Supplementary Material

Table S1 Reasons for patient DOs as reported in the opioid clinical trials

Reasons	Placebo N_{total}, N_{DOs} (%)	Oxycodone N_{total}, N_{DOs} (%)	Oxymorphone N_{total}, N_{DOs} (%)	Tramadol N_{total}, N_{DOs} (%)
AEs	2078, 121 (5.82)	1174, 315 (26.8)	674, 274 (40.7)	3175, 596 (18.8)
LoE	1959, 419 (21.4)	999, 79 (7.91)	674, 42 (6.23)	2814, 321 (11.4)
TDOs	2283, 752 (32.9)	1174, 457 (38.7)	674, 333 (49.4)	3990, 1494 (37.5)

N_{total}: the total number of patients involved in the clinical trials.
N_{DOs}: the total number of patients left (dropped out) the clinical trials.
%: the percentage of DOs.

Table S2 List of tested models with their OF values for primary efficacy endpoint analysis

Model #	Models	OF values	ΔOF
1	Sigmoidal E_{max} model with proportional residual Error	212.103	-
2	Model #1 with adding proportional interindividual variability of E_{max} and ED_{50}	212.103	0
3	Model #1 with adding proportional interindividual variability of PLC	203.913	-8.19
4	Model #3 with adding additive interindividual variability of PLC instead of proportional	203.204	-0.709
5	Model #3 with $\sqrt{N}$	237.000	33.087
6	Model #3 with adding additive residual Error instead of proportional	202.049	-1.864
7	Model #3 with combined both additive and proportional residual Error	202.049	-1.864

N = number of patients.

Table S3 List of tested models with their OF values for efficacy-time course analysis

Model #	Models	OF values	ΔOF
1	Basic model with proportional residual Error	531.558	-
2	Model #1 with adding proportional interindividual variability of PLC	448.427	-83.131
3	Model #2 with adding proportional interindividual variability of PLC_{50}	432.990	-15.437
4	Model #3 with adding proportional interindividual variability of E_{max} and ED_{50}	446.187	13.197
5	Model #3 with $\sqrt{N}$	888.612	455.622
6	Model #3 with adding additive residual Error instead of proportional	446.076	12.086
7	Model #3 with combined both additive and proportional residual Error	432.991	0.001

N = number of patients.

Table S4 Estimated parameters of efficacy-time course analysis

Parameter	Value	%RSE	95% CI
E_{max}(mm)	−31.7	48.0	(−43.4, −19.3)
PLC (mm)	−22.3	8.07	(−25.8, −18.8)
PLC_{50} (week)	1.47	25.7	(0.729, 2.21)
ω^2 of PLC	0.0176	54.9	(−0.0013, 0.0366)
ω^2 of PLC_{50}	0.982	42.0	(0.174, 1.79)
σ^2	0.0225	26.4	(0.0109, 0.0341)

%RSE = relative standard error.
95% CI = 95% confidence interval estimated by PDx-Pop®.

Table S5 List of tested models with their OF values for Safety analysis

a) Gastrointestinal system

Model #	Models	Gastrointestinal					
		constipation	ΔOF	Nausea	ΔOF	vomiting	ΔOF
1	Basic model	7237.132	-	8221.171	-	4476.468	-
2	Model #1 + η of intercept	7044.276	-192.856	7919.521	-301.65	4347.7	-128.768
3	Model #2 + η of slope	7044.277	0.001	7909.961	-9.56	4333.079	-14.621

b) Central nervous system

Model #	Models	Central nervous					
		Dizziness	ΔOF	headache	ΔOF	Somnolence	ΔOF
1	Basic model	6151.785	-	4621.389	-	5026.156	-
2	Model #1 + η of intercept	6034.619	-117.166	4509.463	-111.926	4831.77	-194.386
3	Model #2 + η of slope	6033.195	-1.424	4497.848	-11.615	4831.176	-0.594

c) Locomotor, respiratory, and integumentary systems

Model #	Models	Locomotor		Respiratory		Integumentary	
		Fatigue	ΔOF	Xerostomia	ΔOF	Pruritus	ΔOF
1	Basic model	1773.264	-	2224.401	-	3244.812	-
2	Model #1 + η of intercept	1771.862	-1.402	2124.902	-99.499	3195.039	-49.773
3	Model #2 + η of slope	1771.352	-0.51	2124.903	0.001	3195.041	0.002

