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Supplementary Appendix

Supplemental Table 1. Pimavanserin for Parkinson's Disease Psychosis – Overview of Placebo-Controlled Randomized Clinical Trials

Study, ClinicalTrials.gov Identifier	Key Design Characteristics	Efficacy Outcomes	Safety and Tolerability Outcomes	Summary of Results
ACP-103-020 [pivotal clinical trial that led to approval in the US], NCT01174004	Phase III, 6 weeks of double-blind treatment. On Day 1, subjects were randomized to receive pimavanserin 34 mg or placebo (1:1 ratio). Primary outcome was the SAPS-PD, as rated by a remote rater in real-time using videoconference technology, and who did not have access to the study design, entrance criteria, visit number, treatment assignment, or any study data for the subject or caregiver. Study conducted in the US and Canada 2010-2012.	SAPS-PD; SAPS-H+D; SAPS-H; SAPS-D; CGI-S; CGI-I; SCOPA; CBS	UPDRS Parts II and III; AEs; laboratory tests (hematology, clinical chemistry, and urinalysis); physical examinations; ECGs.	N=199 (PIM 105, PBO 94). PIM demonstrated statistically significant efficacy vs. PBO on the SAPS-PD. Non-inferiority for PIM compared to PBO was observed on UPDRS Parts II+III. Three (3.2%) subjects in the PBO group and 10 (9.6%) subjects in the PIM group discontinued due to AEs.
ACP-103-012, NCT00477672	Phase IIb/III, 6 weeks of double-blind treatment. On Day 1, subjects were randomized to receive PIM 8.5 mg or 34 mg or PBO (1:1:1 ratio). Primary outcome was SAPS-H+D. Study conducted in the US, Europe and India 2007-2009.	SAPS-H+D; SAPS-H; SAPS-D; CGI-S; CGI-I; UPDRS Parts I, IV, V, and VI; SCOPA; CBS; NMS.	UPDRS Parts II and III; AEs; laboratory tests (hematology, clinical chemistry, and urinalysis); physical examinations; ECGs.	N=298 (PIM 8.5 mg 101, PIM 34 mg 99, PBO 98). No statistically significant treatment effects (adjusted for multiplicity) were observed for each PIM group compared with PBO for the SAPS-H+D. [a] Non-inferiority for each PIM group compared to PBO was observed on UPDRS Parts II + III. Three (3.1%) subjects in the PBO group, 7 (7.1%) in the PIM 8.5 mg group, and 6 (6.1%) in the PIM 34 mg group discontinued due to AEs.
ACP-103-014, NCT00658567	Phase IIb/III, 6 weeks of double-blind treatment. On Day 1, subjects were randomized to receive PIM 8.5 mg or 17 mg or PBO (1:1:1 ratio). Primary outcome was SAPS-H+D for the 17 mg dose vs. PBO. Study conducted in the US and Europe 2008-2009.	SAPS-H+D; SAPS-H; SAPS-D; CGI-S; CGI-I; UPDRS Parts I, IV, V, and VI; SCOPA; CBS; NMS.	UPDRS Parts II and III; AEs; laboratory tests (hematology, clinical chemistry, and urinalysis); physical examinations; ECGs.	N=123 (PIM 8.5 mg 42, PIM 17 mg 41, PBO 40). Study terminated early by the sponsor. No statistically significant treatment effects were observed for the PIM 17 mg group compared with PBO for the SAPS-H+D. Non-inferiority for the PIM 17 mg group

				compared to PBO was observed on UPDRS Parts II+III. Four (10.3%) subjects in the PBO group, 2 (4.9%) in the PIM 8.5 mg group, and 3 (7.3%) in the PIM 17 mg group discontinued due to AEs.
ACP-103-006, NCT00087542	Phase II, 4 weeks of double-blind treatment. On Day 1, subjects received PIM 17 mg or PBO (randomized on a 1:1 ratio), with a possible increase to 34 mg daily on Study Day 8 and a further possible increase to 51 mg daily on Study Day 15, depending upon individual clinical response. Subjects were to receive a stable daily dosage from Day 16 until Day 28. Primary outcome was UPDRS Parts II and III. Study conducted in the US 2004-2005.	SAPS-H+D; SAPS-H; SAPS-D; CGI-S; PPRS; ESS; UPDRS Parts I, IV, and VI.	UPDRS Parts II and III; AEs; laboratory tests (hematology, clinical chemistry, and urinalysis); physical examinations; ECGs.	N=60 (PIM 29, PBO 31). A slight, but clinically insignificant, improvement on the UPDRS Parts II and III observed for both PIM and PBO. PIM showed significantly greater improvement in some but not all measures of psychosis, including SAPS global measures of hallucinations and delusions, persecutory delusions, and the UPDRS measure of delusions and hallucinations. Three (5.0%) subjects (2 [6.9%] PIM, 1 [3.2%] PBO) discontinued the study due to AEs.

[a] Of note, at US study centers, SAPS-H+D assessments were conducted via live video interviews by central raters blinded to study design, entrance criteria, visit number, treatment assignment, and any study data for the subject or caregiver, similar to the procedures used for study ACP-103-020. At non-US study centers (i.e., those in Europe and India), site-based raters were trained and certified to administer SAPS assessments in their respective languages. For the US sites the pimavanserin 34 mg dose showed a trend ($p<0.1$) toward improvement compared to placebo (treatment difference 2.5 points; LS mean change from baseline -6.9 for pimavanserin 34 mg, -4.4 for placebo; 95% CI: -5.4 to 0.5; $p=0.099$). At sites where SAPS-H+D was assessed by a site-based rater (i.e., non-US sites), there was no statistical difference between treatment arms.

