

Figure 1

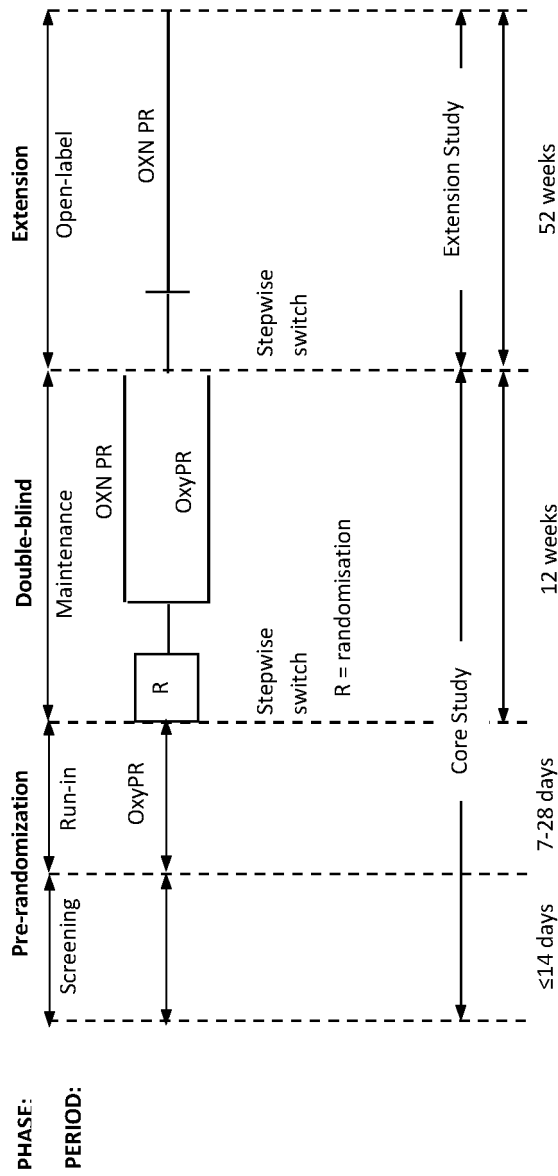


Figure 2

Phase	Pre-Randomisation			Double-Blind				
Period	Screening	Run-in		Maintenance				
Study Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Visit Number	1	2	3	4	5	6	7	8
Study Day			1	8	15	29	57	85
Duration	≤14 days	7 – 28 days		12 weeks				

Figure 3A

Pre-Randomisation Run-in Phase (open-label)

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone prolonged release (OxyPR)	Tablets	10, 20 and 40 mg oxycodone	q12h	Oral

Figure 3B

Double-blind Phase

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone / naloxone prolonged release (OXN PR)	Tablets	10/5, 20/10 and 40/20 mg oxycodone / naloxone combination	q12h	Oral
Matched placebo for OxyPR	Tablets	matching placebos for 10, 20 and 40 mg OXY tablets	q12h	Oral

Figure 3CDouble-blind Phase

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone prolonged release (OxyPR)	Tablets	10, 20 and 40 mg oxycodone	q12h	Oral
Matched placebo for OXN PR	Tablets	Matching placebos for 10/5, 20/10 and 40/20 mg OXN tablets	q12h	Oral

Figure 4

Category	Oxycodone (N=135)	Oxycodone/Naloxone (N=130)	Total (N=265)
Completed	114 (84.4)	108 (83.1)	222 (83.8)
without any major protocol violation	97 (71.9)	96 (73.8)	193 (72.8)
Discontinued due to			
Administrative	21 (15.6)	22 (16.9)	43 (16.2)
Adverse Events	4 (3.0)	8 (6.2)	12 (4.5)
Lack of Therapeutic Effect	4 (3.0)	7 (5.4)	11 (4.2)
Lost to follow-up	2 (1.5)	4 (3.1)	6 (2.3)
Subjects choice	1 (0.7)	0 (0.0)	1 (0.4)
	10 (7.4)	3 (2.3)	13 (4.9)

