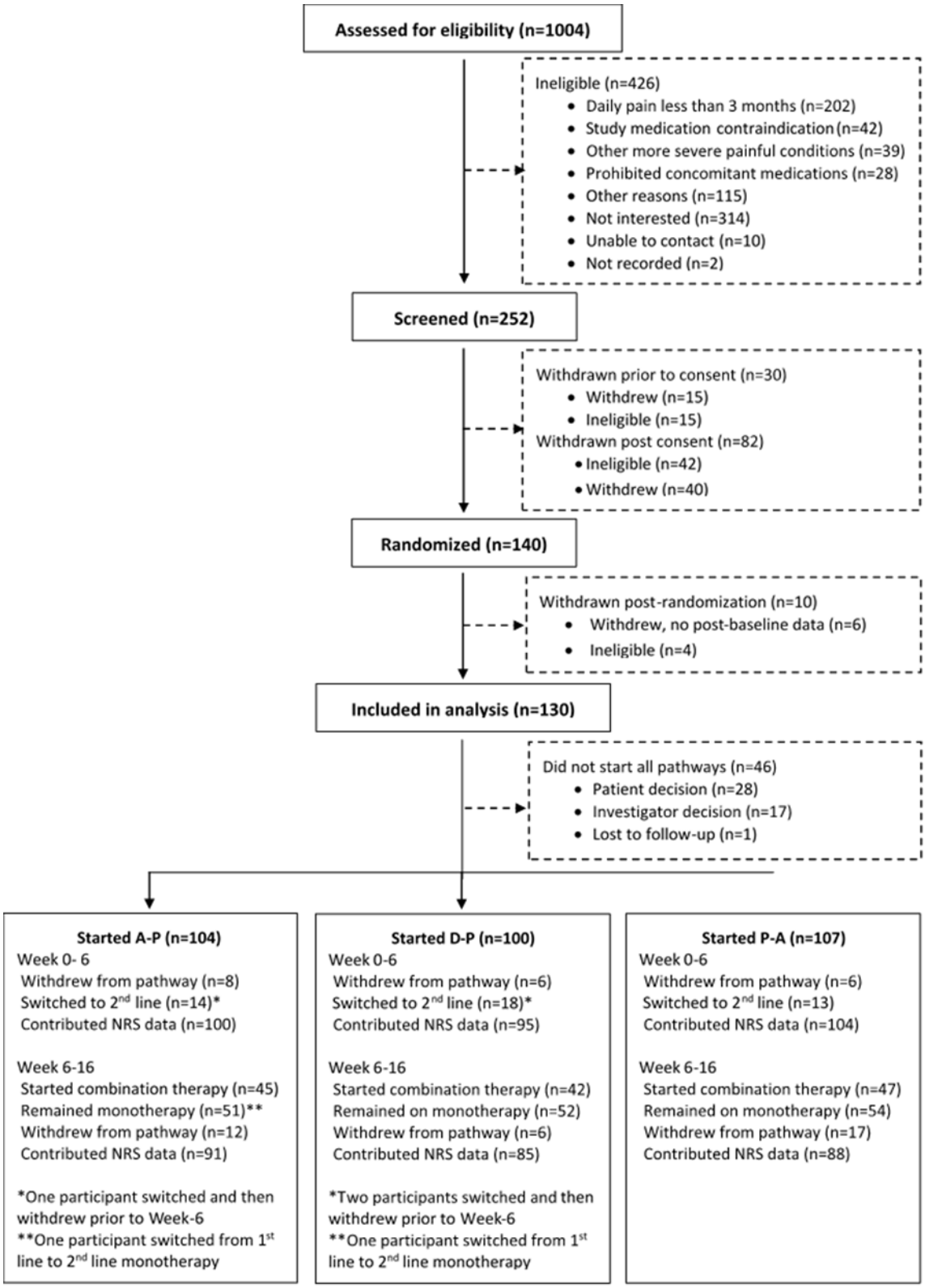
Participant Flow



A-P (amitriptyline supplemented by pregabalin), D-P (duloxetine supplemented by pregabalin) and P-A (pregabalin supplemented by amitriptyline). *switch to second line therapy before week-6, ** switch to second line therapy after week-6