Table S6 List of tested models with their OF values for tolerability analysis

Model #	Models	AEs	ΔOF	LoE	ΔOF
1	**Basic model**	9172.11	-	4874.99	-
2	**Model #1 + η of intercept**	9094.207	-77.903	4598.854	-267.136
3	**Model #2 + η of slope**	9128.149	33.942	4595.126	-3.728

Table S7 Estimated model parameters of tolerability analysis

DO reason	Intercept	ω^2 of intercept	Slope		
			Oxycodone	Oxymorphone	Tramadol
AEs	6.84	0.0241	0.0399	0.0328	0.00445
%RSE	4.78%	27.1%	10.4%	14.5%	14.1%
95% CI	(5.43, 8.58)	(0.0113, 0.0369)	(0.0317, 0.0481)	(0.0235, 0.0421)	(0.00322, 0.00568)
LoE	11.7	0.705	-0.0319	-0.0226	-0.00487
%RSE	26.4%	50.1%	20.4%	45.1%	17.5%
95% CI	(4.41, 27.3)	(0.0131, 1.40)	(-0.04477, -0.0191)	(-0.0426, -0.00261)	(-0.00654, -0.00320)

%RSE = relative standard error.
95% CI = 95% confidence interval estimated by PDx-Pop®.

Table S8 Summary of predicted dropout rates at drug recommended dose range

DO reason	Oxycodone		Oxymorphone		Tramadol	
	20–160 mg/day	**ED_{50}(47.0)**	**10–80 mg/day**	**ED_{50}(83.9)**	**100–300 mg/day**	**ED_{50}(247)**
AEs	14.0 − 97.8 %	32.3 %	9.24−50.3%	53.5 %	10.3–21.8 %	18.1%
LoE	6.53 − 0.0800 %	2.87 %	9.54–2.12%	1.94 %	7.51−2.97 %	3.81%

