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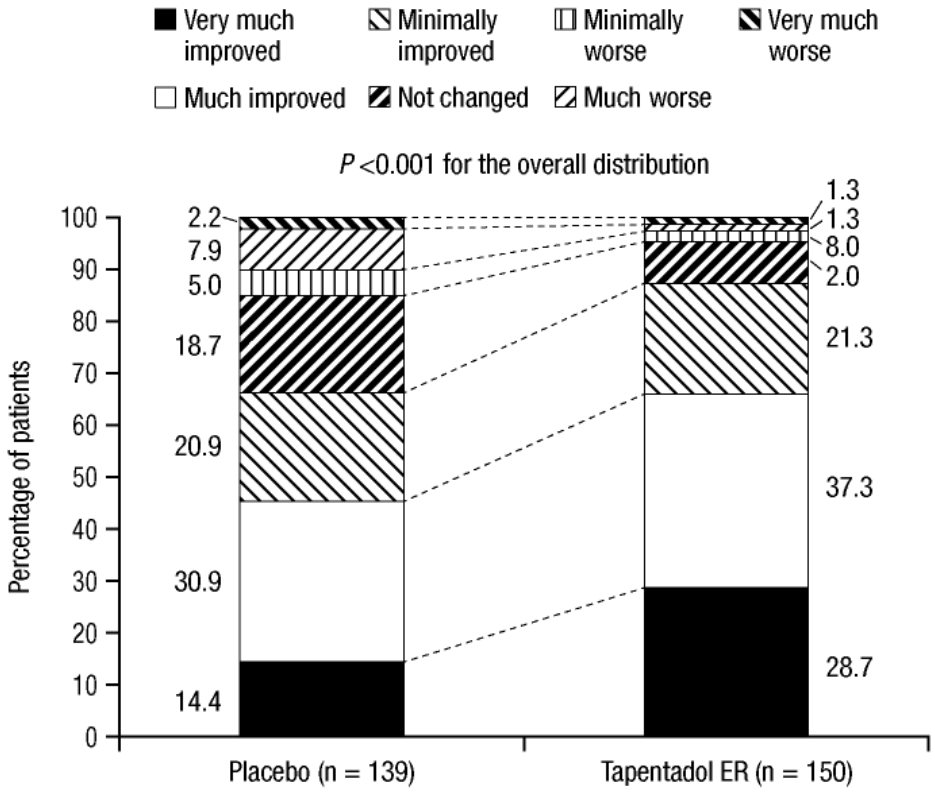
Supplementary Figure 1. Patient global impression of change (PGIC) at endpoint of the double-blind maintenance phase (ITT population).[a]



ITT, intent-to-treat; ER, extended release.
[a]Percentages may not total 100.0% because of rounding.
[b]*P* <0.001 for the overall distribution

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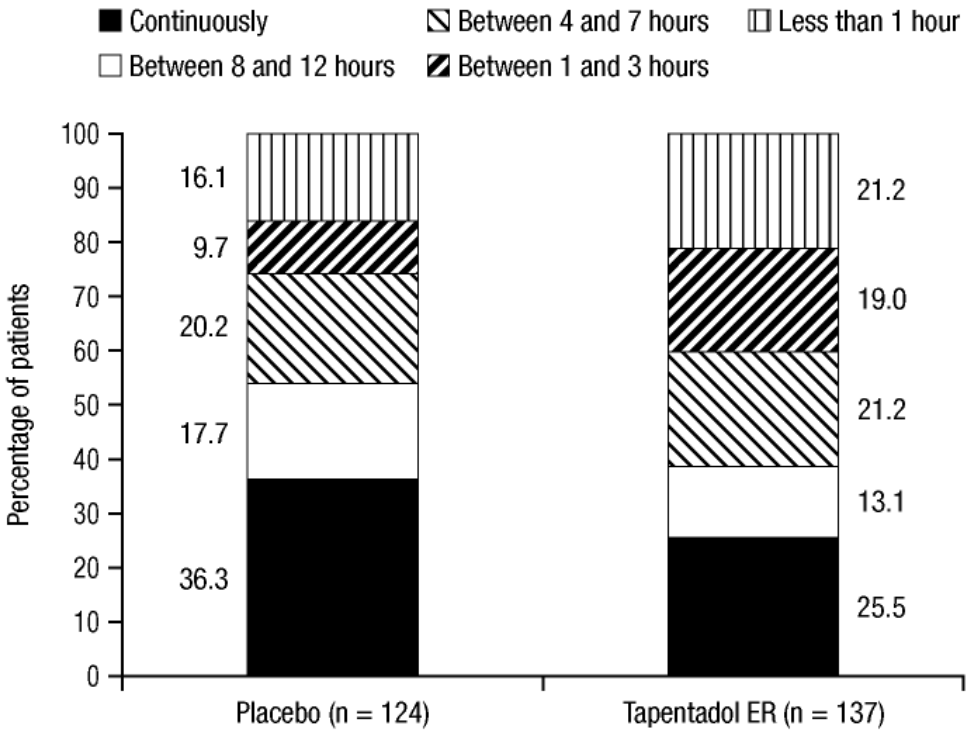
Supplementary Figure 2. Duration of spontaneous pain during the past 24 hours at endpoint of the double-blind maintenance phase (ITT population).