Abbreviations: AE: adverse event; CBS: Caregiver Burden Scale; CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; ECG: electrocardiogram; ESS: Epworth Sleepiness Scale; NMS: Non-Motor Symptoms scale; PBO: placebo; PIM: pimavanserin; PPRS: Parkinson's Psychosis Rating Scale; SAPS: Scale for the Assessment of Positive Symptoms; SAPS-H+D: SAPS hallucinations and delusions items; SAPS-PD: SAPS adapted for Parkinson's Disease; SCOPA: Scales for Outcomes in Parkinson's Disease; UPDRS: Unified Parkinson's Disease Rating Scale

Supplemental Table 2. Pimavanserin for Parkinson's Disease Psychosis Placebo-Controlled Randomized Clinical Trials – Demographics and Baseline Clinical Characteristics [a]

Characteristic	ACP-103-020, NCT01174004		ACP-103-012, NCT00477672			ACP-103-014, NCT00658567			ACP-103-006, NCT00087542	
	PBO	PIM 34 mg/d	PBO	PIM 8.5 mg/d	PIM 34 mg/d	PBO	PIM 8.5 mg/d	PIM 17 mg/d	PBO	PIM 17-51 mg/d
n	90	95	97	98	92	38	38	41	31	28
Age, years	72.4 (7.92)	72.4 (6.55)	69.8 (9.62)	69.5 (8.27)	69.3 (7.80)	73.3 (7.84)	71.6 (6.99)	72.1 (8.15)	70.0 (9.37)	72.2 (7.84)
Sex, female	38 (42%)	31 (33%)	47 (48%)	35 (36%)	24 (26%)	12 (32%)	14 (37%)	17 (41%)	11 (35%)	3 (11%)
Ethnic group, white	85 (94%)	90 (95%)	82 (85%)	84 (86%)	81 (88%)	36 (95%)	37 (97%)	41 (100%)	31 (100%)	27 (96%)
Body mass index, kg/m²	26.4 (5.65)	26.2 (4.57)	26.4 (4.54)	25.6 (5.23)	25.5 (4.29)	25.6 (4.30)	25.3 (4.07)	26.7 (3.82)	26.3 (5.13)	25.3 (4.47)
Mini-Mental State Examination score	26.6 (2.40)	26.0 (2.61)	26.3 (2.52)	26.2 (2.75)	26.2 (2.71)	26.5 (2.89)	26.6 (2.32)	26.0 (2.90)	26.5 (2.68)	25.1 (3.44)
UPDSRS II + III score	52.6 (17.10)	51.5 (17.59)	55.6 (20.51)	51.8 (21.28)	51.4 (21.55)	45.1 (19.68)	47.7 (19.78)	47.1 (18.24)	49.7 (15.49)	47.8 (13.44)
Time since first psychotic symptoms, months	36.4 (39.57)	30.9 (30.01)	23.0 (36.32)	19.7 (20.75)	18.9 (24.03)	26.2 (27.16)	32.2 (29.04)	24.6 (26.96)	NA	NA
Time since Parkinson's Disease diagnosis, months	127.5 (79.91)	115.9 (78.48)	116.6 (82.09)	97.6 (63.73)	85.0 (61.76)	112.8 (64.59)	116.5 (72.02)	107.8 (67.18)	NA	NA
Use of antiparkinson drugs at baseline and throughout trial	89 (99%)	94 (99%)	96 (99%)	96 (98%)	90 (98%)	36 (95%)	37 (97%)	38 (93%)	31 (100%)	28 (100%)
SAPS-PD [b]	14.7 (5.55)	15.9 (6.12)	12.1 (5.77)	14.4 (7.24)	13.0 (5.99)	14.6 (6.97)	13.4 (7.61)	13.2 (5.25)	14.9 (8.20)	15.3 (5.12)
SAPS-H+D	15.8 (6.52)	17.5 (7.57)	14.0 (7.90)	17.1 (9.77)	15.0 (7.87)	17.0 (8.66)	15.8 (10.00)	15.5 (6.60)	17.5 (11.42)	17.9 (7.57)
CGI-S	4.3 (0.91)	4.3 (0.92)	3.8 (0.93)	3.9 (0.97)	3.8 (0.96)	4.0 (0.91)	3.9 (1.09)	4.0 (0.99)	3.7 (1.37)	4.3 (0.48)

[a] Intent-to-treat analysis set (randomized subjects who received at least one dose of study drug and had baseline and at least one post-baseline assessment on the primary outcome measure). Data are mean (SD) or n (%).
[b] SAPS-PD calculated *post hoc* for studies ACP-103-012, ACP-103-014, and ACP-103-006.

Abbreviations: CGI-S: Clinical Global Impression-Severity; NA: not available; PBO: placebo; PIM: pimavanserin; SAPS: Scale for the Assessment of Positive Symptoms; SAPS-H+D: SAPS hallucinations and delusions items; SAPS-PD: SAPS adapted for Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale

Supplemental Table 3. Efficacy Outcomes for Studies ACP-103-020 and ACP-103-012; Pooled Data for Pimavanserin 34 mg/d and Placebo (All Sites)