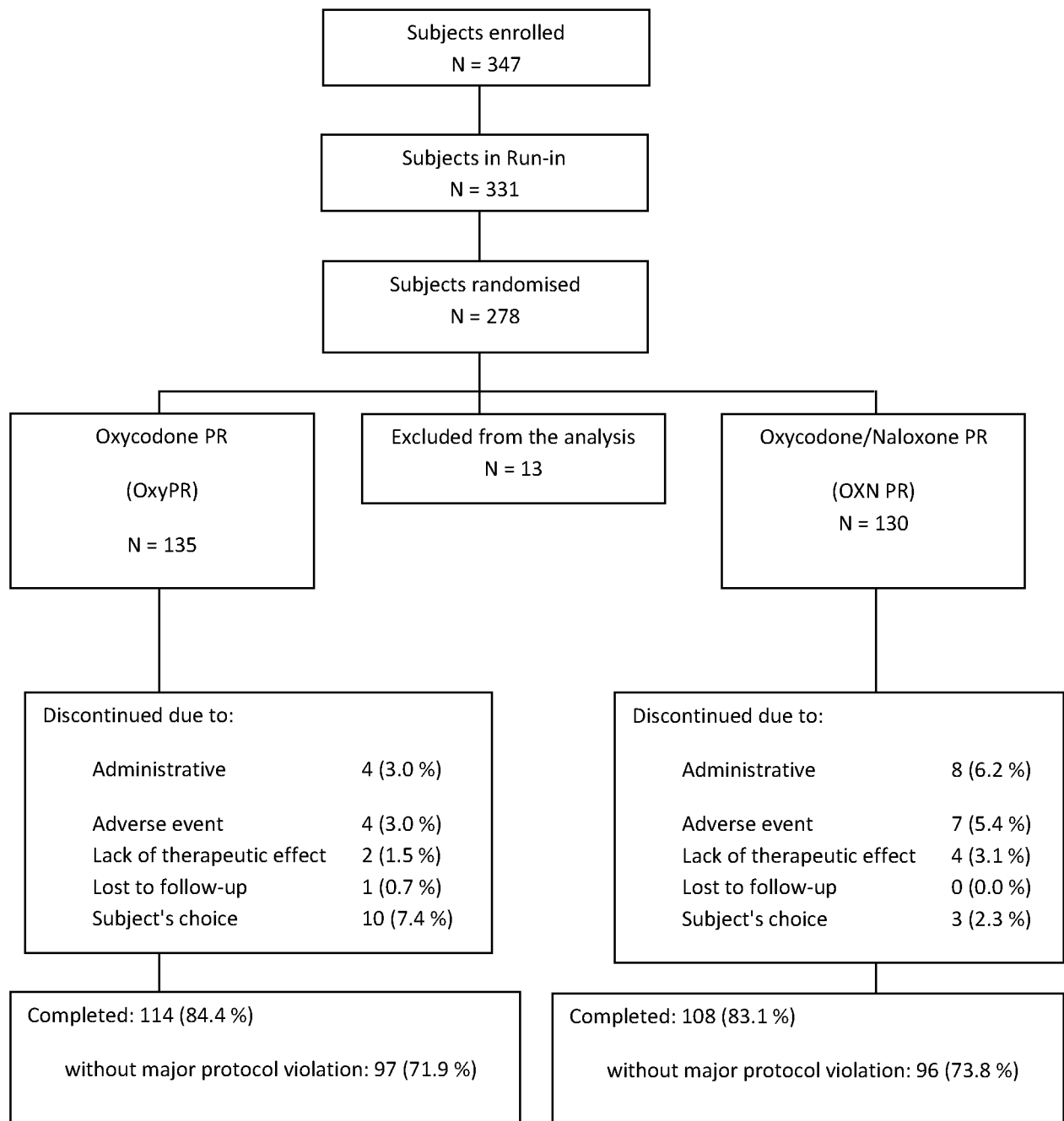
Figure 5

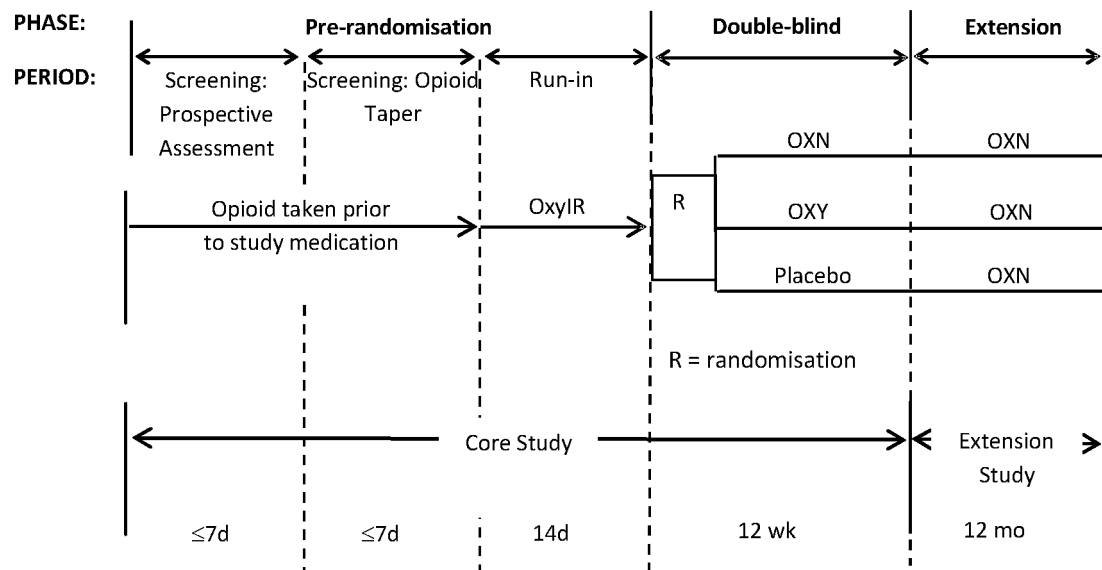
Figure 6

Figure 7

Phase Period	Pre-Randomisation			Double-Blind				
	Screening		Run-In					
	Prospective Assessment ("baseline")	Opioid Taper						
Duration	≤7 d	≤7 d		14 d	12 wk			
Study Visit	V1	V2	V3	V4	V5	V6	V7	V8A ^a
Study Day ^b				1	14	28	56	84
Pain Intensity Scale- "Pain Right Now"		Daily		Daily	Daily			
Pain Intensity Scale- "Average Pain over 24 Hours"		Daily		Daily	Daily			
Patient Bowel Function Measures ^b			X	Daily	Daily			
Patient Bowel Function Self-assessment ⁱ			X	X	X	X	X	X

Figure 8A

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone immediate-release (OxyIR; ie, OxyNorm [®])	Capsules	5 mg	q4-6h PRN	Oral

Figure 8B

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone / naloxone prolonged-release (OXN)	Tablets	10/5 and 20/10 mg oxycodone/ naloxone combination	q12h	Oral

Figure 8C

