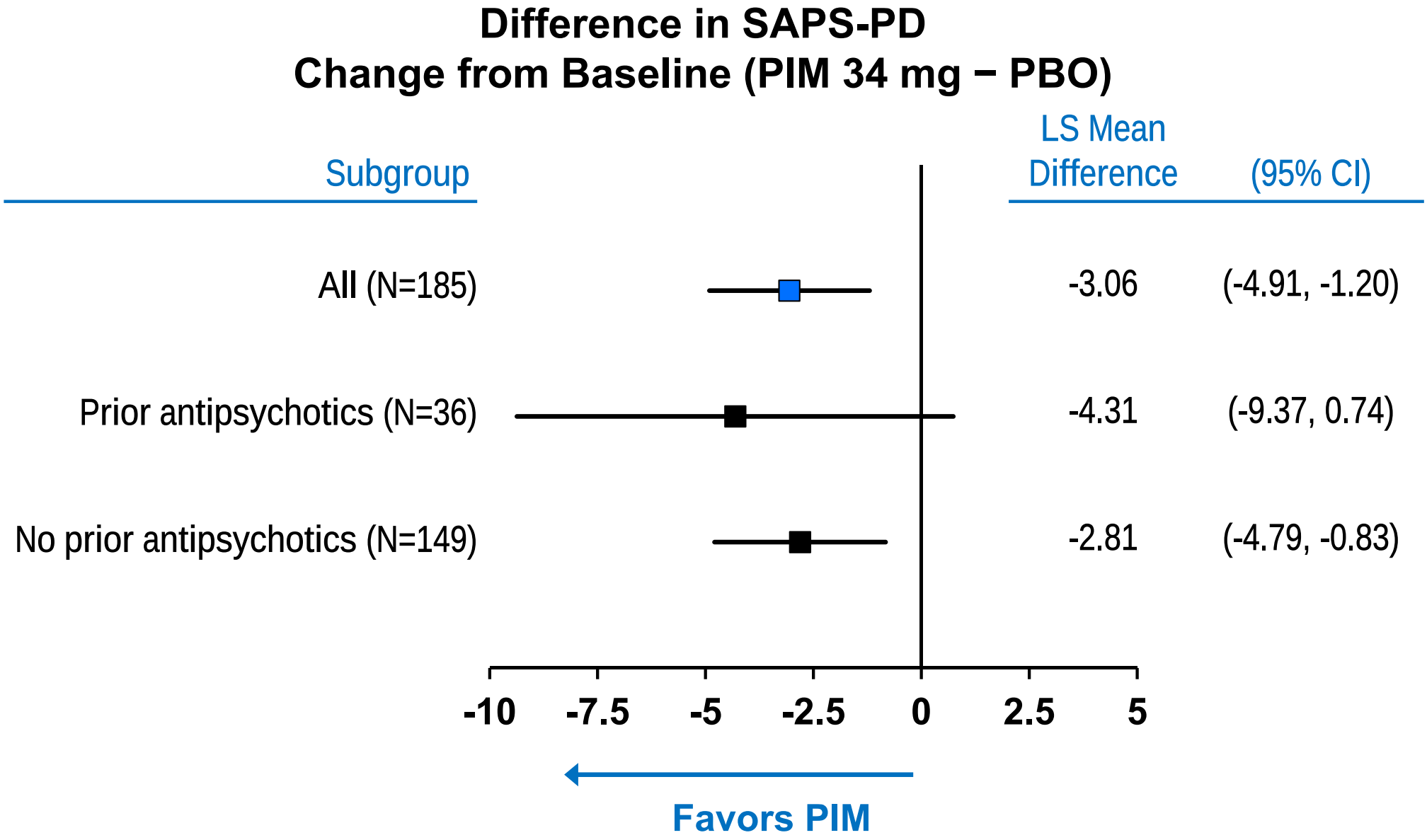


Prior Antipsychotic Medications
PDP6, Safety Population

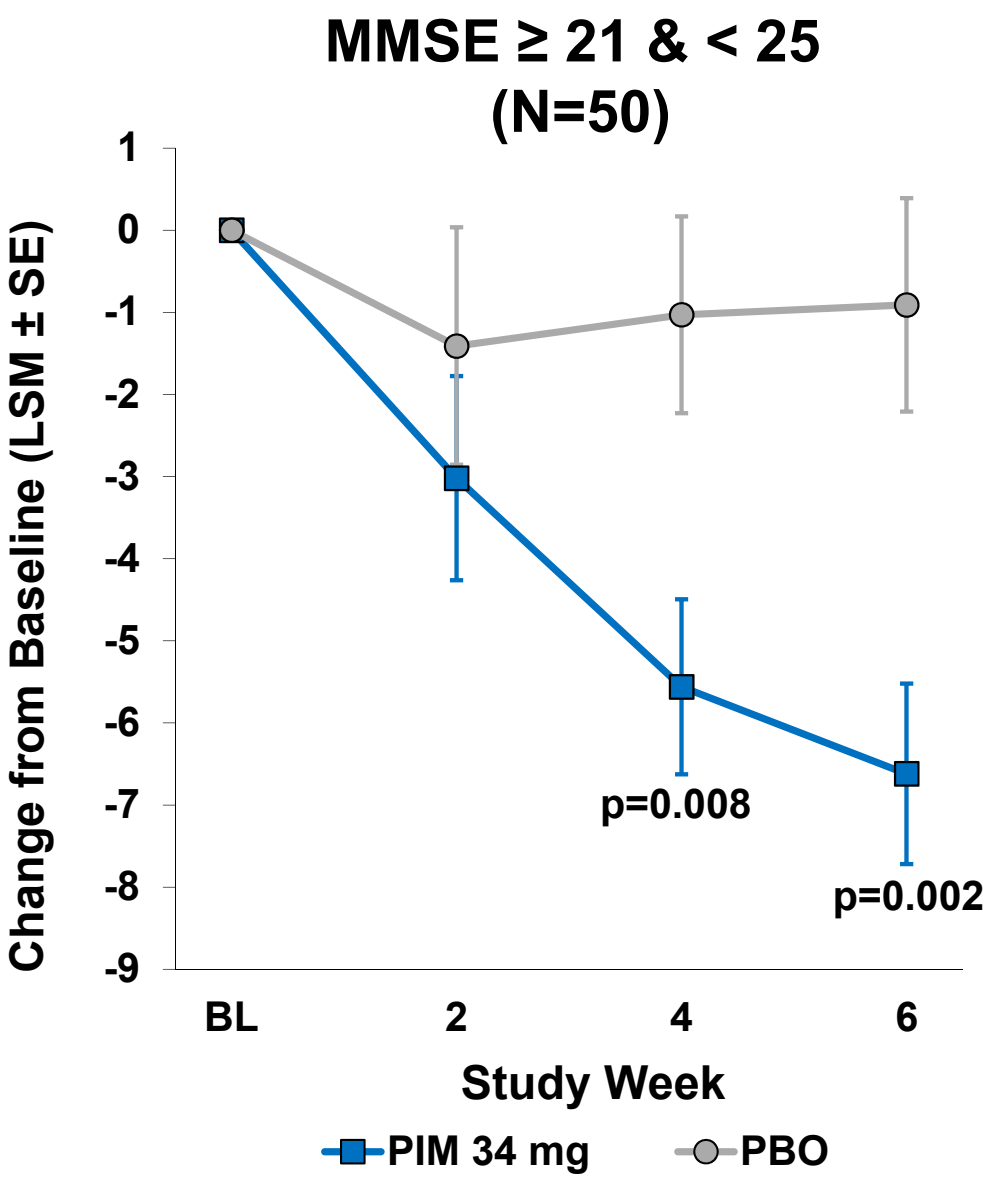
	PIM 34 mg N=202 n (%)	PBO N=231 n (%)
Overall	28 (13.9)	26 (11.3)
Quetiapine	25 (12.4)	23 (10.0)
Clozapine	3 (1.5)	–
Ziprasidone	–	1 (0.4)
Haloperidol	–	1 (0.4)
Risperidone	–	1 (0.4)