Fig. S1 Flowchart of the study selection process

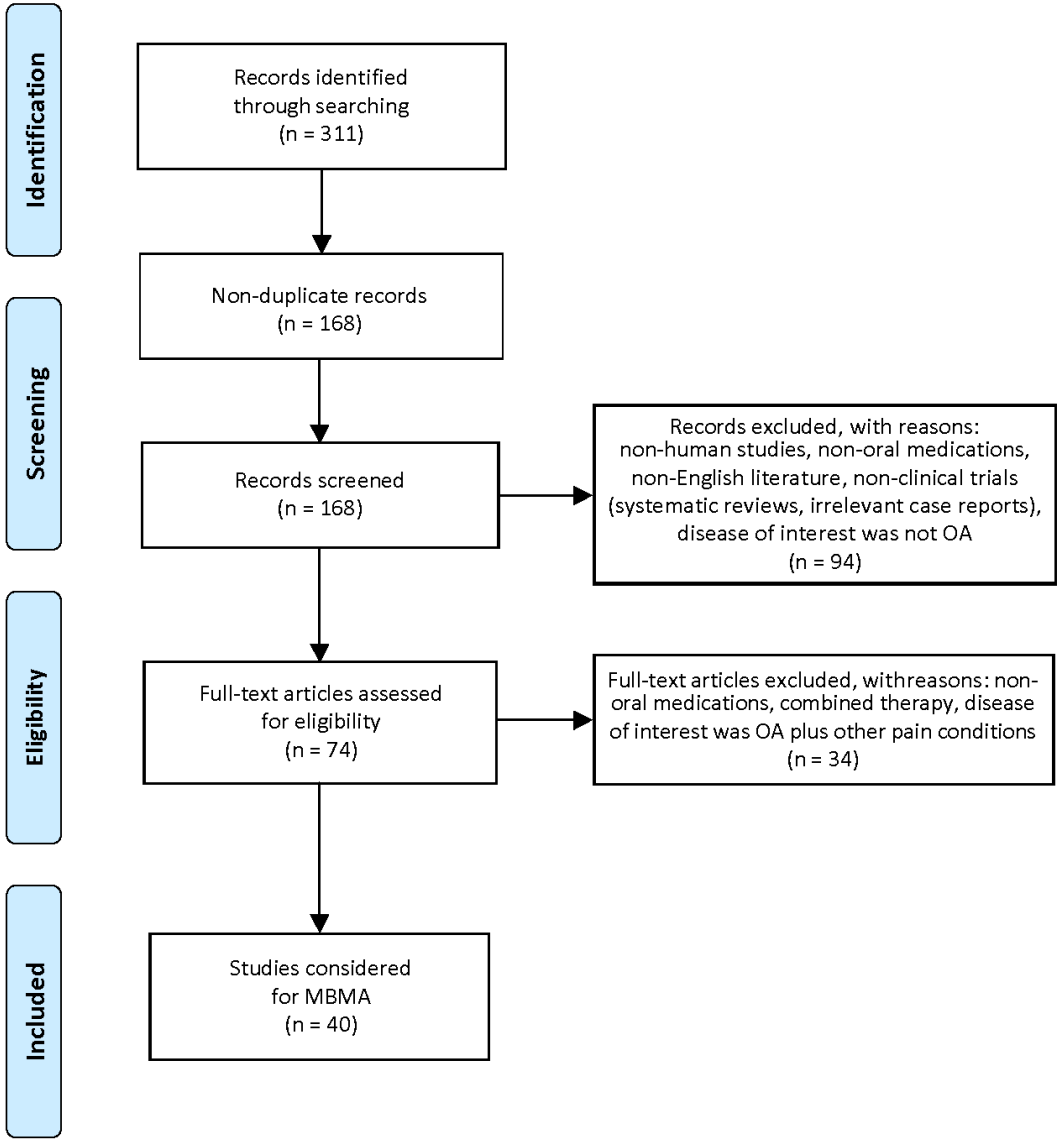

Fig. S2 A schematic drawing of a network diagram for the treatments included in the MBMA. (a) Primary efficacy endpoint analysis; (b) Safety analysis. Each treatment is represented by a node. When direct trial evidence exists, treatments are joined by a line where the width of the line is proportional to number of comparisons. The figures on each line indicate the number of treatment arms for each comparison while n refers to the total number of clinical studies involved in the MBMA

