Table S1—Least squares mean (95% CI) changes from baseline on outcome measures by treatment group for P028+P029.

	Week-1 (Diary)/Night-1 (PSG)/ Week-2 (Ratings)		Month-1		Month-3	
	Suvorexant 20/15mg	Placebo	Suvorexant 20/15mg	Placebo	Suvorexant 20/15mg	Placebo
Diary measures	*N*=479	*N*=740	*N*=463	*N*=728	*N*=425	*N*=664
sTST, min	29.4 (25.5, 33.4)	14.4 (11.2, 17.6)	41.3 (36.4, 46.2)	22.9 (19.0, 26.8)	55.3 (49.9, 60.6)	39.3 (35.0, 43.6)
sTSO, min	-14.4 (-17.1, -11.6)	-8.3 (-10.5, -6.0)	-18.6 (-22.0, -15.2)	-13.0 (-15.8, -10.3)	-24.9 (-28.3, -21.6)	-19.0 (-21.6, -16.3)
sWASO, min	-17.4 (-20.2, -14.7)	-12.1 (-14.3, -9.9)	-26.0 (-29.2, -22.8)	-19.4 (-21.9, -16.8)	-34.5 (-37.8, -31.3)	-29.8 (-32.4, -27.2)
sNAW, n	-0.15 (-0.21, -0.09)	-0.17 (-0.22, -0.13)	-0.31 (-0.38, -0.24)	-0.32 (-0.37, -0.26)	-0.45 (-0.53, -0.38)	-0.48 (-0.54, -0.42)
sQUAL, 1-4 scale	0.24 (0.20, 0.28)	0.15 (0.12, 0.17)	0.35 (0.31, 0.39)	0.21 (0.18, 0.25)	0.21 (0.18, 0.25)	0.34 (0.31, 0.38)
sFRESH, 0-4 scale	0.27 (0.22, 0.32)	0.17 (0.13, 0.20)	0.44 (0.38, 0.50)	0.28 (0.24, 0.33)	0.59 (0.53, 0.66)	0.46 (0.41, 0.52)
PSG measures	*N*=337	*N*=574	*N*=318	*N*=543	*N*=299	*N*=506
LPS, min	-28.0 (-31.8, -24.2)	-16.8 (-19.7, -13.8)	-33.2 (-36.7, -29.6)	-24.1 (-26.8, -21.3)	-32.2 (-36.0, -28.4)	-27.6 (-30.5, -24.7)
WASO, min	-55.1 (-59.3, -50.9)	-20.5 (-23.7, -17.3)	-46.1 (-50.7, -41.4)	-20.6 (-24.2, -17.1)	-48.0 (-52.9, -43.2)	-25.0 (-28.7, -21.3)
TST, min	81.0 (75.8, 86.1)	36.1 (32.2, 40.1)	77.6 (72.1, 83.1)	42.9 (38.8, 47.1)	78.3 (72.5, 84.1)	50.8 (46.3, 55.3)
SE, %[†]	16.9 (15.8, 17.9)	7.5 (6.7, 8.4)	16.2 (15.0, 17.3)	8.9 (8.1, 9.8)	16.3 (15.1, 17.5)	10.6 (9.7, 11.5)
Rating scales	*N*=450	*N*=704	*N*=454	*N*=707	*N*=425	*N*=659
ISI, 0-28 scale	-	-	-4.4 (-4.8, -4.0)	-3.0 (-3.3, -2.7)	-6.2 (-6.6, -5.7)	-4.9 (-5.3, -4.6)
CGI-S, 1-7 scale	-0.8 (-0.9, -0.7)	-0.5 (-0.6, -0.4)	-1.0 (-1.1, -0.9)	-0.6 (-0.7, -0.5)	-1.3 (-1.4, -1.2)	-1.0 (-1.1, -0.9)
PGI-S, 0-5 scale	-0.6 (-0.7, -0.6)	-0.3 (-0.4, -0.3)	-0.8 (-0.9, -0.7)	-0.5 (-0.5, -0.4)	-1.1 (-1.2, -1.0)	-0.8 (-0.9, -0.7)
CGI-I, 1-7 scale #	3.0 (2.9, 3.1)	3.4 (3.3, 3.4)	2.9 (2.8, 2.9)	3.3 (3.2, 3.3)	2.6 (2.5, 2.7)	3.0 (2.9, 3.1)
PGI-I, 1-7 scale #	3.0 (2.9, 3.1)	3.3 (3.3, 3.4)	2.8 (2.7, 2.9)	3.2 (3.2, 3.3)	2.5 (2.4, 2.7)	2.9 (2.8, 3.0)

Ns shown are for sTST (diary measures), LPS (PSG measures) and PGI-S (rating scales); sample sizes differed for some of the other endpoints.