ITT, intent-to-treat; ER, extended release.

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Supplementary Table 1. Patient Demographic and Baseline Characteristics

	OL safety population	**DB safety population**	
Characteristic	**Tapentadol ER (n = 459)**	**Placebo (n = 152)**	**Tapentadol ER (n = 166)**
Gender, n (%)			
Male	266 (58.0)	88 (57.9)	99 (59.6)
Female	193 (42.0)	64 (42.1)	67 (40.4)
Race, n (%)			
White	370 (80.6)	120 (78.9)	138 (83.1)
Black or African American	60 (13.1)	22 (14.5)	23 (13.9)
Asian	9 (2.0)	2 (1.3)	3 (1.8)
American Indian or Alaskan Native	4 (0.9)	2 (1.3)	1 (0.6)
Other	16 (3.5)	6 (3.9)	1 (0.6)
Age, y			
Mean (SD)	59.8 (10.30)	59.0 (9.00)	58.5 (10.63)
Range	28-86	28-82	30-83
Age category, n (%)			
<65 y	305 (66.4)	109 (71.7)	122 (73.5)
≥65 y	154 (33.6)	43 (28.3)	44 (26.5)
Prior opioid use, n (%)[a]			
Yes	148 (32.2)	48 (31.6)	52 (31.3)
No	311 (67.8)	104 (68.4)	114 (68.7)
Body mass index, kg/m^2			
Mean (SD)	34.8 (9.22)	34.5 (7.84)	35.1 (11.47)
Range	17-146	20-63	17-146
Start of OL pain intensity score[b,c]			
Category, n (%)			
Mild	1 (0.2)	0	0
Moderate	58 (12.6)	14 (9.2)	23 (13.9)
Severe	400 (87.1)	138 (90.8)	143 (86.1)
Mean (SD)	7.3 (1.30)	7.5 (1.27)	7.4 (1.27)
Baseline pain intensity score (end of OL)[b,d,e]			
Category, n (%)	7 (1.5)	5 (3.3)	2 (1.2)
None	172 (37.5)	84 (55.3)	88 (53.0)

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Mild Moderate Severe Mean (SD)	92 (20.0) 48 (10.5) 3.6 (1.99)	39 (25.7) 24 (15.8) 3.5 (2.17)	52 (31.3) 23 (13.9) 3.7 (1.78)

OL, open-label; DB, double-blind; ER, extended release; SD, standard deviation; DPN, diabetic peripheral neuropathy.
[a]Prior opioid use was defined as any previous opioid analgesic use for the treatment of painful DPN for ≥3 weeks.
[b]Pain intensity is defined as none = 0, mild = >0 to <4, moderate = 4 to <6, and severe = ≥6 on the 11-point numerical rating scale.
[c]Average of pain scores over 3 days prior to the start of titration.
[d]Average of pain scores over 72 hours prior to randomization.
[e]n = 319 for OL safety population; n = 165 for tapentadol ER DB safety population.