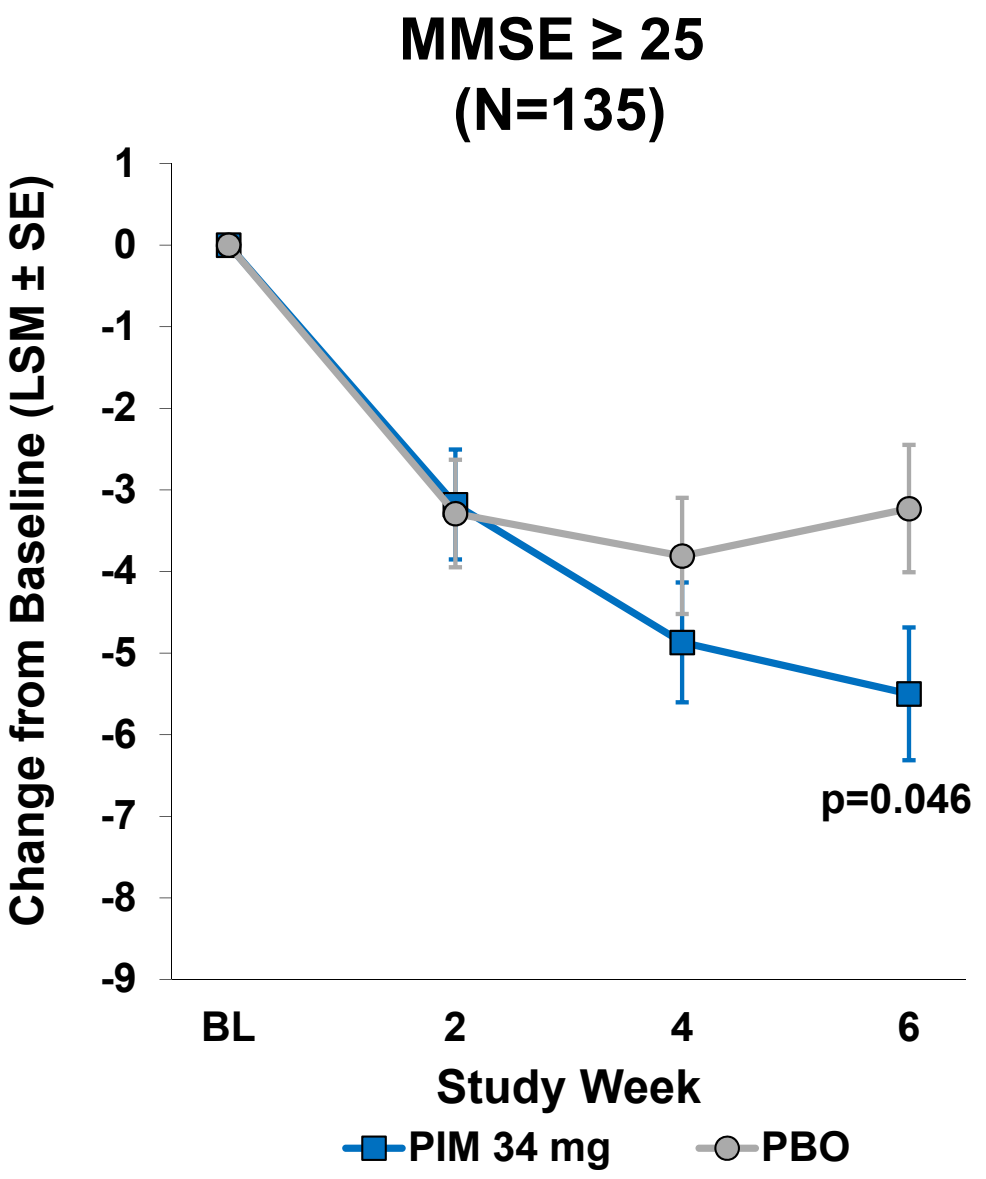
The end date of prior antipsychotics usage was within 21 days from the first dose date

SAPS-PD Change from Baseline at Week 6 by Concomitant or Prior Antipsychotic Usage within 21 Days (Study 020; mITT; MMRM)



SAPS-PD Subgroup Analysis – Screening MMSE
Study 020, mITT; MMRM





Summary AEs by MMSE

Description	PDP6 Population n (%)			
	< 25		≥ 25	
	All PIM N=57	PBO N=59	All PIM N=142	PBO N=174
Any TEAE	34 (57.6)	32 (56.1)	90 (63.4)	109 (62.9)
Any Serious TEAE	4 (6.8)	3 (5.3)	12 (8.5)	5 (2.9)
Any TEAE Resulting in Death	1 (1.7)	1 (1.8)	2 (1.4)	–
Any TEAE Leading to Treatment Discontinuation or Study Termination	4 (6.8)	3 (5.3)	12 (8.5)	7 (4.0)

