

**Supplementary material:**

**Figure S1 :** Algorithm for PCP identification from reference <sup>6</sup>

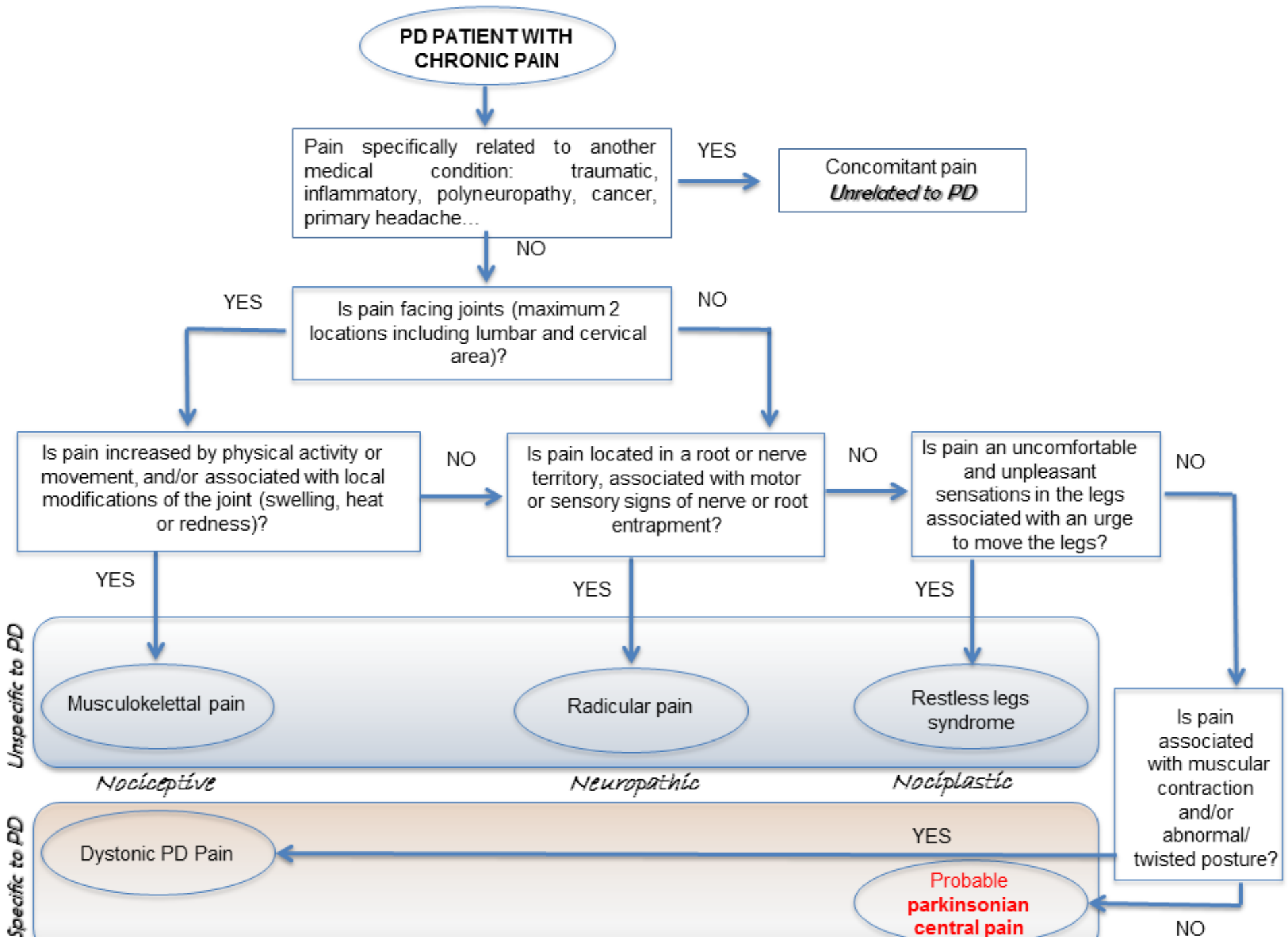
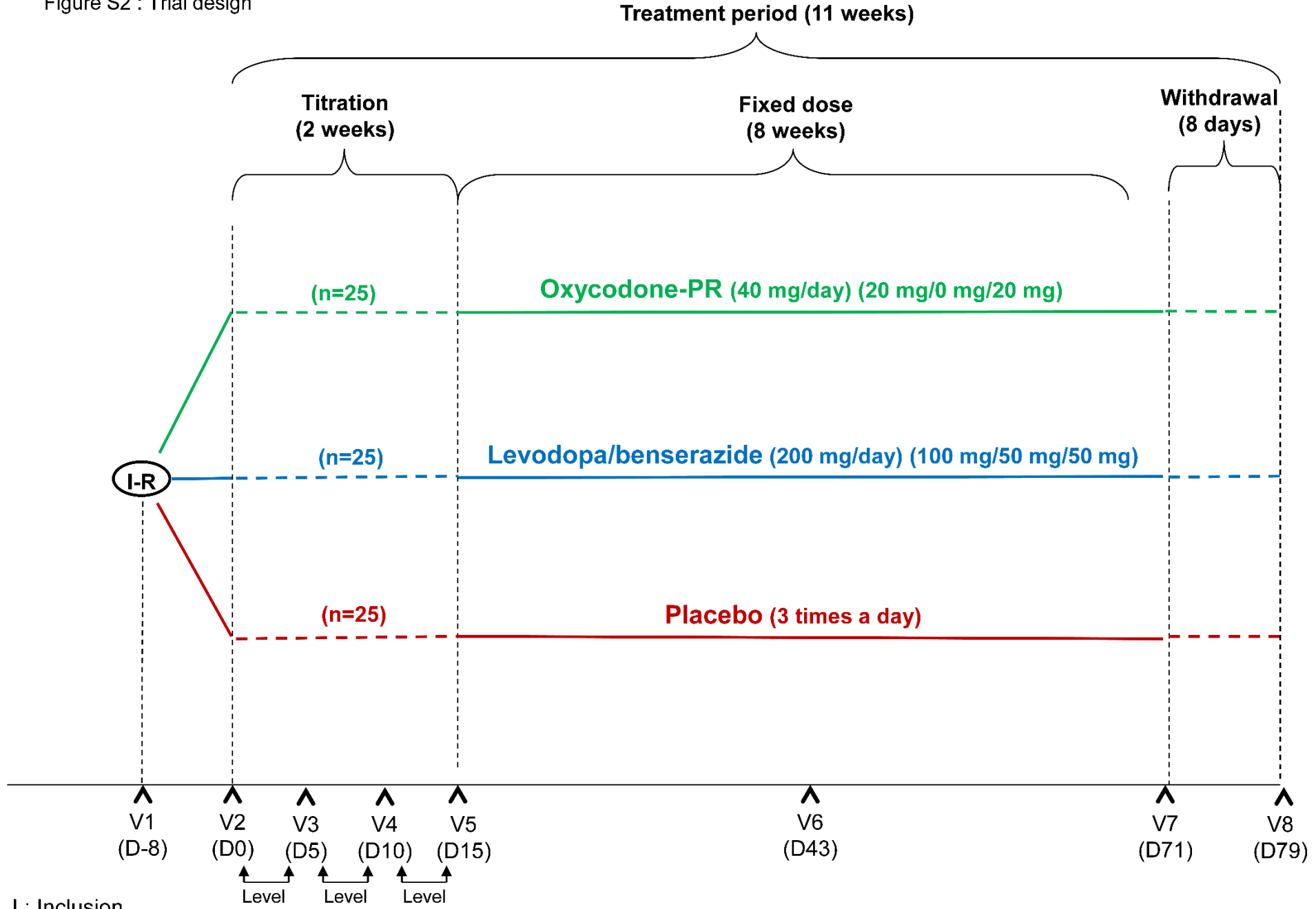