Outcome	Pimavanserin 34 mg/d		Placebo		NNT (95% CI)
	n/N	%	n/N	%	
≥30% decrease from baseline on SAPS-PD	108/186	58.1	84/185	45.4	8 (5-39)
≥50% decrease from baseline on SAPS-PD	79/186	42.5	64/185	34.6	13 (ns)
≥30% decrease from baseline on SAPS-H+D	106/186	57.0	87/185	47.0	10 (ns)
≥50% decrease from baseline on SAPS-H+D	79/186	42.5	62/185	33.5	12 (ns)
≥3 point decrease from baseline on SAPS-PD	124/186	66.7	94/185	50.8	7 (4-17)
≥5 point decrease from baseline on SAPS-PD	100/186	53.8	75/185	40.5	8 (5-32)
≥7 point decrease from baseline on SAPS-PD	76/186	40.9	56/185	30.3	10 (5-111)
≥10 point decrease from baseline on SAPS-PD	59/186	31.7	34/185	18.4	8 (5-22)
≥1 point decrease from baseline on the CGI-S	101/186	54.3	87/184	47.3	15 (ns)
≥2 point decrease from baseline on the CGI-S	56/186	30.1	38/184	20.7	11 (6-156)
Score of 1 (very much improved) on the CGI-I	40/187	21.4	15/184	8.2	8 (5-17)
Score of 1 (very much improved) or 2 (much improved) on the CGI-I	81/187	43.3	60/184	32.6	10 (5-112)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 2	91/187	48.7	78/185	42.2	16 (ns)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 4	110/187	58.8	92/185	49.7	11 (ns)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 6 or endpoint	118/187	63.1	97/185	52.4	10 (5-146)
100% decrease from baseline on SAPS-PD	29/186	15.6	15/185	8.1	14 (8-105)

CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; n – numerator; ns – not significant; N - denominator [randomized subjects who received at least one dose of study drug and had at least one post-baseline assessment]; SAPS-H+D: Scale for the Assessment of Positive Symptoms hallucinations and delusions items; SAPS-PD: Scale for the Assessment of Positive Symptoms adapted for Parkinson's Disease

Supplemental Table 4. Efficacy Outcomes for Study ACP-103-020 for Subjects with Baseline Scale for the Assessment of Positive Symptoms Adapted for Parkinson's Disease is ≥ Median Score of 14

Outcome	Pimavanserin 34 mg/d		Placebo		NNT (95% CI)
	n/N	%	n/N	%	
≥30% decrease from baseline on SAPS-PD	30/57	52.6	21/51	41.2	9 (ns)
≥50% decrease from baseline on SAPS-PD	21/57	36.8	17/51	33.3	29 (ns)
≥30% decrease from baseline on SAPS-H+D	32/57	56.1	21/51	41.2	7 (ns)
≥50% decrease from baseline on SAPS-H+D	21/57	36.8	16/51	31.4	19 (ns)
≥3 point decrease from baseline on SAPS-PD	45/57	78.9	27/51	52.9	4 (3-12)
≥5 point decrease from baseline on SAPS-PD	36/57	63.2	23/51	45.1	6 (ns)
≥7 point decrease from baseline on SAPS-PD	29/57	50.9	21/51	41.2	11 (ns)
≥10 point decrease from baseline on SAPS-PD	24/57	42.1	14/51	27.5	7 (ns)
≥1 point decrease from baseline on the CGI-S	34/57	59.6	19/51	37.3	5 (3-25)
≥2 point decrease from baseline on the CGI-S	16/57	28.1	11/51	21.6	16 (ns)
Score of 1 (very much improved) on the CGI-I	9/57	15.8	2/51	3.9	9 (5-100)
Score of 1 (very much improved) or 2 (much improved) on the CGI-I	28/57	49.1	13/51	25.5	5 (3-17)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 2	22/57	38.6	20/51	39.2	-162 (ns) [a]
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 4	33/57	57.9	25/51	49.0	12 (ns)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 6 or endpoint	38/57	66.7	23/51	45.1	5 (3-31)
100% decrease from baseline on SAPS-PD	3/57	5.3	1/51	2.0	31 (ns)

[a] A "negative" NNT results from when the rate of the efficacy outcome is higher for placebo than for pimavanserin. In this instance, the result was not statistically significant.

CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; n – numerator; ns – not significant; N - denominator [randomized subjects who received at least one dose of study drug and had at least one post-baseline assessment]; SAPS-H+D: Scale for the Assessment of Positive Symptoms hallucinations and delusions items; SAPS-PD: Scale for the Assessment of Positive Symptoms adapted for Parkinson's Disease

Supplemental Table 5. Efficacy Outcomes for Studies ACP-103-020 and ACP-103-012 for Subjects with Baseline Scale for the Assessment of Positive Symptoms Adapted for Parkinson's Disease is ≥ Median Score (14 for ACP-103-020 and 11.5 for ACP-103-012); Pooled Data for Pimavanserin 34 mg/d and Placebo (All Sites)