Results based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, trial, time point, and treatment-by-time point interaction as covariates; cohort was also included in models for Diary and Rating scale measures.

[†] Post hoc analysis

Value at timepoint (not change from baseline)

Table S2—Number (%) of patients with any adverse event and with somnolence over the 3-month primary treatment phase by age and gender subgroups for P028+P029.

	Suvorexant 20/15mg	**Placebo**
Age		
≥1 adverse event		
<65 years	130/291 (44.7)	196/449 (43.7)
≥65 years	99/202 (49.0)	162/318 (50.9)
Somnolence		
<65 years	22/291 (7.6)	13/449 (2.9)
≥65 years	11/202 (5.4)	12/318 (3.8)
Gender		
≥1 adverse event		
Men	71/174 (40.8)	119/275 (43.3)
Women	158/319 (49.5)	239/492 (48.6)
Somnolence		
Men	6/174 (3.4)	10/275 (3.6)
Women	27/319 (8.5)	15/492 (3.0)

Table S3—Number (%) of patients with vital sign or ECG measurements that met predetermined criteria over 3 months for P028+P029.

		Suvorexant 20/15mg (N=493)	**Placebo (N=767)**
Parameter	Predefined Limit	n/m (%)	n/m (%)
Vital Sign			
Diastolic Blood Pressure	Value ≤50 mm Hg and Decrease ≥15 mm Hg	2/ 487 (0.4)	2/ 757 (0.3)
	Value ≥105 mmHg and Increase ≥15 mm Hg	1/ 487 (0.2)	1/ 757 (0.1)
Systolic Blood Pressure	Value ≤90 mm Hg and Decrease ≥20 mm Hg	4/ 487 (0.8)	2/ 757 (0.3)
	Value ≥180 mm Hg and Increase ≥20 mm Hg	1/ 487 (0.2)	3/ 757 (0.4)
Pulse Rate	Value ≤50 bpm and Decrease ≥15 bpm	1/ 487 (0.2)	2/ 757 (0.3)
	Value ≥120 bpm and Increase ≥15 bpm	1/ 487 (0.2)	0/ 757 (0.0)
Temperature	Value ≥38.3°C and Increase ≥1°C	0/ 487 (0.0)	0/ 757 (0.0)
Weight	≥7% Decrease	7/ 485 (1.4)	5/ 757 (0.7)
	≥7% Increase	10/ 485 (2.1)	11/ 757 (1.5)
ECG			
QTc Interval Bazett	Prolongation compared to baseline ≥30 to ≤60 msec	48/ 482 (10.0)	79/ 752 (10.5)
	Prolongation compared to baseline >60 msec	1/ 482 (0.2)	5/ 752 (0.7)
	Value ≥500 msec	0/ 483 (0.0)	0/ 755 (0.0)

N = Number of patients treated (took at least one tablet of study drug) during the indicated phase.

m = number of treated patients with valid pre- and post-treatment values of the parameter (except for the ECG "Value ≥500 msec" parameter where m = number of treated patients with valid post-treatment value).

n = Number of patients meeting the predefined limit criteria.

Vital signs and ECGs were collected at each clinic visit - baseline, Week 2, Month 1, and Month 3, and additionally at Month 2 for vital signs.

Table S4—Summary of rebound as assessed by mean change from baseline values (in minutes) on self-report endpoints during the first 3 nights of the run-out phase, and on PSG endpoints during the first night of the run-out, for P028+P029.*

	Suv→Pbo			**Pbo→Pbo**		
Run-out night	N	Mean (SD)	95% CI	N	Mean (SD)	95% CI
sTST						
Night 1	206	23.8 (100.5)	(10.0, 37.6)	605	41.3 (98.4)	(33.4, 49.1)
Night 2	195	51.4 (84.9)	(39.4, 63.4)	610	53.7 (96.5)	(46.0, 61.3)
Night 3	201	41.0 (90.8)	(28.4, 53.6)	594	52.8 (92.6)	(45.3, 60.3)
sTSO						
Night 1	206	-7.1 (87.5)	(-19.1, 5.0)	605	-19.8 (91.3)	(-27.1, -12.5)
Night 2	195	-22.5 (58.2)	(-30.7, -14.3)	610	-24.4 (86.4)	(-31.2, -17.5)
Night 3	201	-17.2 (68.9)	(-26.8, -7.6)	594	-24.2 (74.2)	(-30.2, -18.2)
WASO						
Night 1	129	-23.0 (64.1)	(-34.2, -11.8)	436	-31.8 (50.6)	(-36.5, -27.0)
LPS						
Night 1	131	-34.5 (58.0)	(-44.5, -24.4)	439	-32.7 (45.5)	(-37.0, -28.5)

* Timing of run-out for self-report endpoints: in P028 after 3 months of treatment for patients who did not enter the extension or after 6 months for patients who entered the extension, in P029 after 3 months of treatment. Timing of run-out for PSG endpoints: 3 months after treatment in both P028+P029 (PQ-cohort).