Baseline Characteristics

Table 1: Demographics and Baseline Characteristics

Characteristic	Completers N=77	*Non completers N=53*	Total N=130
Demographics			
Age	61.3 (10.9)	*62.5 (11.2)*	61.8 (11.0)
No (%) female	22 (29%)	*12 (23%)*	34 (26%)
BMI (Kg/m2)	31.7 (6.3)	*31.7 (7.0)*	31.7 (6.6)
Diabetes characteristics			
Type 1	12 (16%)	*10 (19%)*	22 (17%)
Type 2	63 (82%)	*43 (81%)*	106 (82%)
Missing	2 (3%)	*0*	2 (2%)
HbA1c (mmol/mol)	65.4 (13.2)	*68.4 (17.2)*	66.6 (15.0)
Duration of diabetes (years)	14.9 (9.0)	*15.6 (9.7)*	15.1 (9.3)
Duration of neuropathic pain (years))	4.8 (4.1)	*5.0 (4.1)*	4.9 (4.1)
Previous medication use			
Amitriptyline	30 (39%)	*19 (36%)*	49 (38%)
Pregabalin	27 (35%)	*18 (34%)*	45 (35%)
Duloxetine	28 (36%)	*19 (36%)*	47 (36%)
Gabapentin	27 (35%)	*17 (32%)*	44 (34%)
Any opioid	27 (35%)	*20 (38%)*	47 (36%)
Pain characteristics			
NRS pain	6.7 (1.5)	*6.5 (1.4)*	6.6 (1.5)
[0-10; higher scores indicate greater pain]			
Brief Pain Inventory			
[0-10; higher scores indicate greater pain]			
Pain severity score	6.1 (1.6)	*6.1 (1.9)*	6.1 (1.7)
Pain interference score	5.8 (2.3)	*6.1 (2.5)*	5.9 (2.4)
Neuropathic pain symptom inventory			
[0-10; higher scores indicate greater pain]			
Superficial spontaneous burning pain	6.0 (2.8)	*6.0 (3.1)*	6.0 (2.9)
Deep spontaneous pressing pain	4.8 (2.8)	*4.7 (2.7)*	4.8 (2.8)
Paroxysmal pain	5.3 (2.9)	*5.8 (2.9)*	5.5 (2.9)
Evoked pain	4.6 (2.5)	*3.9 (2.8)*	4.3 (2.6)
Paraesthesia /dysesthesia	6.3 (2.4)	*6.4 (3.0)*	6.3 (2.7)
NPSI Total score	52.6 (18.1)	*52.1 (21.6)*	52.4 (19.5)
[*0-100; higher scores indicate greater pain*			

Continuous scores are summarised as Mean (SD).

Outcome Measures

Table 2: Response to treatment by maximum tolerated doses of monotherapies at 6 weeks and at the end of Treatment Pathways at 16 weeks by ITT.