Outcome	Pimavanserin 34 mg/d		Placebo		NNT (95% CI)
	n/N	%	n/N	%	
≥30% decrease from baseline on SAPS-PD	63/104	60.6	50/97	51.5	12 (ns)
≥50% decrease from baseline on SAPS-PD	43/104	41.3	37/97	38.1	32 (ns)
≥30% decrease from baseline on SAPS-H+D	62/104	59.6	53/97	54.6	21 (ns)
≥50% decrease from baseline on SAPS-H+D	43/104	41.3	37/97	38.1	32 (ns)
≥3 point decrease from baseline on SAPS-PD	81/104	77.9	60/97	61.9	7 (4-29)
≥5 point decrease from baseline on SAPS-PD	67/104	64.4	52/97	53.6	10 (ns)
≥7 point decrease from baseline on SAPS-PD	57/104	54.8	44/97	45.4	11 (ns)
≥10 point decrease from baseline on SAPS-PD	47/104	45.2	33/97	34.0	9 (ns)
≥1 point decrease from baseline on the CGI-S	60/104	57.7	45/96	46.9	10 (ns)
≥2 point decrease from baseline on the CGI-S	32/104	30.8	24/96	25.0	18 (ns)
Score of 1 (very much improved) on the CGI-I	21/104	20.2	7/97	7.2	8 (5-27)
Score of 1 (very much improved) or 2 (much improved) on the CGI-I	50/104	48.1	33/97	34.0	8 (4-167)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 2	48/104	46.2	39/97	40.2	17 (ns)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 4	62/104	59.6	56/97	57.7	54 (ns)
≥30% decrease from baseline on the SAPS-PD or a score of 1 (very much improved) *or* 2 (much improved) on the CGI-I at Week 6 or endpoint	71/104	68.3	55/97	56.7	9 (ns)
100% decrease from baseline on SAPS-PD	12/104	11.5	7/97	7.2	24 (ns)

CGI-I: Clinical Global Impression-Improvement; CGI-S: Clinical Global Impression-Severity; n – numerator; ns – not significant; N - denominator [randomized subjects who received at least one dose of study drug and had at least one post-baseline assessment]; SAPS-H+D: Scale for the Assessment of Positive Symptoms hallucinations and delusions items; SAPS-PD: Scale for the Assessment of Positive Symptoms adapted for Parkinson's Disease

Supplemental Table 6. Safety and Tolerability Outcomes from Studies ACP-103-020, ACP-103-012, ACP-103-014, and ACP-103-006; Pooled Data for Pimavanserin (All Doses) and Placebo

Outcome	Pimavanserin		Placebo		NNH
	n/N	%	n/N	%	(95% CI)
AE (incidence >2% for subjects treated with pimavanserin)					
Fall	25/412	6.1	24/262	9.2	-33 (ns) [a]
Urinary tract infection	21/412	5.1	16/262	6.1	-99 (ns) [a]
Nausea	21/412	5.1	11/262	4.2	112 (ns)
Confusional state	21/412	5.1	9/262	3.4	61 (ns)
Dizziness	19/412	4.6	14/262	5.3	-137 (ns) [a]
Peripheral edema	18/412	4.4	7/262	2.7	59 (ns)
Hallucination	16/412	3.9	12/262	4.6	-144 (ns) [a]
Constipation	16/412	3.9	7/262	2.7	83 (ns)
Somnolence	14/412	3.4	7/262	2.7	138 (ns)
Headache	12/412	2.9	15/262	5.7	-36 (ns) [a]
Insomnia	11/412	2.7	7/262	2.7	-53972 (ns) [a]
Diarrhea	10/412	2.4	6/262	2.3	730 (ns)
Blood creatine phosphokinase increased	10/412	2.4	3/262	1.1	78 (ns)
Discontinuation because of an AE	30/412	7.3	11/262	4.2	33 (ns)
Worsening from baseline on the UPDRS (LOCF) Parts II and III (any)	140/399	35.1	100/256	39.1	-26 (ns) [a]
Worsening from baseline on the UPDRS (LOCF) Parts II and III (>=5%)	100/399	25.1	69/256	27.0	-53 (ns) [a]
Worsening from baseline on the UPDRS (LOCF) Parts II and III (>=10%)	74/399	18.5	53/256	20.7	-47 (ns) [a]
Worsening from baseline on the UPDRS (LOCF) Parts II and III (>=20%)	40/399	10.0	21/256	8.2	55 (ns)
Increase in weight (LOCF) from baseline ≥7%	4/377	1.1	3/244	1.2	-594 (ns) [a]
Decrease in weight (LOCF) from baseline ≥7%	12/377	3.2	2/244	0.8	43 (23-384)
Orthostatic hypotension at any post-baseline timepoint	126/403	31.3	103/259	39.8	-12 (-7 to -99) [a]
Orthostatic hypotension with no orthostatic hypotension at baseline	66/320	20.6	58/200	29.0	-12 (-7 to -147) [a]
ECG QTcF >450 msec at any post-baseline timepoint	42/404	10.4	20/260	7.7	37 (ns)
ECG QTcF >450 msec with baseline QTcF ≤450msec	33/392	8.4	11/249	4.4	25 (13-401)
ECG QTcF >500 msec at any post-baseline timepoint [b]	1/404	0.2	1/260	0.4	-730 (ns) [a]
ECG QTcF change from baseline ≥60 msec at any post-baseline timepoint	13/404	3.2	3/260	1.2	49 (ns)

[a] A “negative” NNH results from when the rate of the safety or tolerability outcome is higher for placebo than for pimavanserin. In these instances, with the exception of orthostatic hypotension at any post-baseline timepoint, the results were not statistically significant.

[b] No subjects had a baseline ECG QTcF >500 msec.

