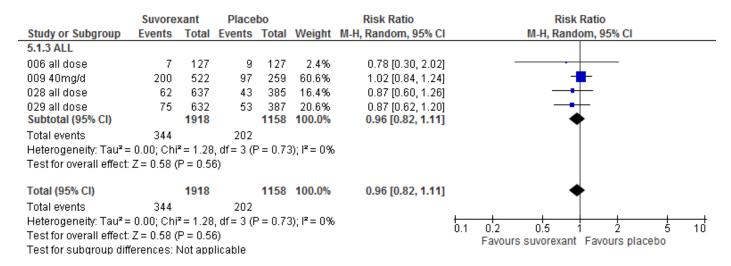
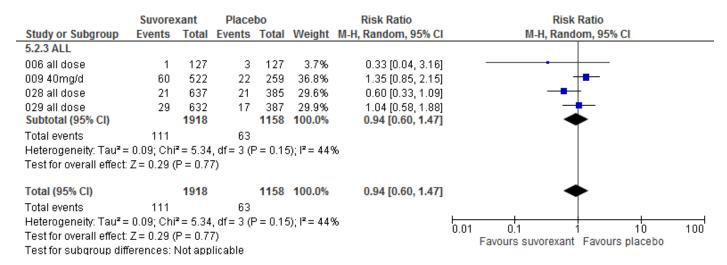
S2 Fig. Forest plots of safety secondary outcomes.

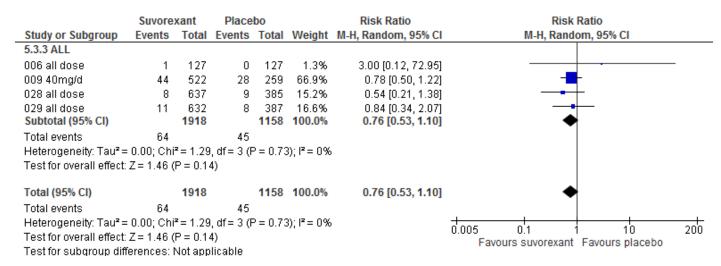
S2-1 Fig. Discontinuation due to all cause



S2-2 Fig. Discontinuation due to intolerability



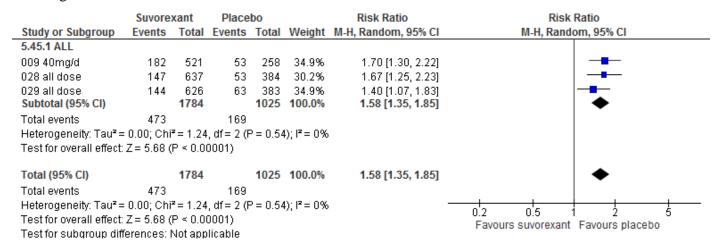
S2-3 Fig. Discontinuation due to inefficacy



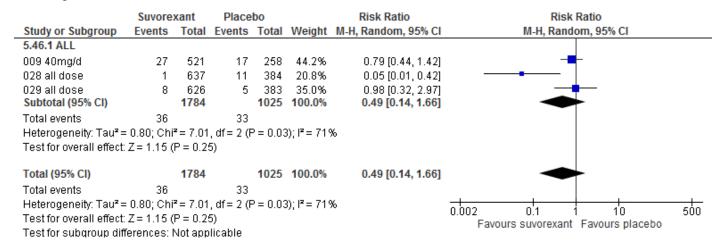
S2-4 Fig. At least one adverse event

	Suvore	xant	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.44.3 ALL							
009 40mg/d	362	521	164	258	43.0%	1.09 [0.98, 1.22]	 •
028 all dose	324	637	191	384	31.7%	1.02 [0.90, 1.16]	
029 all dose Subtotal (95% CI)	292	626 1784	167	383 1025	25.3% 100.0%	1.07 [0.93, 1.23] 1.06 [0.99, 1.14]	
Total events	978		522				
Heterogeneity: Tau ² =	= 0.00; Chi	z = 0.63	df = 2 (F)	P = 0.73	3); I² = 0%		
Test for overall effect:	Z = 1.72 (P = 0.09	9)				
Total (95% CI)		1784		1025	100.0%	1.06 [0.99, 1.14]	•
Total events	978		522				
Heterogeneity: Tau² =	= 0.00; Chi	z = 0.63	df = 2 (F)	P = 0.73	3); I² = 0%		0.7 0.85 1 1.2 1.5
Test for overall effect:	Z = 1.72 (P = 0.09	9)				Favours suvorexant Favours placebo
Test for subgroup dif	ferences: I	Not app	licable				1 avours suvorexame 1 avours pracedo