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Supplementary Table 2. Average Pain Intensity Changes From Start to Week 12 of the DB Maintenance Phase Using Different Imputation Methods: Sensitivity Analyses of the Primary Endpoint (ITT Population)

	Placebo (n = 152)	**Tapentadol ER (n = 166)**
LOCF		
Mean (SD) score at start of DB phase	3.53 (2.17)	3.70 (1.78)
Mean (SD) change at Week 12 of DB phase	1.30 (2.43)	0.28 (2.04)
LSMD vs placebo (95% CI)		−0.95 (−1.42 to −0.49)
P value (minus placebo)		<0.001
BOCF		
Mean (SD) score at start of DB phase	3.53 (2.17)	3.70 (1.78)
Mean (SD) change at Week 12 of DB phase	0.68 (1.82)	−0.00 (1.57)
LSMD vs placebo (95% CI)		−0.64 (−1.01 to −0.28)
P value (minus placebo)		<0.001
Modified BOCF		
Mean (SD) score at start of DB phase	3.53 (2.17)	3.70 (1.78)
Mean (SD) change at Week 12 of DB phase	0.77 (2.03)	0.05 (1.78)
LSMD vs placebo (95% CI)		−0.65 (−1.05 to −0.26)
P value (minus placebo)		0.001
PMI		
Mean (SD) score at start of DB phase	3.53 (2.17)	3.70 (1.78)
Mean (SD) change at Week 12 of DB phase	0.94 (2.22)	0.17 (1.90)
LSMD vs placebo (95% CI)		−0.67 (−1.04 to −0.30)
P value (minus placebo)		<0.001
WOCF		
Mean (SD) score at start of DB phase	3.53 (2.17)	3.70 (1.78)
Mean (SD) change at Week 12 of DB phase	2.00 (2.58)	0.87 (2.17)
LSMD vs placebo (95% CI)		−1.10 (−1.58 to −0.61)
P value (minus placebo)		<0.001
Observed case		
Mean (SD) score at start of DB phase	3.53 (2.17)	3.70 (1.78)
Mean (SD) change at Week 12 of DB phase	1.05 (2.31)	−0.04 (1.97)
LSMD vs placebo (95% CI)		−1.11 (−1.65 to −0.57)
P value (minus placebo)		<0.001

DB, double-blind; ITT, intent-to-treat; ER, extended release; LOCF, last observation carried forward; SD, standard deviation; LSMD, least-squares mean difference; CI, confidence interval; BOCF, baseline observation carried forward; PMI, placebo mean imputation; WOCF, worst observation carried forward.

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Supplemental Table 3. Average Pain Intensity and Change in Pain Intensity by Supplemental Tapentadol ER Use During Double-blind Treatment (LOCF; ITT Population)[a]

	Placebo		Tapentadol ER	
Mean (SD) pain intensity	**Supplemental tapentadol ER used (n = 112)**	**Supplemental tapentadol ER not used (n = 40)**	**Supplemental tapentadol ER used (n = 106)**	**Supplemental tapentadol ER not used (n = 59)**
Mean (SD) pain intensity at the start of open-label titration	7.6 (1.32)	7.1 (1.30)	7.5 (1.23)	7.2 (1.10)
Mean (SD) pain intensity at the start of double-blind treatment	3.7 (2.26)	3.2 (1.88)	3.8 (1.84)	3.5 (1.66)
Mean (SD) pain intensity at Week 12 of double-blind treatment	5.2 (2.58)	3.9 (2.46)	4.3 (2.35)	3.5 (1.81)
Mean (SD) change in pain intensity from the start to Week 12 of double-blind treatment	1.5 (2.53)	0.7 (2.03)	0.4 (2.28)	0.0 (1.52)

ER, extended release; LOCF, last observation carried forward; ITT, intent-to-treat; SD, standard deviation.

[a]In both treatment groups, supplemental tapentadol ER 25 mg bid was permitted as additional analgesia during the first 4 days and once per day from Day 5 onward during the double-blind treatment period.

Supplementary Table 4. Brief Pain Inventory (BPI) Mean Pain Intensity and Pain Interference Score Changes From Start of the OL Phase to DB Endpoint (ITT Population)[a]

	Placebo (n = 137)	**Tapentadol ER (n = 147)**
Pain intensity subscale score		
Mean (SD) score at start of OL phase	6.8 (1.54)	6.6 (1.52)
Mean (SD) change at DB endpoint	−2.3 (2.33)	−3.0 (2.16)
P value (minus placebo)[b]		0.003
Pain interference score		
Mean (SD) score at start of OL phase	5.9 (2.30)	5.6 (2.32)
Mean (SD) change at DB endpoint	−2.6 (2.38)	−3.0 (2.07)
P value (minus placebo)[b]		0.050

ITT, intent-to-treat; ER, extended release; SD, standard deviation; OL, open-label; DB, double-blind.