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone / naloxone prolonged-release (OXN)	Tablets	10/5, 20/10, and 40/20 mg oxycodone/ naloxone combination	q12h	Oral

Figure 8D

<u>Study Medication</u>	<u>Dosage Form</u>	<u>Unit Strength</u>	<u>Dosing Frequency</u>	<u>Mode of Administration</u>
Oxycodone prolonged-release (OXY)	Tablets	10 and 20 mg	q12h	Oral
Matched placebo for OXN	Tablets	0 mg	q12h	Oral
Matched placebo for OXY	Tablets	0 mg	q12h	Oral

Figure 9**Subject Disposition: Double-blind Safety Population**

	Treatment Groups			
	Placebo	Oxycodone	Oxycodone/ Naloxone	Total
	(N=158)	(N=151)	(N=154)	(N=463)
Completed n (%)				
Yes	133 (84.18)	133 (88.08)	136 (88.31)	402 (86.83)
No	25 (15.82)	18 (11.92)	18 (11.69)	61 (13.17)
Reason for Discontinuation n (%)				
Administrative	0 (0.00)	1 (0.66)	2 (1.30)	3 (0.65)
Adverse event	13 (8.23)	6 (3.97)	6 (3.90)	25 (5.40)
Lack of Therapeutic Effect	6 (3.80)	5 (3.31)	4 (2.60)	15 (3.24)
Lost to follow-up	0 (0.00)	1 (0.66)	0 (0.00)	1 (0.22)
Subject's choice	6 (3.80)	5 (3.31)	6 (3.90)	17 (3.67)