AE: adverse event; ECG: electrocardiogram; LOCF – last observation carried forward; n – numerator; ns – not significant; N - denominator [for safety outcomes: all randomized subjects who received at least one dose of study drug and who have at least one post-baseline assessment on the tolerability or safety measure of interest; not applicable for spontaneously reported adverse events where the study population is the number of all randomized subjects who have received at least one dose of study drug]; NA – not applicable; UPDRS: Unified Parkinson’s Disease Rating Scale

Supplemental Table 7. Double-Blind Randomized Clinical Trials of Second-Generation Antipsychotics in Parkinson's Disease Psychosis - Study Characteristics

Citation	Total N	Mean dose (mg/d)	Duration (weeks)	Psychosis assessments
Clozapine [a]				
FCPSG, 1999 (39); Pollak et al., 2004 (45)	60	36	4	PANSS-Positive, CGI-S
PSG, 1999 (46)	60	25	4	BPRS, BPRS-Modified, SAPS, CGI-S
Olanzapine				
Ondo et al., 2002 (43)	30	4.6	9	UPDRS item 2 (thought disorder), hallucinations interview
Breier et al., 2002 (Study 1) (38)	93	4.2	4	BPRS, BPRS subsets, CGI-S, NPI; BPRS-positive was primary
Breier et al., 2002 (Study 2) (38)	77	4.1	4	BPRS, BPRS subsets, CGI-S, NPI; BPRS-positive was primary
Nichols et al., 2013 (42)	23	Fixed dose 2.5 or 5	4	BPRS-positive, CGI-S
Quetiapine [b]				
Ondo et al., 2005 (44)	31	52% received the top dose of 200	12	BPRS, hallucination questionnaire
Rabey et al., 2007 (47)	58	119	12	BPRS, CGI-I
Shotbolt et al., 2009 (48)	24	73	12	BPRS, NPI, hallucinations scale at week 6
Fernandez et al., 2009 (50)	16	58	4	CGI-S, BPRS, BPRS-hallucinations item

[a] A third placebo-controlled study of clozapine was found, but was very small with only 6 participants and 3 completers (48) and was excluded from further consideration

[b] An additional study for quetiapine was identified that focused on both agitation and psychosis, and included patients with dementia with Lewy bodies and Alzheimer disease with parkinsonian features, but only 9 participants with actual Parkinson's disease (40) and was excluded from further consideration

BPRS – Brief Psychiatric Rating Scale; CGI-I - Clinical Global Impression-Improvement; CGI-S - Clinical Global Impression-Severity; NPI – Neuropsychiatric Inventory; PANSS – Positive and Negative Syndrome Scale; SAPS - Scale for the Assessment of Positive Symptoms; UPDRS - Unified Parkinson's Disease Rating Scale

Supplemental Table 8. Double-Blind Randomized Clinical Trials of Second-Generation Antipsychotics in Parkinson's Disease Psychosis - Summary of Psychopathological Outcome (s)

Citation	Outcome	Drug N	Mean score (SD) at baseline for drug	Placebo N	Mean score (SD) at baseline for placebo	Change for drug (SD)	Change for placebo (SD)	Difference in change (+ in favor of drug)	Statistically significant?
Clozapine									
FCPSG, 1999 (39); Pollak et al., 2004 (45)	PANSS-Positive	32	17.8 (4.7)	28	15.3 (5.0)	-5.6 (3.9)	-0.8 (2.8)	4.8	Yes
	CGI-S	32	5.1 (0.8)	28	4.9 (0.9)	-1.8 (1.5)	-0.6 (1.1)	1.2	Yes
PSG, 1999 (46)	BPRS-Modified	27	38.6 (12.1)	27	40.6 (12.1)	-8.6 (6.2)	-2.5 (6.8)	6.1	Yes
	SAPS	27	20.9 (13.0)	27	22.4 (12.3)	-11.8 (9.9)	-3.8 (10.4)	8.0	Yes
	CGI-S	27	4.4 (0.8)	27	4.4 (1.0)	-1.6 (1.0)	-0.5 (1.6)	1.1	Yes
Olanzapine									
Ondo et al., 2002 (43)	UPDRS Item 2	16	3.3 (0.7)	11	3.4 (0.7)	-1.5	-0.7	0.8	No
	Hallucinations	16	13.0 (4.2)	11	13.9 (3.3)	-3.5	-2.8	0.7	No
Breier et al., 2002 (Study 1) (38)	BPRS-Positive	41	6.7 (3.2)	42	6.9 (4.0)	-1.7 (3.5)	-1.6 (3.9)	0.1	No
Breier et al., 2002 (Study 2) (38)	BPRS Positive	46	7.5 (3.0)	27	8.2 (3.5)	-2.3 (4.1)	-2.9 (3.4)	-0.6	No
Nichols et al., 2013 (42)	BPRS-Positive	9 (3 on 2.5mg; 6 on 5mg)	2.5mg: 9 (3); 5mg: 7.8 (2.1)	9	7.9 (2)	+0.8 (from figure)	0 (from figure)	-0.8	No
Quetiapine									
Ondo et al., 2005 (44)	BPRS	21	45 (from figure)	10	48 (from figure)	0 (from figure)	-8 (from figure)	-8	No
Rabey et al., 2007 (47)	BPRS	29	34.2 (5.0)	27	36.0 (8.8)	-0.2	-4.1	-3.9	No
	CGI-I	*CGI-I of 1 or 2 = 4/29 (14%) for quetiapine and 8/27 (30%) for placebo*							
Shotbolt et al., 2009 (48)	BPRS at week 6	11	39.2 (8.4)	13	41.5 (6.5)	-4.2	-2.5	1.7	No
Fernandez et al., 2009 (50)	CGI-S	8	Not reported	8	Not reported	Not reported	Not reported	Not reported	Yes
	BPRS	8	31.2 (9.4)	8	30.2 (7.5)	+1.0 (7.0)	-0.28 (7.6)	-1.28	No
	BPRS-hallucinations item	8	3.5 (1.1)	8	3.3 (0.92)	-1.32 (1.1)	-0.04 (0.82)	1.28	Yes

BPRS – Brief Psychiatric Rating Scale; CGI-I - Clinical Global Impression-Improvement; CGI-S - Clinical Global Impression-Severity; PANSS – Positive and Negative Syndrome Scale; SAPS - Scale for the Assessment of Positive Symptoms; UPDRS - Unified Parkinson's Disease Rating Scale