		Week 6 (Monotherapy phase)			Week 16 (Combination therapy phase)		
	Baseline (N=130)	A-P (N=104)	D-P (N=100)	P-A (N=107)	A-P (N=104)	D-P (N=100)	P-A (N=107)
Average weekly pain (numeric rating scale; 0-10)							
Number of patients included	130	100	95	104	91	85	88
NRS pain [mean (SD)]	6.6 (1.5)	3.8 (2.0)	3.9 (1.9)	4.1 (2.1)	3.3 (1.8)	3.3 (1.8)	3.3 (1.8)
Change from baseline [mean (SD)]		2.9 (2.0)	2.8 (2.0)	2.5 (2.2)	3.4 (2.1)	3.5 (2.1)	3.3 (2.1)
≥30% reduction from baseline [no. (%)]		68 (65%)	63 (63%)	60 (56%)	68 (65%)	68 (68%)	68 (64%)
≥50% reduction from baseline [no. (%)]		42 (40%)	35 (35%)	43 (40%)	50 (48%)	46 (46%)	47 (44%)
NRS ≤3 [no. (%)]		38 (37%)	32 (32%)	36 (34%)	50 (48%)	43 (43%)	50 (47%)
Pairwise contrast		**Mean difference (98.3% CI)**		**p**	**Mean difference (98.3% CI)**		**p**
D-P v A-P		0.1 (-0.3, 0.5)		0.649	-0.1 (-0.5, 0.3)		0.613
P-A v A-P		0.3 (-0.1, 0.8)		0.049	-0.1 (-0.5, 0.3)		0.611
P-A v D-P		0.3 (-0.2, 0.7)		0.137	0.0 (-0.4, 0.4)		0.996
Combined arms		**n=299**			**n=265**		
Change from baseline [mean (98.3% CI); p]		2.8 (2.3, 3.0); p<0.001			3.4 (3.0, 3.8); p<0.001,*		
≥50% reduction from baseline [no. (%)]		120 (40%)			143 (54%)		
NRS ≤3 [no. (%)]		106 (35%)			143 (54%)		

Change from week-6 to week-16 (NRS [mean (98.3% CI) Patients on combination therapy Patients on monotherapy All patients			1.0 (0.6, 1.3) 0.2 (-0.1, 0.5) 0.6 (0.3, 0.8)

NRS, numeric rating scale; Δ, change; NRS≤3 equivalent to mild pain achieved by "Responders". Data are mean (SD), or percentage (rating on a scale of 0–10) and pairwise comparisons are mean difference (98.3%CI). For items rated on a scale of 0–10, increasing numbers indicate increasing pain. *p<0.001 for the difference between the combined arms of monotherapy and combination treatment. †Measured for 7 days at baseline, and for 7 days at maximum tolerated dose at week-6 and -16. A-P, amitriptyline supplemented by pregabalin, D-P, duloxetine supplemented by pregabalin and P-A, pregabalin supplemented by amitriptyline.

Table 3: Patient reported tolerability

	Week 6			Week 16		
	A-P (N=104)	D-P (N=100)	P-A (N=107)	A-P (N=104)	D-P (N=100)	P-A (N=107)
Tolerability (0-10; higher scores are less tolerated)						
Number of responses	92	86	96	83	84	83
Discontinued due to adverse effect or poor response	6 (6%)	2 (2%)	6 (6%)	10 (10%)	4 (4%)	8 (8%)
Tolerability of unwanted side effects over past 7 days mean (SD)	2.2 (2.5)	2.1 (2.3)	2.4 (2.9)	2.3 (2.5)	2.1 (2.6)	1.9 (2.5)

Table 4: Quality of life, health utility and anxiety/depression

	Week 6			Week 16		
	A-P	D-P	P-A	A-P	D-P	P-A
Number starting pathway	104	100	107	104	100	107
EQ-5D (Higher scores indicate better health state)						
EQ-5D-5L (Crosswalk)						
n	93	87	99	86	86	86
Mean (SD)	0.516 (0.266)	0.540 (0.237)	0.489 (0.251)	0.509 (0.253)	0.511 (0.276)	0.537 (0.243)
Pairwise comparisons	Mean difference (98.3% CI)		p	Mean difference (98.3% CI)		p
D-P versus A-P	0.029 (-0.023, 0.081)		0.187	-0.006 (-0.057, 0.044)		0.766
P-A versus A-P	-0.031 (-0.082, 0.020)		0.149	0.009 (-0.041, 0.059)		0.673
P-A versus D-P	-0.060 (-0.111, -0.008)		0.005	0.015 (-0.035, 0.065)		0.468
EQ-5D (Thermometer)						
n	92	87	99	86	85	86