Figure S2 : Trial design

Figure S2 : Trial design



I : Inclusion  
R : Randomisation

Table S3 : Changes in Average and Maximal VAS in Per Protocol Population between D0 and D71.

Outcomes	Oxycodone-PR group N= 14	Levodopa/benserazide group N=16	Placebo group N=15	Treatment effect adjusted <sup>o</sup> Mean difference (97.5%CI), p value		
				Oxycodone-PR vs placebo	Levodopa/benserazide vs placebo	Levodopa/benserazide vs Oxycodone-PR
Average VAS (mm)	-18.4±23.4 (-34.3 to -2.6)	-7.7±12.1 (-15.2 to -0.2)	-17.1±19.2 (-29.6 to -4.7)	0.10 (-23.5 to 23.66) p =0.9	11.86 (-4.10 to 27.82) p=0.09	10.15 (-7.08 to 27.38) p=0.2
Maximal VAS (mm)	-18.3±26.8 (-33.8 to -2.8)	-13.6±14.8 (-21.5 to -5.7)	-14±25.7 (-28.2 to 0.2)	-2.2 (-31.2 to 26.74) p=0.9	5.72 (-13.7 to 25.14) p=0.5	4.77 (-15.6 to 25.15) p=0.6

Data are mean ± SD

<sup>o</sup> Adjustment variables: age at inclusion, mean VAS score for the week before inclusion, centre and LEDD at baseline.

Table S4: Changes in Clinical Secondary Endpoints between D0 and D71.

Outcomes	Oxycodone-PR group	Levodopa/benserazide group	Placebo group	Treatment effect Mean difference (95%CI), p value		
				Oxycodone-PR vs placebo	Levodopa/benserazide vs placebo	Levodopa/benserazide vs Oxycodone-PR
<b>HADS</b>						
Total score	-0.1±4.5 (-2.6 to 2.4)	-0.8±4.4 (-3 to 1.5)	-0.6±5.4 (-3.4 to 2.3)	0.4 (-3.2 to 4.1) p=0.8	-0.2 (-3.7 to 3.3) p=0.9	-0.6 (-3.8 to 2.6) p=0.7
Anxiety	0.5±3.9 (-1.7 to 2.6)	-0.6±3.5 (-2.4 to 1.2)	-0.4±2.6 (-1.7 to 1)	0.8 (-1.6 to 3.3) p=0.5	-0.2 (-2.4 to 2.0) p=0.8	-1.1 (-3.7 to 1.6) p=0.4
Depression	-0.6±2.2 (-1.8 to 0.6)	-0.2±2.1 (-1.3 to 0.9)	-0.2±3.1 (-1.8 to 1.5)	-0.4 (-2.4 to 1.6) p=0.7	0.0 (-1.9 to 1.9) p=0.9	0.4 (-1.1 to 2.0) p=0.6
N of patients	15	17	16			
<b>LARS Total Score</b>	-2.1±5.5 (-5.3 to 1.1)	0.3±6.5 (-3.1 to 3.8)	-1.6±6.7 (-5.2 to 1.9)	0.5 (-5.1 to 4.1) p=0.8	1.9 (-2.8 to 6.7) p=0.4	2.5 (-2.1 to 7.0) p=0.3
N of patients	14	16	16			
<b>FSS</b>	-0.4±1.2 (-1.1 to 0.3)	-0.9±1.5 (-1.7 to -0.1)	-0.2±1.4 (-1 to 0.6)	-0.2 (-1.2 to 0.8) p=0.6	-0.8 (-1.8 to 0.3) p=0.2	-0.5 (-1.6 to 0.5) p=0.3
N of patients	14	16	16			
<b>PSQI</b>	-3.6±3.2 (-5.6 to -1.7)	0.4±3 (-1.2 to 1.9)	-0.4±1.9 (-1.4 to 0.6)	-3.2 (-5.2 to -1.3) p=0.002	0.7 (-1.1 to 2.5) p=0.4	4.0 (1.6 to 6.3) p=0.002
N of patients	13	17	16			
<b>PDQ-39 Total score</b>	-18.6±85 (-67.7 to 30.5)	-21.6±76.7 (-64.1 to 20.9)	-35.5±64.5 (-72.8 to 1.7)	16.9 (-41.7 to 75.5) p=0.6	14.0 (-40.3 to 68.2) p=0.6	-3.0 (-64.6 to 58.7) p=0.9
N of patients	14	15	14			
<b>MDS-UPDRS Part I</b>	-0.4±5.4	-1.2±4.2	-2.4±3.9	2.0 (-1.5 to 5.4)	1.1 (-1.7 to 4.0)	-0.8 (-4.3 to 2.6)