Figure 10

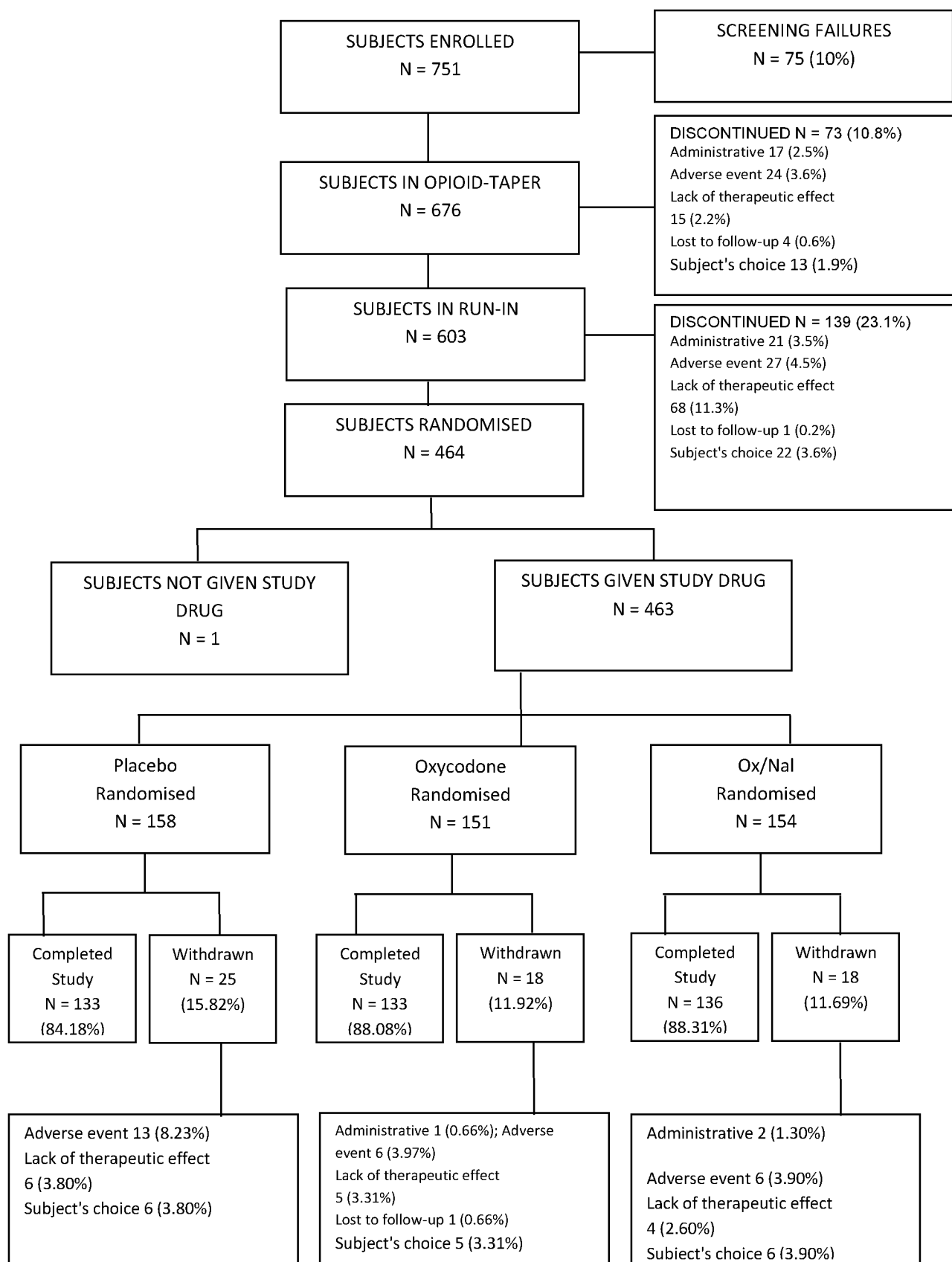
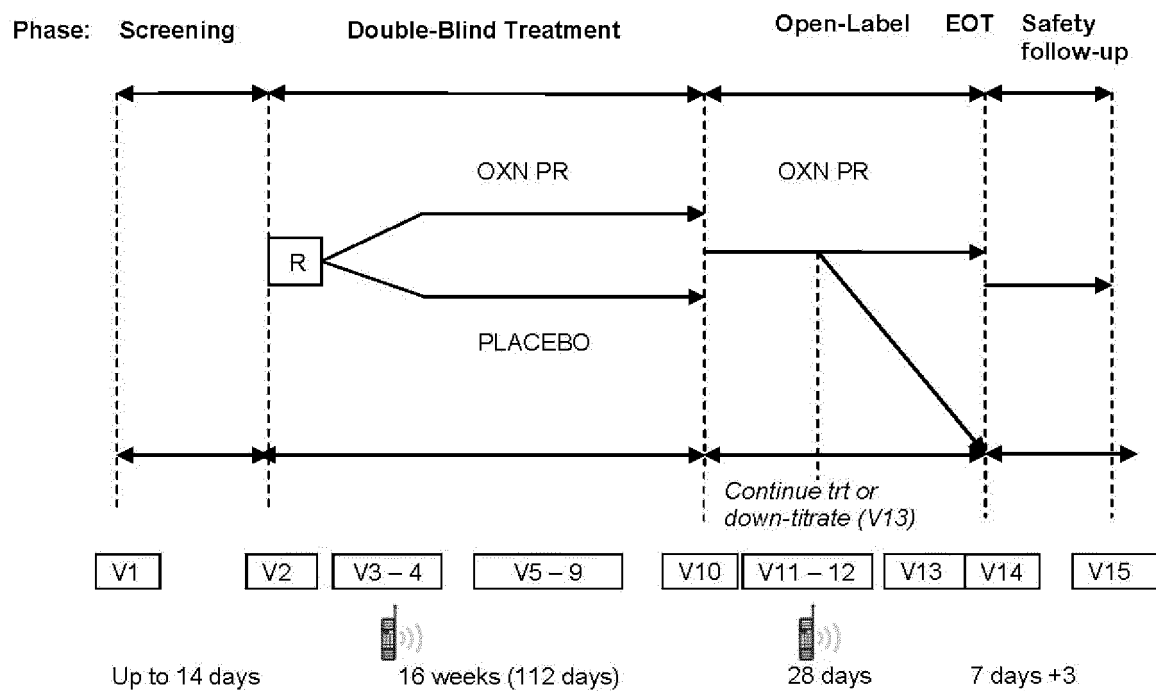