Mean (SD)	56.5 (22.1)	55.4 (20.4)	56.3 (21.7)	55.7 (22.4)	57.3 (22.4)	57.7 (22.4)
Pairwise comparisons	Mean difference (98.3% CI)		p	Mean difference (98.3% CI)		p
D-P versus A-P	-0.4 (-5.2, 4.4)		0.847	2.2 (-3.1, 7.5)		0.316
P-A versus A-P	-0.8 (-5.5, 3.9)		0.673	1.6 (-3.6, 6.9)		0.451
P-A versus D-P	-0.4 (-5.2, 4.3)		0.821	-0.6 (-5.8, 4.7)		0.793
RAND SF-36 (Higher scores indicate better quality of life)						
Physical health component						
n	93	87	99	86	86	86
Mean (SD)	25.4 (12.5)	22.6 (12.6)	24.5 (13.3)	23.6 (13.0)	24.1 (13.8)	24.1 (13.1)
Pairwise comparisons	Mean difference (98.3% CI)		p	Mean difference (98.3% CI)		p
D-P versus A-P	-2.9 (-4.9, -0.9)		<0.001	0.4 (-1.9, 2.7)		0.711
P-A versus A-P	-1.4 (-3.4, 0.5)		0.078	-0.4 (-2.6, 1.9)		0.699
P-A versus D-P	1.5 (-0.5, 3.4)		0.067	-0.7 (-3.0, 1.5)		0.444
Mental health component						

n	93	87	99	86	86	86
Mean (SD)	46.7 (13.0)	47.8 (11.8)	47.6 (12.2)	46.6 (12.8)	46.3 (11.0)	47.4 (12.3)
Pairwise comparisons	Mean difference (98.3% CI)		p	Mean difference (98.3% CI)		p
D-P versus A-P	1.3 (-1.0, 3.6)		0.182	-0.2 (-2.5, 2.2)		0.855
P-A versus A-P	1.1 (-1.1, 3.4)		0.229	0.8 (-1.5, 3.1)		0.417
P-A versus D-P	-0.1 (-2.4, 2.1)		0.875	1.0 (-1.4, 3.3)		0.317
HADS (Higher scores indicate greater symptoms)						
Anxiety						
n	93	85	99	86	86	86
Mean (SD)	7.5 (5.1)	7.4 (4.6)	6.7 (4.4)	7.7 (5.4)	7.3 (4.8)	7.0 (4.6)
Pairwise comparisons	Mean difference (98.3% CI)		p	Mean difference (98.3% CI)		p
D-P versus A-P	-0.1 (-0.9, 0.7)		0.826	-0.3 (-1.2, 0.6)		0.449
P-A versus A-P	-0.5 (-1.3, 0.3)		0.138	-0.4 (-1.4, 0.5)		0.253
P-A versus D-P	-0.4 (-1.2, 0.4)		0.213	-0.1 (-1.1, 0.8)		0.705

Depression						
n	93	85	99	86	86	86
Mean (SD)	7.4 (4.7)	7.3 (4.4)	7.0 (4.5)	7.3 (4.9)	7.5 (4.5)	7.2 (4.5)
Pairwise comparisons	Mean difference (98.3% CI)		p	Mean difference (98.3% CI)		p
D-P versus A-P	-0.2 (-1.0, 0.6)		0.489	-0.1 (-0.9, 0.6)		0.698
P-A versus A-P	-0.4 (-1.1, 0.4)		0.274	-0.0 (-0.8, 0.7)		0.903
P-A versus D-P	-0.1 (-0.9, 0.7)		0.705	0.1 (-0.6, 0.8)		0.786

Table 5: Neuropathic Pain Symptom Inventory (NPSI) and Brief Pain Inventory (BPI)