Supplemental Table 9. Double-Blind Randomized Clinical Trials of Second-Generation Antipsychotics in Parkinson's Disease Psychosis - Effect sizes of Psychopathological Outcome (s)

Citation	Outcome	Cohen's d	Bias corrected (Hedges)	95% Confidence Interval
Clozapine				
FCPSG, 1999 (39); Pollak et al., 2004 (45)	PANSS-Positive	1.40	1.38	0.82, 1.94
	CGI-S	0.90	0.89	0.39, 1.42
PSG, 1999 (46)	BPRS-Modified	0.93	0.92	0.36, 1.48
	SAPS	0.79	0.78	0.22, 1.33
	CGI-S	0.83	0.82	0.27, 1.38
Olanzapine				
Ondo et al., 2002 (43)	UPDRS Item 2	*Insufficient information to calculate*		
	Hallucinations	*Insufficient information to calculate*		
Breier et al., 2002 (Study 1) (38)	BPRS-Positive	0.02	0.02	-0.41, 0.45
Breier et al., 2002 (Study 2) (38)	BPRS Positive	-0.16	-0.15	-0.63, 0.32
Nichols et al., 2013 (42)	BPRS-Positive	*Insufficient information to calculate*		
Quetiapine				
Ondo et al., 2005 (44)	BPRS	*Insufficient information to calculate*		
Rabey et al., 2007 (47)	BPRS	*Insufficient information to calculate*		
	CGI-I of 1 or 2	*NNT = -12 (ns), denoting a numerical disadvantage for quetiapine*		
Shotbolt et al., 2009 (48)	BPRS at week 6	*Insufficient information to calculate*		
Fernandez et al., 2009 (50)	CGI-S	*Insufficient information to calculate*		
	BPRS	-0.18	-0.16	-1.15, 0.82
	BPRS-hallucinations item	1.30	1.22	0.15, 2.29

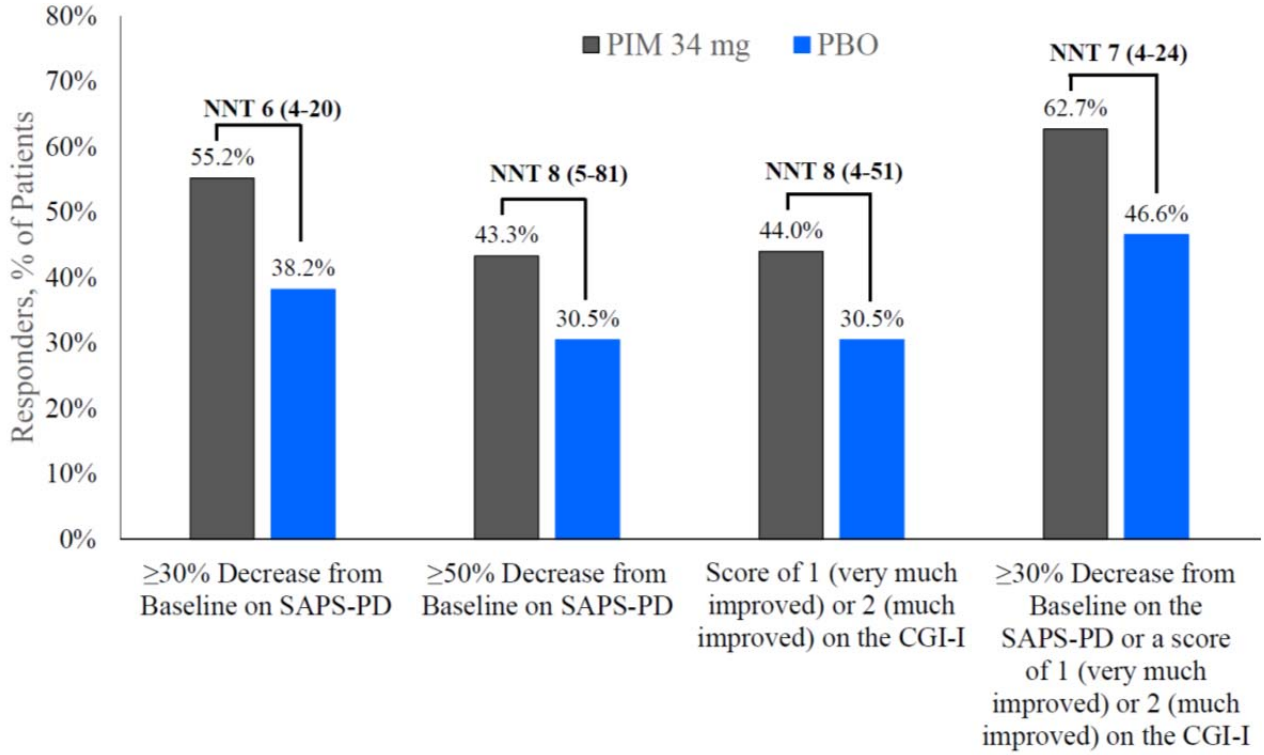
BPRS – Brief Psychiatric Rating Scale; CGI-I - Clinical Global Impression-Improvement; CGI-S - Clinical Global Impression-Severity; NNT – number needed to treat; PANSS – Positive and Negative Syndrome Scale; SAPS - Scale for the Assessment of Positive Symptoms; UPDRS - Unified Parkinson's Disease Rating Scale