Suv = suvorexant 20/15mg, Pbo = placebo; treatment x→treatment y = treatment received during the treatment phase→treatment received during the run-out phase
N = Number of randomized patients who took at least one dose of run-out phase study medication and had a value at baseline and during the run-out phase.

Table S5— Number and percentage of patients meeting Tyrer Withdrawal Symptom Questionnaire criteria for withdrawal during the first 3 nights of the run-out phase for P028+P029.*

	Suv→Suv		**Suv→Pbo**		**Difference (95% CI)†**
	N	n (%)	N	n (%)	Suv→Suv vs. Suv→Pbo
Night 1	157	6 (3.8)	184	7 (3.8)	0.1 (-4.3, 4.8)
Night 2	160	5 (3.1)	186	13 (7.0)	-3.9 (-8.9, 0.9)
Night 3	151	7 (4.6)	182	9 (4.9)	-0.2 (-5.0, 5.1)
Across Nights 1, 2 and 3[#]	172	11 (6.4)	197	17 (8.6)	-2.1 (-7.7, 3.5)

* Timing of run-out: in P028 after 3 months of treatment for patients who did not enter the extension or after 6 months for patients who entered the extension, in P029 after 3 months of treatment.

Suv = suvorexant 20/15mg, Pbo = placebo; treatment x→treatment y = treatment received during the treatment phase→treatment received during the run-out phase

N = Number of randomized patients who took at least one dose of run-out phase study medication and had a value at baseline and during the run-out phase.
n = Number of patients with withdrawal (3 or more emergent or worsening withdrawal symptoms out of 20 withdrawal symptom items on the Tyrer Withdrawal Symptom Questionnaire).

† 95% CI computed using Miettinen and Nurminen method. [37]
[#] Total of 3 or more symptoms across the 3 nights (e.g., 1 withdrawal symptom on Night 1 and 2 other withdrawal symptoms on Night 3).

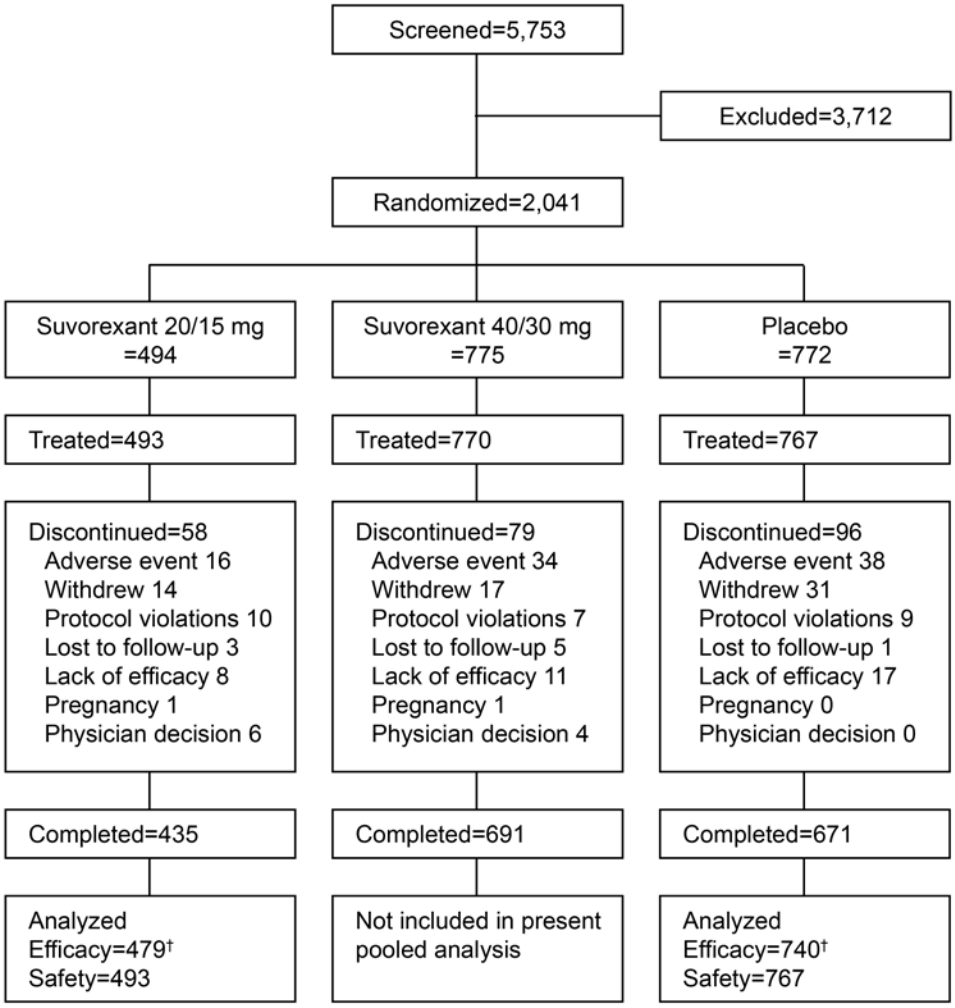
Table S6—Least squares mean change from baseline (95% CI) for Digit Symbol Substitution Test scores for P028+P029.