Part II	(-3.4 to 2.6) -1±2.9	(-3.4 to 0.9) -1.5±2.7	(-4.5 to -0.3) -0.1±4.3	p=0.2 -0.9 (-3.6 to 1.9)	p=0.4 -1.4 (-3.9 to 1.2)	p=0.6 -0.5 (-2.5 to 1.5)
Part III	(-2.6 to 0.6) -2.7±8.2	(-2.8 to -0.1) -2.7±7	(-2.4 to 2.2) 1±7.6*	p=0.5 -3.7 (-9.7 to 3.4)	p=0.3 -3.7 (-9.1 to 1.7)	p=0.6 -0.0 (-5.5 to 5.5)
Part IV	(-7.2 to 1.9) -1.2±3.6	(-6.3 to 0.9) -0.2±4.7	(-3.4 to 5.4) -0.4±3.1	p=0.2 -0.8 (-3.3 to 1.6)	p=0.2 0.2 (-2.6 to 3.0)	p=1 1.0 (-2.0 to 4.1)
N of patients	(-3.2 to 0.8) 15	(-2.6 to 2.2) 17	(-2.0 to 1.3) 16	p=0.5	p=0.9	p=0.5

N of patients represents the number of patients with available data for each outcome.

Data are mean ± SD, (95% CI). HADS: Hospital Anxiety and Depression Scale, LARS: Lille Apathy Rating Scale, FSS: Fatigue Severity Scale, PSQI: Pittsburg Sleep Quality Index, PDQ-39: Parkinson's Disease Questionnaire 39 items, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.

\*n=14

Table S5 : Adverse Events in the Safety Analysis Population

	Oxycodone-PR group	Levodopa/benserazide group	Placebo group
Patients with $\geq 1$ adverse event	23 (100%)	18 (90%)	18 (90%)
Most common all-cause adverse events†			
Nausea	17 (74%)	6 (30%)	5 (25%)
Constipation	15 (65%)	5 (25%)	4 (20%)
Somnolence	11 (48%)	2 (10%)	2 (10%)
Dyskinesia	1 (4%)	9 (45%)	1 (5%)
Pain	5 (22%)	9 (45%)	7 (35%)
Vomiting	8 (35%)	1 (5%)	-
Headache	4 (17%)	6 (30%)	3 (15%)
Vertigo	3 (13%)	-	-
Decreased appetite	3 (13%)	-	-
Paraesthesia	3 (13%)	-	-
Sleep disorder	3 (13%)	4 (20%)	1 (5%)
Nasopharyngitis	-	2 (10%)	1 (5%)
Fatigue	3 (13%)	1 (5%)	3 (15%)
Myalgia	1 (4%)	-	2 (10%)
Upper abdominal pain	2 (9%)	1 (5%)	1 (5%)
Decreased weight	2 (9%)	1 (5%)	1 (5%)
Dizziness	2 (9%)	1 (5%)	1 (5%)
Hyperhidrosis	2 (9%)	-	-
Patients with $\geq 1$ serious adverse event	2 (9%)	1 (5%)	1 (5%)
Patients with $\geq 1$ treatment-related adverse event*	23 (100%)	15 (75%)	11 (55%)
Most common treatment-related adverse events†			
Nausea	17 (74%)	4 (20%)	5 (25%)



Constipation	15 (65%)	5 (25%)	3 (15%)
Somnolence	11 (48%)	-	2 (10%)
Dyskinesia	1 (4%)	8 (40%)	1 (5%)
Vomiting	8 (35%)	1 (5%)	-
Pain	2 (9%)	3 (15%)	-
Decreased appetite	3 (13%)	-	-
Fatigue	3 (13%)	1 (5%)	3 (15%)
Dizziness	2 (9%)	1 (5%)	1 (5%)
Sleep disorder	2 (9%)	1 (5%)	1 (5%)
Patients with $\geq 1$ adverse event leading to study drug discontinuation	9 (39%)	1 (5%)	3 (15%)

† Occurring in > 5% of patients in either treatment group. \*Considered by the investigator to be unlikely, possibly, probably, or definitely related to the study drug.