	Baseline (N=130)	A-P (N=104)	D-P (N=100)	P-A (N=107)	A-P (N=104)	D-P (N=100)	P-A (N=107)
		Monotherapy phase (week 6)			Combination treatment phase (week 16)		
Number of patients included	130	93	87	99	86	86	86
NPSI							
Individual components (range 0-10; higher is greater pain)							
Superficial spontaneous burning pain	6.0 (2.9)	3.4 (2.9)	3.6 (2.7)	3.9 (3.0)	3.2 (3.0)	3.7 (2.8)	3.4 (2.8)
Deep spontaneous pressing pain	4.8 (2.8)	3.0 (2.7)	2.9 (2.4)	3.3 (2.9)	2.9 (2.8)	3.4 (2.5)	3.1 (2.8)

Paroxysmal pain	5.5 (2.9)	3.5 (2.9)	3.4 (2.5)	3.6 (2.8)	3.3 (3.0)	3.8 (2.9)	3.6 (2.8)
Evoked pain	4.3 (2.6)	2.9 (2.5)	2.7 (2.3)	2.9 (2.3)	3.2 (2.7)	3.0 (2.5)	3.0 (2.6)
Paresthesia/dysesthesia	6.3 (2.7)	4.2 (2.7)	4.3 (2.7)	4.3 (2.8)	4.1 (3.0)	4.0 (2.9)	4.4 (2.9)
Total score (range 0-50)	52.4 (19.5)	33.7 (21.9)	33.2 (20.1)	34.6 (20.9)	33.8 (24.4)	35.0 (21.5)	33.9 (21.9)

BPI- (score 0-10; higher is greater pain)

Pain severity score	6.1 (1.7)	3.8 (2.0)*	3.9 (1.7)	4.3 (2.2)	3.7 (2.0)	3.8 (1.9)	3.5 (2.0)
Pain interference score	5.9 (2.4)	4.0 (2.6)	4.2 (2.5)	4.3 (2.7)	4.1 (2.7)	4.0 (2.6)	3.7 (2.5)
Worst pain in last 24 hours	7.2 (1.8)	4.3 (2.2)**	4.5 (2.0)	5.0 (2.5)	4.4 (2.3)	4.5 (2.3)	4.3 (2.5)
Least pain in last 24 hours	5.0 (2.2)	3.1 (2.2)	3.2 (1.9)	3.5 (2.4)	3.0 (2.2)	3.0 (2.0)	2.8 (2.0)
Average pain	6.1 (1.7)	4.0 (1.9)	4.1 (1.6)	4.4 (2.2)	3.8 (2.0)	3.9 (1.9)	3.7 (2.0)
Pain right now	6.0 (2.2)	3.5 (2.3)	3.7 (2.1)	4.1 (2.6)	3.5 (2.4)	3.6 (2.3)	3.2 (2.3)

* A-P lower pain than P-A; mean difference 0.5 (98.3%CI 0.0, 1.0, p=0.012)

** A-P lower pain than P-A; mean difference 0.7 (98.3%CI 0.1, 1.3, p=0.005)

Table 6: Insomnia Severity Index

	Baseline (N=130)	A-P (N=104)	D-P (N=100)	P-A (N=107)	A-P (N=104)	D-P (N=100)	P-A (N=107)
		Monotherapy phase (week 6)			Combination treatment phase (week 16)		
e	130	93	87	99	86	86	86
ISI Total score (0-28; Higher scores indicate greater insomnia)	18.1 (5.9)	11.8 (7.3)*	13.8 (6.3)	12.1 (7.1)	11.4 (7.3)*	13.3 (6.8)	12.1 (6.4)

*A-P lower insomnia than P-A at week-6 (mean difference 1.5, 98.3% CI 0.0, 3.1, p=0.016) and week-16 (mean difference 1.5, 98.3% CI 0.1, 3.0, p=0.010)