S2-5 Fig. At least one side effect



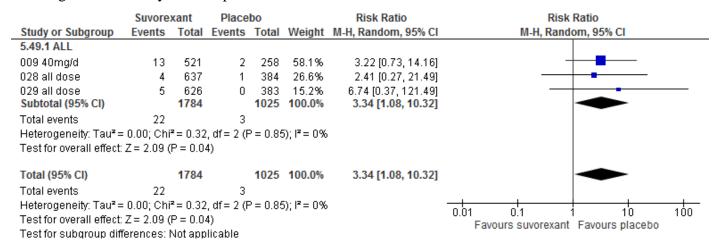
S2-6 Fig. Serious adverse event



S2-7 Fig. Somnolence

	Suvore	xant	Place	bo		Risk Ratio		Risk Ratio)	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 9	95% CI	
5.48.1 ALL										
009 40mg/d	69	521	7	258	23.6%	4.88 [2.28, 10.47]		-	_	
028 all dose	54	637	13	384	39.1%	2.50 [1.39, 4.53]		-	_	
029 all dose Subtotal (95% CI)	60	626 1784	12	383 1025	37.3% 100.0%	3.06 [1.67, 5.61] 3.16 [2.18, 4.57]		-	•	
Total events	183		32							
Heterogeneity: Tau ²	= 0.00; Chi	² = 1.88	df = 2 (F)	P = 0.39	$3); I^2 = 0\%$					
Test for overall effect	t: Z = 6.08 (P < 0.0	0001)							
Total (95% CI)		1784		1025	100.0%	3.16 [2.18, 4.57]		•	•	
Total events	183		32							
Heterogeneity: Tau ²	= 0.00; Chi	² = 1.88	df = 2 (F)	P = 0.39	$3); I^2 = 0\%$				40	400
Test for overall effect	t: Z = 6.08 ($P \leq 0.01$	0001)				0.01	0.1 1 Favours suvorexant Favo	10	100
Test for subgroup di	fferences:	Not app	licable					i avouis suvoi examt. Favo	ours pracebo	

S2-8 Fig. Excessive daytime sleepiness/sedation



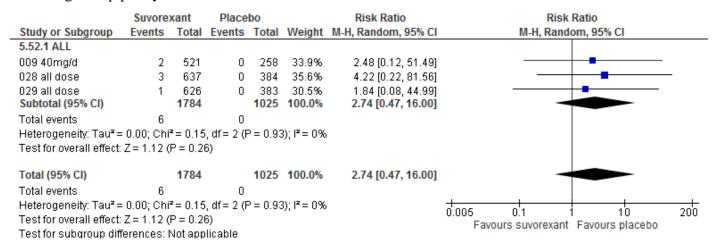
S2-9 Fig. Fatigue

	Suvore	orexant Placebo			Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	lom, 95% CI	
5.50.1 ALL										
009 40mg/d	34	521	5	258	33.0%	3.37 [1.33, 8.51]				
028 all dose	14	637	3	384	21.9%	2.81 [0.81, 9.73]		-	 	
029 all dose Subtotal (95% CI)	23	626 1784	11	383 1025	45.1% 100.0%	1.28 [0.63, 2.59] 2.09 [1.08, 4.06]		_	•	
Total events	71		19							
Heterogeneity: Tau ² :	= 0.12; Chi	= 3.10	0, df = 2 (F)	P = 0.21	l); l² = 35°	%				
Test for overall effect	t: Z= 2.18 (P = 0.0	3)							
Total (95% CI)		1784		1025	100.0%	2.09 [1.08, 4.06]			•	
Total events	71		19							
Heterogeneity: Tau ² :	= 0.12; Chi	² = 3.10	0, df = 2 (F)	P = 0.21	l); l² = 35°	%	0.04	n 1	1 10	100
Test for overall effect	t: Z = 2.18 (P = 0.0	3)				0.01	Favours suvorexant		100
Test for subaroup di	fferences:	Not app	licable					i avoura auvorexam	i avoura pracebo	