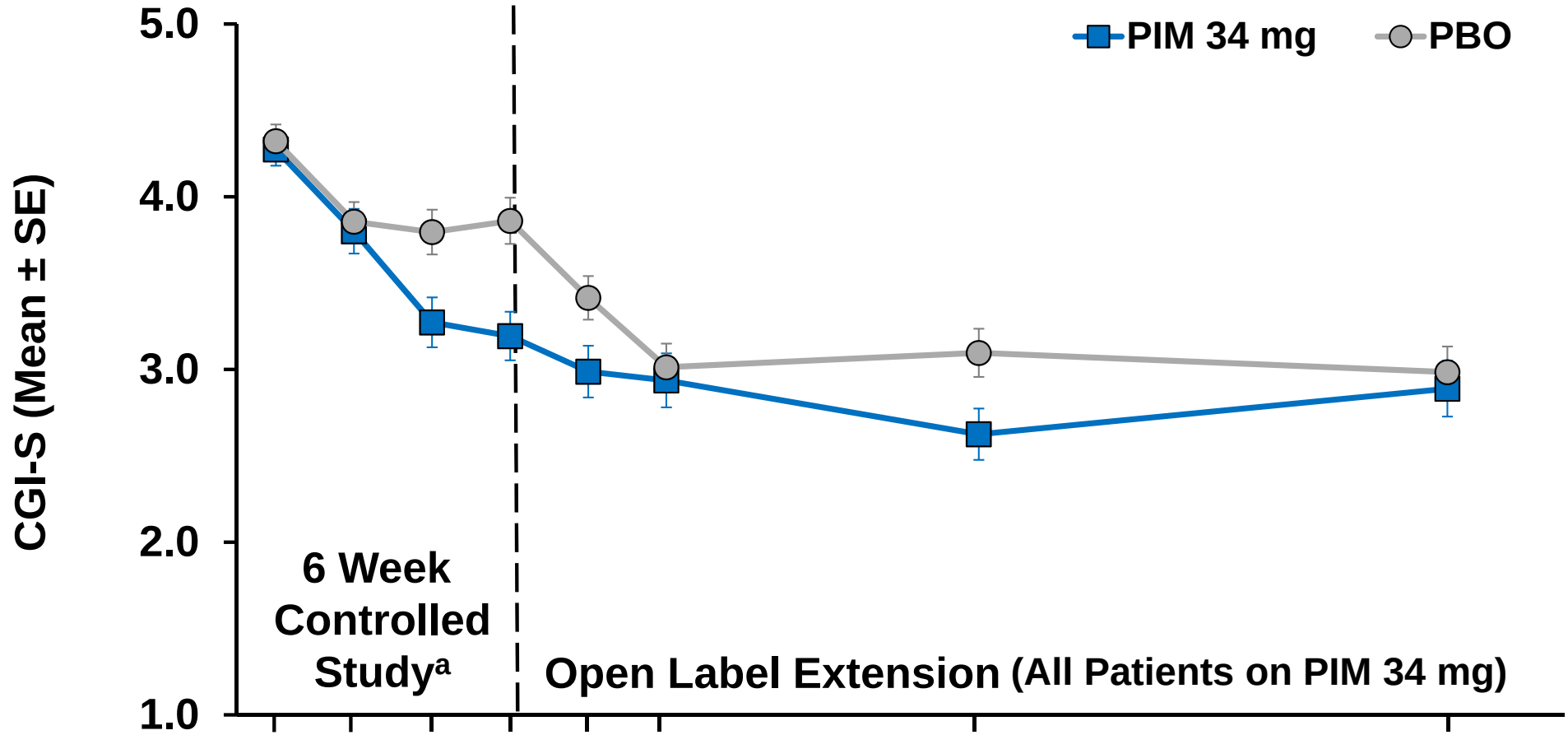
A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurred on or after the administration of first study drug dose and before or on the last dose date (+30 days).
The PDP6 Population is from placebo-controlled 6-week studies and the PDPLT Population is from open-label long-term studies.

PD Prevalence by Race

Race	Incidence, %
White	80.0%
Black	4.7%
Hispanic	8.0%
Asian	7.1%

Parkinson's disease cases and population by race/ethnicity, Kaiser Permanente, 1994–1995. Am J Epidemiol June 1, 2003 vol. 157 no. 11 1015-1022

Study 020/015 Open-Label Extension: Uncontrolled Long-Term Efficacy Data (CGI-S, OC)



PIM 34 mg, n=	95	95	88	88	81	79	72	63
PBO, n=	90	90	88	86	82	77	73	65

a. Patients from Study 020 rolled over into Study 015.

Study 015 Open-Label Extension: Uncontrolled Long-Term Efficacy Data (CGI-S, OC)