Figure 11

Study Design Graphic:



R = randomisation

trt = treatment

EOT = End of treatment

Additionally, unscheduled visits for titration will be conducted as required

Figure 12

Table 1. Screening (Visit 1) Schedule of Visits and Procedures/CRF Modules

Note: Procedures in *italics* will be collected in the CRF/Diaries. All procedures (italic and non italic) should be collected in the source documents (excluding questionnaires and diary questions). Procedures should be completed in the order presented here as far as is practicable.

Phase ¹	Screening
Visit Number (Conducted in clinic)	1
Study Day	-14 to 0
<i>Informed consent</i>	✓
<i>Informed consent for pharmacogenomic analysis</i>	✓
<i>Demography (including height)</i>	✓
Physical exam	✓
<i>Vital signs measurements (BP, pulse, respiration rate, temperature, weight)</i>	✓
<i>12-lead ECG</i>	✓
<i>NMSQuest (subject)</i>	✓
<i>Non Motor Symptom Assessment Scale for PD (Investigator)</i>	✓
<i>Hoehn & Yahr staging disease assessment</i>	✓
<i>24 hour pain diary issued (data collected for 7 days prior to Visit 2)</i>	✓
<i>Assessment of pain type (Chaudhuri/Schapira scale)</i>	✓
<i>MMSE</i>	✓
<i>Medical history and current medical conditions</i>	✓
<i>PD medication history including current</i>	✓
<i>Analgesic medication history including current</i>	✓
<i>Current medication</i>	✓
<i>Clinical laboratory tests (haematology, chemistry, urinalysis)</i>	✓
Drug screen (urine)	✓
Pregnancy test (urine) ²	✓
<i>Pharmacogenomic sampling (optional)</i>	✓
<i>Review of all Inclusion/Exclusion criteria</i>	✓
<i>Contact IRT to register subject (including screen failures)</i>	✓

Footnotes providing further detail for tests / procedures in Table 1

1. All questionnaires are to be completed whilst the subject is in the "on" state where possible.
2. Serum FSH for post-menopausal females only if a country-specific requirement.

Figure 13

Table 2. Schedule of Visits and Procedures/CRF Modules from Randomisation (Visit 2) to End of Study

Note: Procedures in *italics* will be collected in the CRF/Diaries. All procedures (*italic* and non *italic*) will be collected in the source documents (excluding questionnaires and diary questions). Procedures should be completed in the order presented here as far as is practicable.