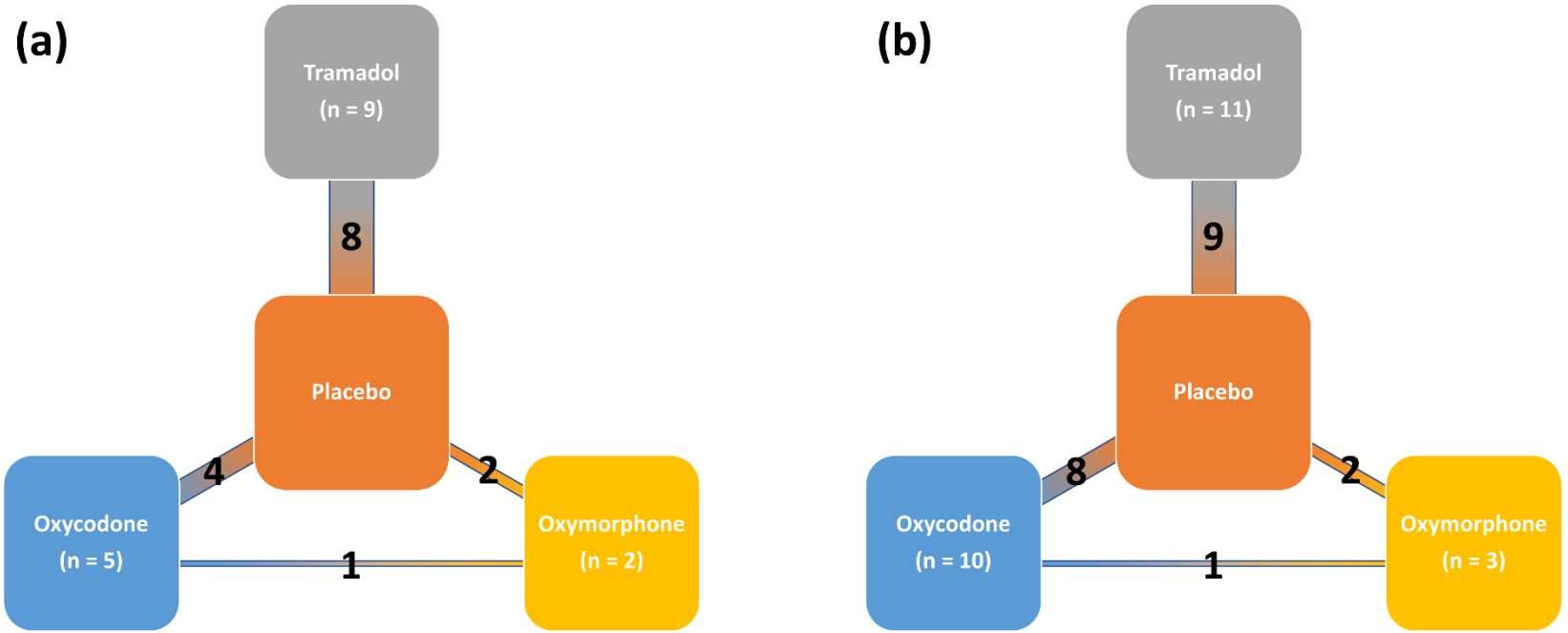

Fig. S3 Visual goodness-of-fit plots of the selected model for primary efficacy endpoint analysis

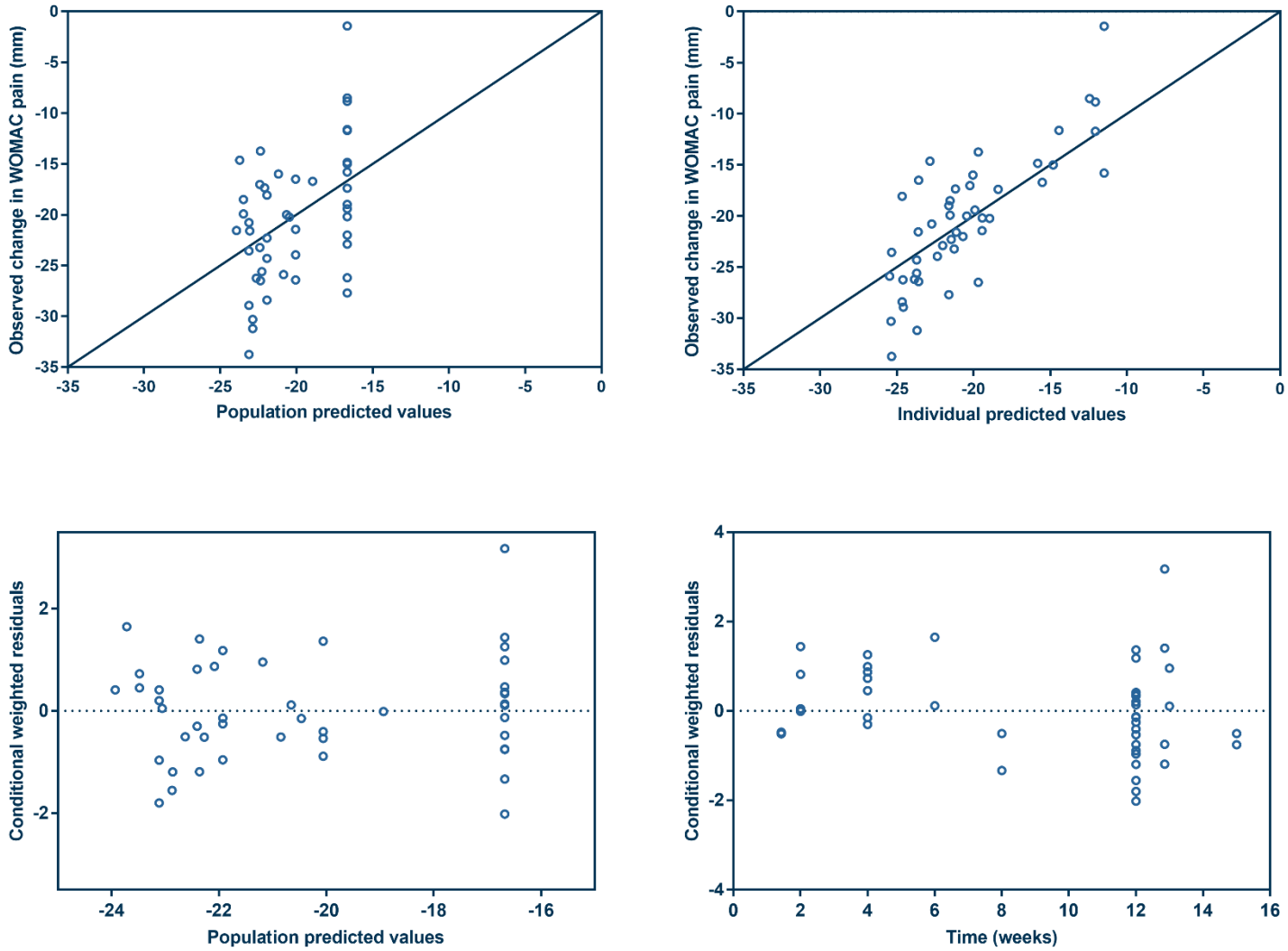

Fig. S4 Visual goodness-of-fit plots of the selected model for efficacy-time course analysis