[a]Results are presented for all patients who had observations at both the start of the OL phase and at the endpoint of the DB maintenance phase.

[b]Tested using an analysis of covariance model with treatment, pooled analysis site, and dose category as factors and start of OL value as a covariate.

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Supplementary Table 5. Short Form-36 (SF-36) Mean Subscale and Summary Scores Changes From Start of the DB Phase to Endpoint of the DB Maintenance Phase (ITT Population)

SF-36 subscale or summary score	Placebo (n = 131)	Tapentadol ER (n = 146)
Physical functioning subscale		
Mean (SD) score at start of DB phase	38.2 (11.35)	37.3 (10.49)
Mean (SD) change at DB endpoint	−1.7 (7.44)	0.1 (7.50)
LSMD vs placebo (95% CI)		1.5 (−0.21 to 3.23)
P value (minus placebo)		0.085
Role-physical subscale		
Mean (SD) score at start of DB phase	41.9 (10.33)	41.7 (9.89)
Mean (SD) change at DB endpoint	−2.1 (7.14)	0.8 (8.12)
LSMD vs placebo (95% CI)		2.6 (0.85 to 4.29)
P value (minus placebo)		0.004
Bodily pain subscale		
Mean (SD) score at start of DB phase	44.2 (7.34)	42.4 (7.03)
Mean (SD) change at DB endpoint	−3.9 (8.80)	−0.0 (7.55)
LSMD vs placebo (95% CI)		3.0 (1.24 to 4.69)
P value (minus placebo)		<0.001
General health subscale		
Mean (SD) score at start of DB phase	42.2 (9.02)	42.0 (9.35)
Mean (SD) change at DB endpoint	−0.8 (6.39)	−0.4 (6.04)
LSMD vs placebo (95% CI)		0.6 (−0.87 to 1.99)
P value (minus placebo)		0.444
Vitality subscale		
Mean (SD) score at start of DB phase	45.8 (9.11)	45.5 (9.13)
Mean (SD) change at DB endpoint	−0.6 (8.00)	0.3 (8.85)
LSMD vs placebo (95% CI)		1.0 (−0.95 to 3.01)
P value (minus placebo)		0.307
Social functioning subscale		
Mean (SD) score at start of DB phase	44.0 (10.54)	44.4 (9.10)
Mean (SD) change at DB endpoint	−1.2 (8.81)	0.1 (8.65)
LSMD vs placebo (95% CI)		1.7 (−0.29 to 3.59)
P value (minus placebo)		0.095
Role-emotional subscale		
Mean (SD) score at start of DB phase	43.4 (11.72)	43.6 (11.02)
Mean (SD) change at DB endpoint	−1.9 (11.21)	0.5 (10.15)
LSMD vs placebo (95% CI)		2.2 (−0.22 to 4.53)
P value (minus placebo)		0.075
Mental health subscale		
Mean (SD) score at start of DB phase	47.5 (10.20)	47.2 (10.24)
Mean (SD) change at DB endpoint	−1.1 (10.03)	−0.1 (8.66)
LSMD vs placebo (95% CI)		1.0 (−1.16 to 3.11)
P value (minus placebo)		0.371
Physical component summary		
Mean (SD) score at start of DB phase	40.1 (8.87)	39.1 (8.52)
Mean (SD) change at DB endpoint	−2.3 (6.40)	0.1 (6.52)

LSMD vs placebo (95% CI) *P* value (minus placebo)		2.1 (0.67 to 3.57) 0.004
Mental component summary		
Mean (SD) score at start of DB phase	47.7 (10.79)	48.1 (10.12)
Mean (SD) change at DB endpoint	−0.8 (9.37)	0.2 (9.00)
LSMD vs placebo (95% CI)		1.1 (−0.97 to 3.18)
P value (minus placebo)		0.296

[a]Results are presented for all patients who had observations at both the start of the DB phase and at the endpoint of the DB maintenance phase.