Table 7: Patient impression of change and treatment preference

	A-P	D-P	P-A
Number starting pathway	104	100	107
Patient Global Impression of Change			
Very much improved	11 (11%)	8 (8%)	12 (12%)
Much improved	32 (33%)	33 (35%)	36 (37%)
Minimally improved	25 (26%)	26 (27%)	22 (23%)
No change	19 (20%)	17 (18%)	16 (16%)
Minimally worse	6 (6%)	8 (8%)	10 (10%)
Much worse	4 (4%)	3 (3%)	1 (1%)
Kruskal-Wallis test for difference between groups:	p=0.702		
Preferred treatment			
Stated preference at end of study*	11 (24%)	15 (33%)	20 (43%)
Chi-squared test for difference between groups:	p=0.266		

* Note: excludes participants who expressed equal preference for two different pathways. 1 patient stated D-P and P-A; 1 stated D-P and A-P

Table 8: Total number of patients incurring resource use at six and sixteen weeks for each Treatment Pathway

	A-P		D-P		P-A	
	Week 6	Week 16	Week 6	Week 16	Week 6	Week 16
A&E visit	0	3	1	2	1	4
Hospitalisations	0	1	1	2	2	2
Out-patient	21	23	27	22	24	23
GP – surgery visit	13	21	11	14	11	15
GP home visit	1	0	0	1	0	0
GP phone call	7	5	2	5	6	6
Practice nurse	8	16	15	15	10	9
Practice nurse phone call	2	3	5	2	2	8
Prescription	50	59	46	38	45	49
Meals on wheels	0	0	0	0	0	0
Home help	2	2	3	1	3	1
Social worker	0	0	1	0	0	1
Pain management	0	1	5	1	3	0
Physiotherapy	2	3	5	4	4	4
Occupational therapy	1	1	1	0	1	1
Podiatry – NHS	30	34	36	29	36	36
Podiatry – private	3	3	1	1	1	3
Other – NHS*	3	2	4	3	1	3
Other – private*	1	0	0	0	0	0

* Other services included: councillors, psychiatrists, psychologists, vascular surgery, eye clinic, diabetic clinics and aromatherapy (private)

Table 9: Summary of mean treatment cost (95% bootstrapped confidence intervals)

	A-P N = 88	D-P N = 88	P-A N = 87
Treatment medications	£19 (£17, £21)	£33 (£29m £36)	£24 (£22, £26)
Treatment visits	£1,077 (£1,031, £1,118)	£1,092 (£1,047, £1,136)	£1,096 (£1,051, £1,140)
Treatment total*	£1,424 (£1,376, £1,466)	£1,452 (£1,405, £1,500)	£1,448 (£1,401, £1,493)
Concomitant medications	£38 (£26, £58)	£24 (£15, £36)	£33 (£24, £44)
Other resource use	£549 (£357, £963)	£555 (£377, £830)	£461 (£325, £701)
Total costs	£2,012 (£1,808, £2,421)	£2,032 (£1,852, £2,304)	£1,942 (£1,800, £2,179)

* Treatment total = treatment medications _ Treatment visits + £328 for laboratory costs which all patients incurred