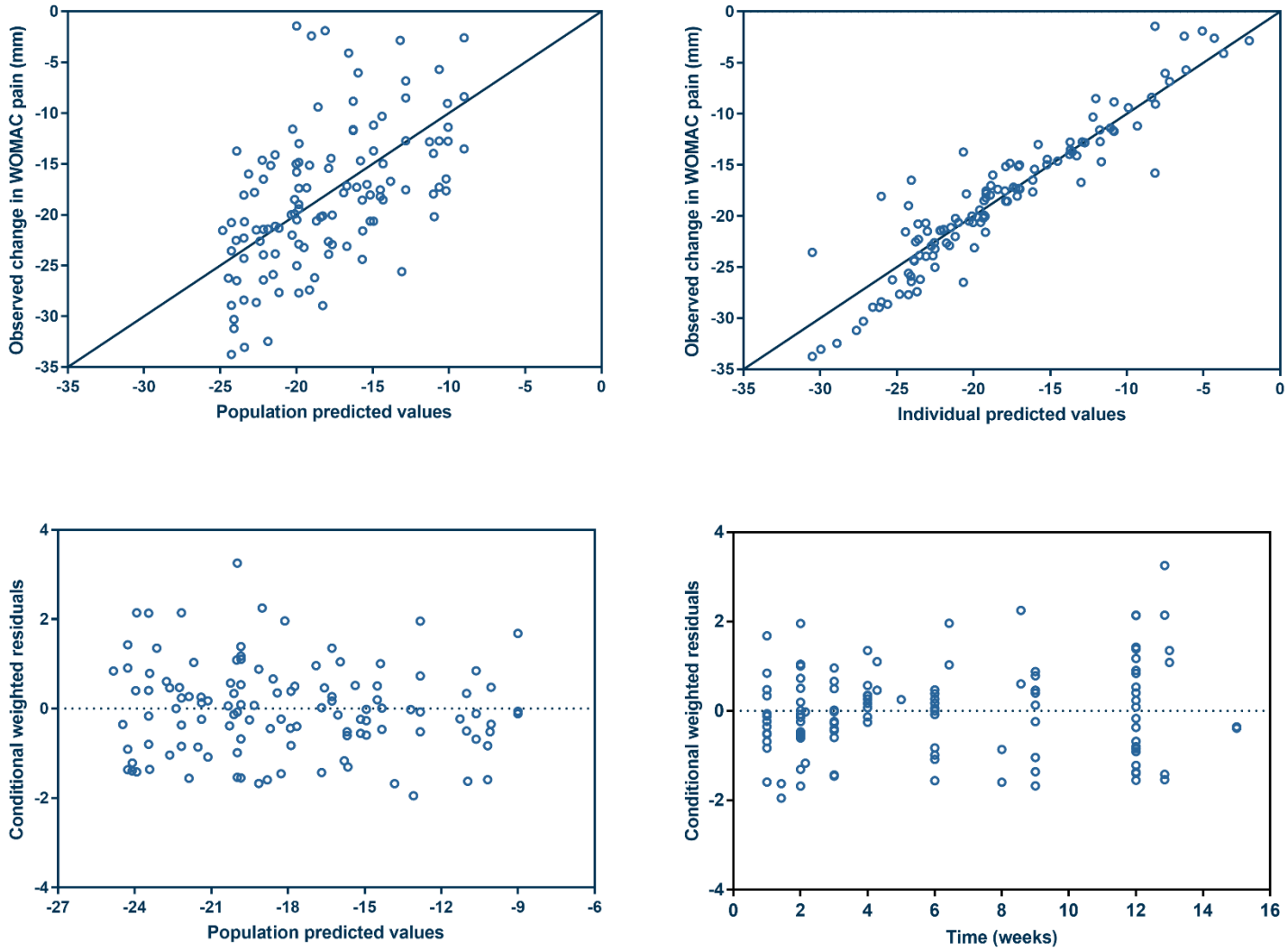

Fig. S5 Efficacy-time course analysis of tested doses in the clinical trials. Symbols represent the observed data over time course whilst the solid curves represent the fit at given doses (using population predicted values). PLC_{50} is represented by the dashed line