	Night 1		Month 1		Month 3	
	Suvorexant 20/15mg	Placebo	Suvorexant 20/15mg	Placebo	Suvorexant 20/15mg	Placebo
N	338	578	321	551	307	516
Correct responses	1.6 (0.8, 2.5)	2.3 (1.7, 3.0)	1.8 (0.8, 2.8)	2.2 (1.4, 2.9)	2.4 (1.3, 3.4)	2.9 (2.1, 3.7)
Difference vs. placebo	-0.7 (-1.8, 0.4)	-	-0.4 (-1.7, 0.9)	-	-0.5 (-1.9, 0.8)	-
Attempted responses	1.6 (0.7, 2.4)	2.3 (1.6, 3.0)	1.7 (0.7, 2.7)	2.2 (1.4, 3.0)	2.3 (1.2, 3.3)	2.8 (2.0, 3.6)
Difference vs. placebo	-0.7 (-1.8, 0.4)	-	-0.5 (-1.8, 0.8)	-	-0.5 (-1.8, 0.8)	-

Based on a mixed effects model with terms for baseline value, age category (<65, ≥65), region, gender, treatment, timepoint, and treatment-by-time point interaction as covariates.

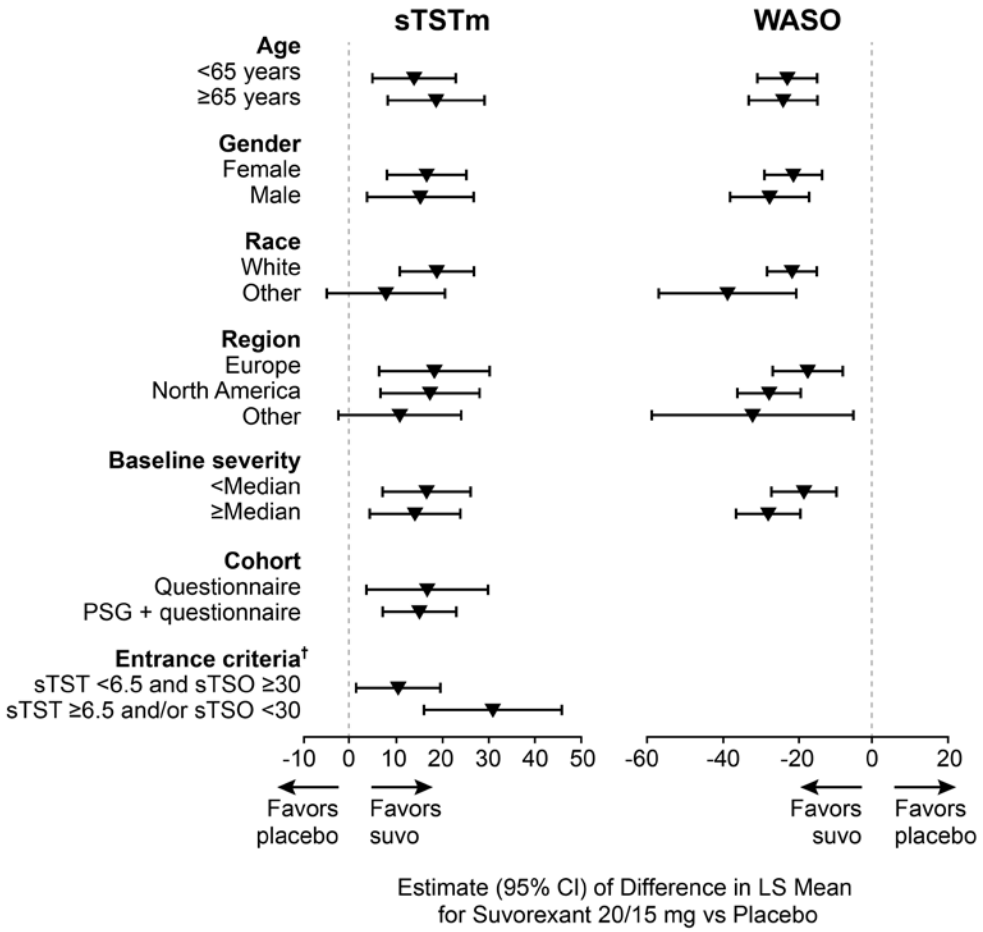
Mean scores at baseline were as follows: correct responses – suvorexant 20/15mg = 51, placebo = 52; attempted responses – suvorexant 20/15mg = 51, placebo = 52.