Phase ¹	Unscheduled Visit	Double-Blind Phase (Treatment)																End of D/B Start O/L	Open-Label				End of O/L	End of Study ⁹ (Safety Follow-Up)
Visit Number		2	3	4	5	6	7	8	9	10 / ED ⁷	11	12	13	14 / ED ⁷	15									
Clinic or Telephone Visit		C	T	T	C	C	C	C	C	C	T	T	C	C	C									
Study Day		0	2	4	7	14	28	56	84	112	114	116	126	140	147									
Duration		16 weeks ⁸																28 days ⁸				7 days + 3 ⁹		
Review/Inclusion/Exclusion Criteria		✓								✓														
Physical exam										✓					✓									
Vital signs (BP, pulse, respiration rate, temperature) ²	✓	✓				✓	✓	✓	✓	✓					✓	✓								
12-lead ECG																✓								
Alertness	✓	✓	✓	✓							✓	✓												
Telephone monitoring: check if pain scores indicate a need for up-titration, alertness and record AEs ³	✓ ³		✓									✓												
Pain diary: Averaged pain over the last 24 hours		✓																						
Assessment of pain type (Chaudhuri/Schapiira scale)										✓														
Non Motor Symptom Assessment Scale for PD (Investigator)														✓										
WOQ-9 (subject)		✓					✓	✓	✓	✓				✓		✓								
UPDRS Part III/IV: Motor exam & complications		✓					✓	✓	✓	✓				✓		✓								
PDDS-2 (subject)		✓					✓	✓	✓	✓				✓		✓								
PDQ-8 (subject)		✓					✓	✓	✓	✓				✓		✓								
CGH (Investigator)							✓	✓	✓	✓														
PGH (subject)							✓	✓	✓	✓														
HADS (subject)		✓						✓		✓														
EQ-5D (subject)		✓								✓						✓								
CISI-PD (subject)		✓					✓	✓	✓	✓														
PD medication: current	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓								
Analgesic medication: historical and current		✓																						
Any other current medication																								
Clinical lab tests (haematology, chemistry, urinalysis)										✓					✓									
Pregnancy test (urine) ⁵										✓					✓									
Pain Rescue Medication Use										Daily in diaries														
Concomitant Medication Use	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓								
AEs (Non-elicited reporting)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓								

Daily in diaries

Figure 13 continued

Phase ¹	Unscheduled Visit	Double-Blind Phase (Treatment)												End of D/B Start O/L	Open-Label			End of O/L	End of Study ⁹ (Safety Follow-Up)	
Visit Number		2	3	4	5	6	7	8	9		10 / ED ⁷	11	12	13	14 / ED ⁷	15				
Clinic or Telephone Visit		C	T	T	C	C	C	C	C		C	T	T	C	C	C				
Study Day		0	2	4	7	14	28	56	84		112	114	116	126	140	147				
Duration		16 weeks ⁸																28 days ⁸		7 days + 3 ⁹
Call IRT to update subject status information ⁴	✓	✓				✓	✓	✓	✓		✓				✓					
Randomisation		✓																		
Study medication dispensed		✓				✓	✓	✓	✓		✓			✓						
Subject diary dispensed		✓				✓	✓	✓	✓		✓			✓						
Telephone patient to remind to begin pain diary										-7 days before visit					-7 days before					
Subject diary collection: Check completion compliance						✓	✓	✓	✓	✓	✓			✓	✓					
Drug accountability and drug compliance						✓	✓	✓	✓					✓						
Early Discontinuation from Double-Blind Phase											✓					✓ ⁶				
Post study pain management ⁷											✓					✓				
Early discontinuation from Open-Label Phase															✓	✓ ⁶				

Footnotes providing further detail for tests / procedures in Table 2

1. All questionnaires are to be completed whilst the subject is in the "on" state where possible.
2. Vital signs will also be performed at any unscheduled visit or any titration visit.
3. Telephone monitoring will also be completed following any titration visit.
4. Urine pregnancy tests may be performed more frequently if required by specific country requirements. Serum FSH should be conducted only if country requirements specify this.
5. IRT calls should also be made at unscheduled visits and for early discontinuations and screen failures.
6. Post study pain management will be collected once at the subject's last treatment visit, Visit 10 or Visit 14 or at early discontinuation.
7. ED = Early Discontinuation. Subjects will complete discontinuation assessments which will be the same as those required for Visit 10 or Visit 14 for early discontinuation from the Double-Blind or Open-Label Phase respectively.
8. Visit windows – Visits 5 & 6 = +/- 3 days; Visits 7 – 10, 13 & 14 = +/- 5 days.
9. The Safety Follow-Up Visit should be performed 7 (+3) days after the last treatment visit which may be sooner than day 147 if the subject discontinues early from either the Double-Blind or Open-Label Phases.