Supplemental Table 10. Double-Blind Randomized Clinical Trials of Second-Generation Antipsychotics in Parkinson's Disease Psychosis - Safety and Tolerability – Highlights

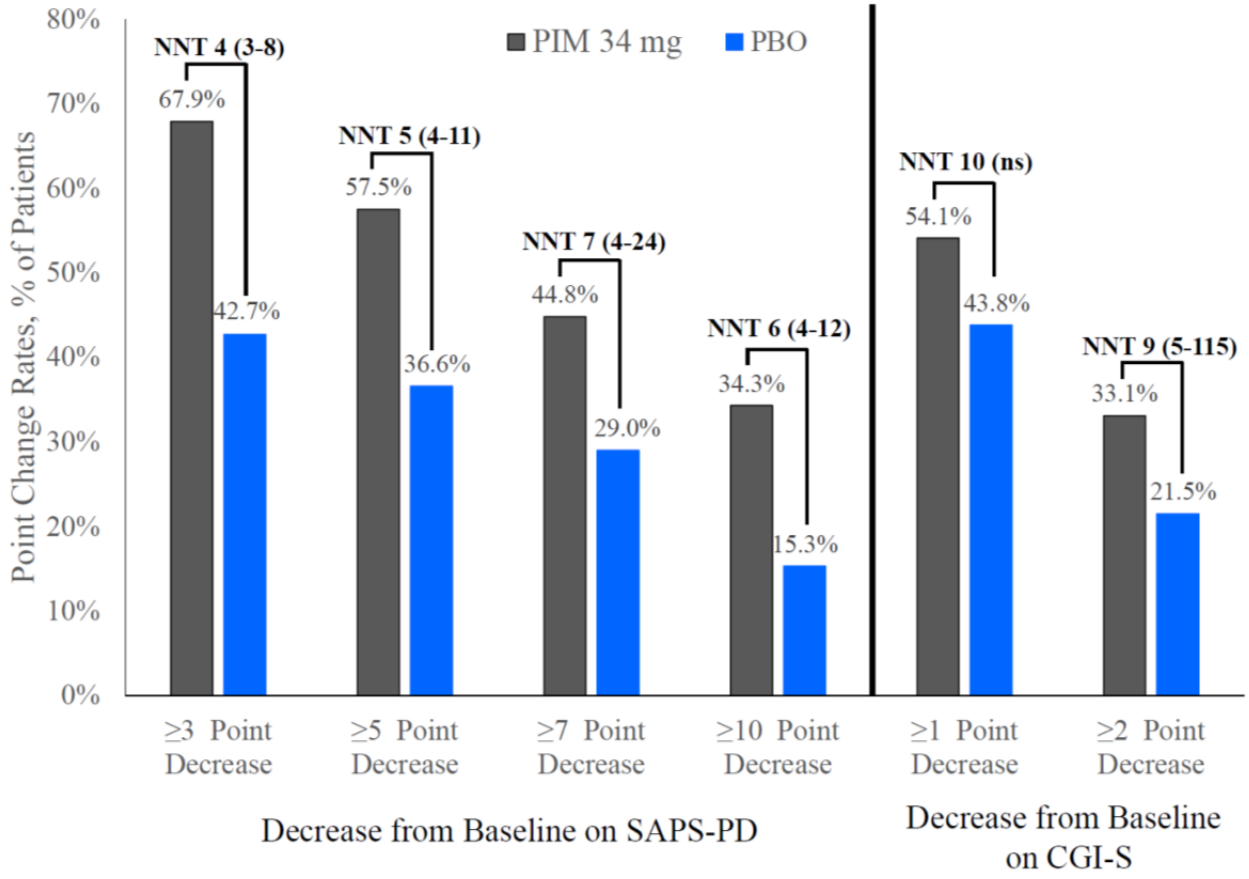
Citation	Commentary
Clozapine	
FCPSG, 1999 (39); Pollak et al., 2004 (45)	Somnolence more frequent with clozapine (53%) than with placebo (18%). Worsening of PD more common with clozapine (22%) than with placebo (4%), however, no patient discontinued because of worsening of PD. SAEs in 4/32 on clozapine and 7/28 on placebo.
PSG, 1999 (46)	Somnolence was as frequent in the placebo group as in the clozapine group. No worsening of motor symptoms in either group. Three on placebo discontinued (2 because of worsening of psychiatric condition). Three on clozapine discontinued (leukopenia, MI, sedation); 6/53 died during the 3-month open-label extension.
Olanzapine	
Ondo et al., 2002 (43)	Motor symptoms modestly worsened on olanzapine.
Breier et al., 2002 (Study 1) (38)	Eleven patients in total discontinued due to AEs, including 10 olanzapine patients (24.4%) and 1 placebo patient (2.4%). SAEs 12.2% with olanzapine and 7.1% with placebo. Three of the olanzapine patients (7.3%) discontinued due to extrapyramidal syndrome. Two deaths were reported in the olanzapine-treated patients.
Breier et al., 2002 (Study 2) (38)	Nine patients in total discontinued due to AEs, including 8 olanzapine patients (16.3%) and 1 placebo patient (3.6%). Four of the olanzapine patients (8.2%) discontinued due to extrapyramidal syndrome. SAEs 9 (18.4%) with olanzapine and 1 (3.6%) with placebo. One death was reported during the study or within 30 days of discontinuation from the study - randomized to olanzapine.
Nichols et al., 2013 (42)	Of the 9 who withdrew, 3 had a worsening of motor symptoms and all were on olanzapine. SAEs 2 (14%) on olanzapine (all on 5mg) and 1 (11%) on placebo.
Quetiapine	
Ondo et al., 2005 (44)	No discontinuations because of an AE. Quetiapine AEs include sedation (43%) and worsening of PD (19%). Sedation was also reported in 40% of placebo subjects. No SAEs.
Rabey et al., 2007 (47)	Somnolence observed in 7 (24%) receiving quetiapine (and 2 discontinued because of somnolence), and in 2 (7%) for placebo.
Shotbolt et al., 2009 (48)	No worsening on motor function with quetiapine. Three patients (27%) dropped out on quetiapine due to AEs (drowsiness) and 3 (23%) on placebo (two drowsiness, one confusion).
Fernandez et al., 2009 (50)	More patients on the quetiapine arm experienced drowsiness (3 vs. 1) and loss of balance/increase in Parkinsonism (3 vs. 0), while more patients on the placebo arm experienced syncope/dizziness (4 vs. 0). The worsening of Parkinsonism was noted to be mild in all cases, and no patients discontinued quetiapine because of Parkinsonism. However, four patients randomized to the quetiapine arm eventually dropped out: two were due to the lack of efficacy in controlling the hallucinations, one was due to drowsiness, and one was lost to the follow-up.