Figure S1—Patient accounting flowchart for P028+P029 0-3 months.



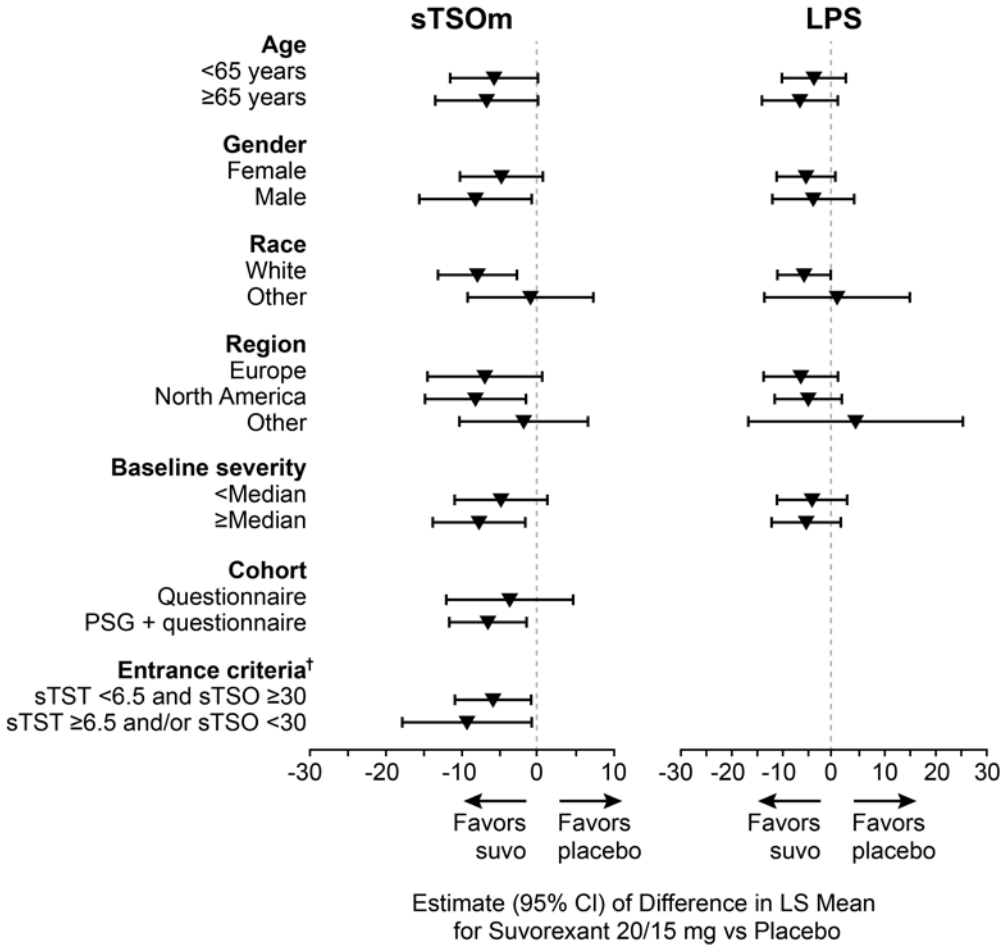
†Number analyzed for efficacy = the number included in the assessment of sTST at Week-1; fewer than the number treated due to missing data and also because data from one site in P029 were excluded due to concerns about data integrity.

Figure S2—Summary of sleep maintenance efficacy at Month 3 by subgroups for P028+P029.



†PQ cohort only.

Figure S3—Summary of sleep onset efficacy at Month 3 by subgroups for P028+P029.



†PQ cohort only.