Adverse Events

Table 10: AEs by pathway

	A-P (N=104)		D-P (N=100)		P-A (N=107)		
AE category	No. of events	No. (%) patients	No. of events	No. (%) patients	No. of events	No. (%) patients	p
Fatigue	25	21 (20%)	23	18 (18%)	25	22 (21%)	0.880
Dizziness	12	12 (12%)	17	16 (16%)	33	26 (24%)	0.036
Dry Mouth	34	33 (32%)	8	8 (8%)	20	18 (17%)	<0.001
Sedation	22	21 (20%)	14	11 (11%)	18	15 (14%)	0.167
Diarrhoea	22	18 (17%)	17	16 (16%)	11	9 (8%)	0.122
Fall	12	7 (7%)	17	12 (12%)	17	10 (9%)	0.880
Oedema	10	9 (9%)	13	10 (10%)	18	17 (16%)	0.150
Nausea	5	5 (5%)	27	23 (23%)	8	7 (7%)	0.001
Constipation	13	11 (11%)	15	13 (13%)	9	8 (7%)	0.469
Headaches	11	9 (9%)	16	14 (14%)	10	8 (7%)	0.335
Vomiting	8	7 (7%)	12	11 (11%)	8	8 (7%)	0.513
Excessive Sweating	11	9 (9%)	10	10 (10%)	6	6 (6%)	0.576
Insomnia	8	6 (6%)	9	8 (8%)	7	7 (7%)	0.901
Abdominal Cramping	6	5 (5%)	8	6 (6%)	4	4 (4%)	0.580
Ataxia	6	4 (4%)	4	4 (4%)	8	8 (7%)	0.415
Pruritus	2	2 (2%)	9	8 (8%)	5	5 (5%)	0.170
Weight Gain	3	3 (3%)	1	1 (1%)	10	10 (9%)	NC
Decreased Appetite	5	5 (5%)	5	5 (5%)	2	2 (2%)	0.401
Inability To Concentrate	5	5 (5%)	1	1 (1%)	6	6 (6%)	0.242
Cardiac Ischaemia	3	2 (2%)	3	3 (3%)	5	5 (5%)	NC
Hypoglycaemia	4	4 (4%)	3	3 (3%)	4	4 (4%)	NC
Blurred Vision	2	2 (2%)	1	1 (1%)	5	5 (5%)	NC
Low Mood	6	6 (6%)	1	1 (1%)	1	1 (1%)	0.112
Hypotension	1	1 (1%)	5	5 (5%)	1	1 (1%)	NC
Restless Legs	2	2 (2%)	5	5 (5%)	0	-	NC
Anxiety	2	2 (2%)	2	1 (1%)	2	2 (2%)	NC

Hyperglycaemia	3	2 (2%)	1	1 (1%)	2	2 (2%)	NC
Dysarthria	1	1 (1%)	0	-	4	4 (4%)	NC
Kidney Dysfunction	1	1 (1%)	2	2 (2%)	2	2 (2%)	NC
Hallucinations	3	1 (1%)	0	-	1	1 (1%)	NC
Heart Failure	0	-	2	2 (2%)	1	1 (1%)	NC
Liver Dysfunction	1	1 (1%)	1	1 (1%)	1	1 (1%)	NC
Tachycardia	2	1 (1%)	1	1 (1%)	0	-	NC
Transient Ischaemic Attack	0	-	3	3 (3%)	0	-	NC
Increased Appetite	2	1 (1%)	0	-	0	-	NC
Urinary Retention	1	1 (1%)	1	1 (1%)	0	-	NC
Seizure	0	-	1	1 (1%)	0	-	NC
Other	180	72 (69%)	180	70 (70%)	190	77 (72%)	

Table 11: Serious Adverse Events

	A-P (N=104)		D-P (N=100)		P-A (N=107)	
AE category	No. of events	No. (%) patients	No. of events	No. (%) patients	No. (%) patients	No. (%) patients
Any SAE	6	4 (4%)	12	10 (9%)	13	10 (9%)
Vomiting	1	1 (1%)	1	1 (1%)	1	1 (1%)
Cardiac Ischaemia	0	-	0	-	2	2 (2%)
Dizziness	0	-	0	-	2	2 (2%)
Headaches	0	-	2	1 (1%)	0	-
Hyperglycaemia	2	1 (1%)	0	-	0	-
Hypoglycaemia	0	-	1	1 (1%)	1	1 (1%)
Kidney Dysfunction	0	-	0	-	1	1 (1%)
Transient Ischaemic Attack	0	-	1	1 (1%)	0	-
Other	3	3 (3%)	7	7 (7%)	6	6 (6%)