AE - adverse event; PD – Parkinson's disease; SAE – serious adverse event

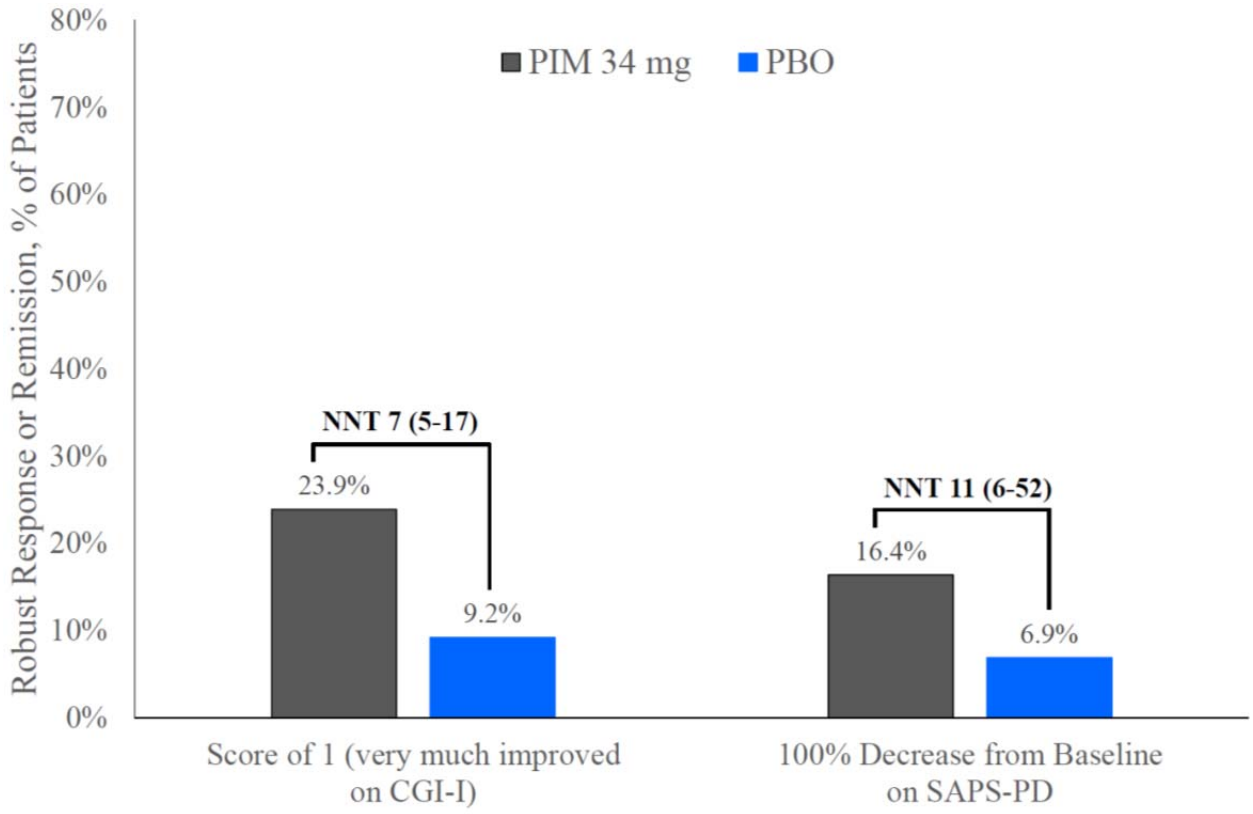
Supplemental Figure 1. Response Rates for Pimavanserin 34 mg/d (PIM) vs. Placebo (PBO), Studies ACP-103-020 and ACP-103-012; Pooled Data for Pimavanserin 34 mg/d and Placebo (US Sites for ACP-103-012)



Supplemental Figure 2. Response Rates as Measured by Point Change for Pimavanserin 34 mg/d (PIM) vs. Placebo (PBO), Studies ACP-103-020 and ACP-103-012; Pooled Data for Pimavanserin 34 mg/d and Placebo (US Sites for ACP-103-012)



Supplemental Figure 3. Robust Response/Remission Rates for Pimavanserin 34 mg/d (PIM) vs. Placebo (PBO), Studies ACP-103-020 and ACP-103-012; Pooled Data for Pimavanserin 34 mg/d and Placebo (US Sites for ACP-103-012)



Supplemental Figure 4. Overall Tolerability as Assessed by Discontinuation Because of an Adverse Event