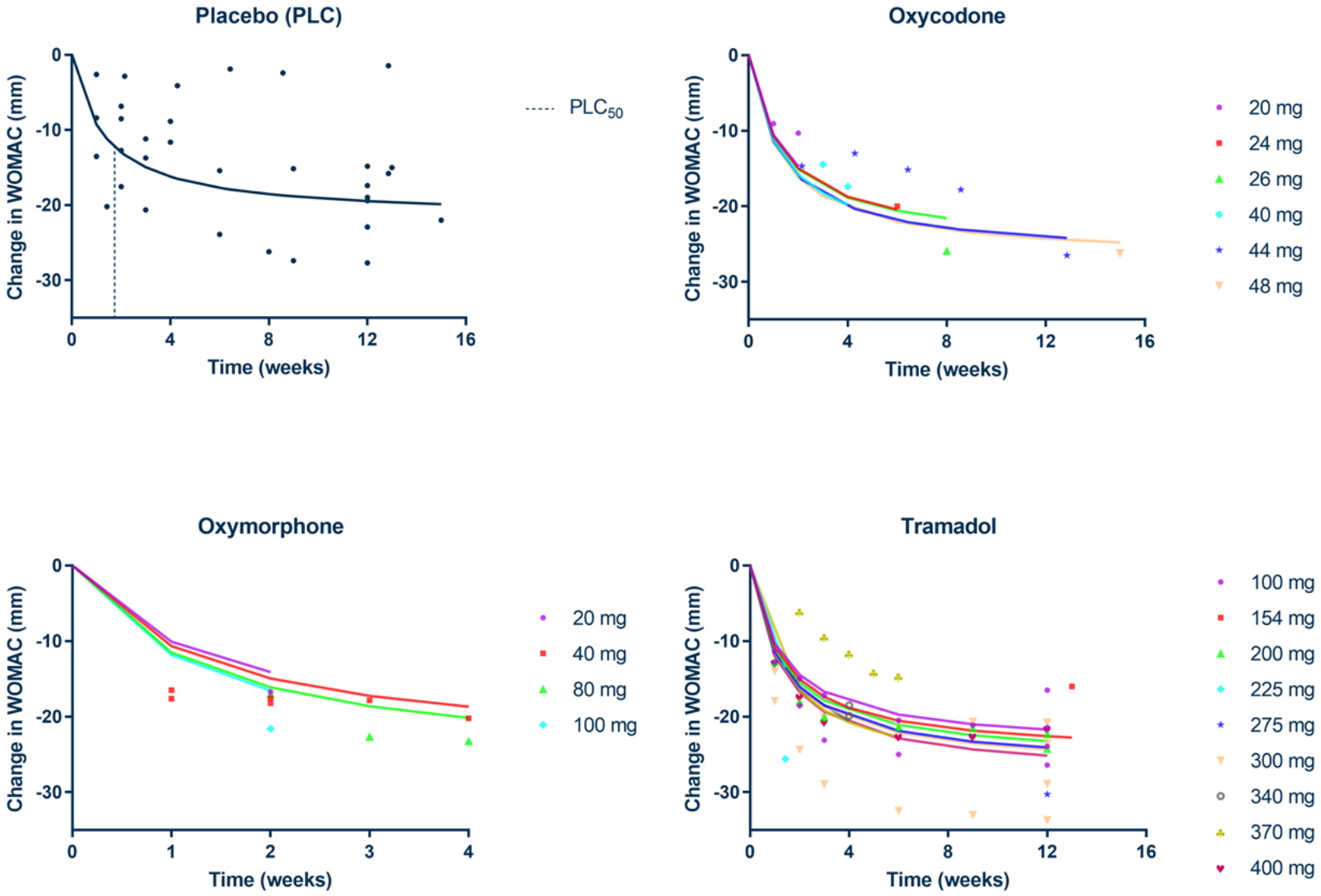

Fig. S6 Incidence of the dropouts (DOs) associated with opioid compounds. The black circles represent the observed data whilst the best fitting analysis is represented by the solid line (curve). The percentage of DOs at daily dose = 0 represents the placebo arm in each study