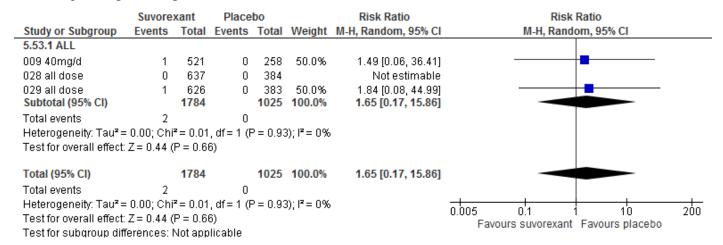
S2-10 Fig. Cataplexy

	Suvore	xant	Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.51.1 ALL							
009 40mg/d	0	521	0	258		Not estimable	
028 all dose	0	637	0	384		Not estimable	
029 all dose Subtotal (95% CI)	0	626 1784	0	383 1025		Not estimable Not estimable	
Total events Heterogeneity: Not a Test for overall effect		cable	0				
Total (95% CI)		1784		1025		Not estimable	
Total events	0		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Not appli	cable					0.1 0.2 0.5 1 2 5 10 Favours suvorexant Favours placebo
Test for subgroup di	fferences: I	Not app	licable				ravours suvorexamt Favours pracedo

S2-11 Fig. Sleep paralysis



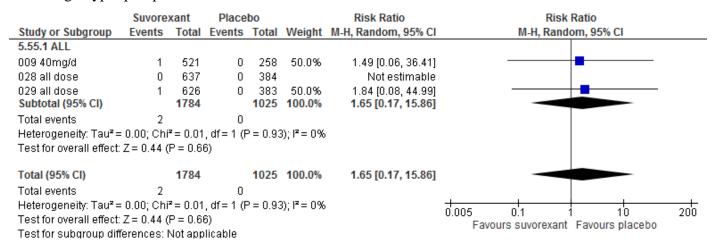
S2-12 Fig. Complex sleep-related behaviours



S2-13 Fig. Hypnagogic hallucination

	Suvore	Suvorexant Placebo			Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.54.1 ALL							
009 40mg/d	3	521	0	258	36.9%	3.47 [0.18, 66.99]	
028 all dose	1	637	0	384	31.6%	1.81 [0.07, 44.33]	
029 all dose Subtotal (95% CI)	1	626 1784	0	383 1025	31.6% 100.0%	1.84 [0.08, 44.99] 2.31 [0.38, 13.95]	
Total events	5		0				
Heterogeneity: Tau ²	= 0.00; Chi	$r^2 = 0.12$	df = 2 (F)	9 = 0.94	$(1); I^2 = 0\%$		
Test for overall effect							
Total (95% CI)		1784		1025	100.0%	2.31 [0.38, 13.95]	
Total events	5		0				
Heterogeneity: Tau ²	= 0.00; Chi	r = 0.12	df = 2 (F)	P = 0.94	$(1); I^2 = 0\%$		0.005 0.1 1 10 200
Test for overall effect	t: Z = 0.91 (P = 0.31	6)				0.005 0.1 1 10 200 Favours suvorexant Favours placebo
Test for subgroup di	fferences: I	Not app	licable				Favours suvorexame Favours placebo

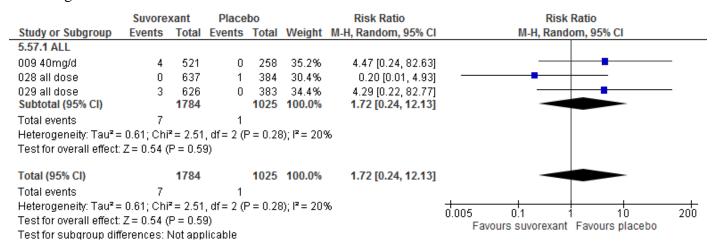
S2-14 Fig. Hypnopompic hallucination



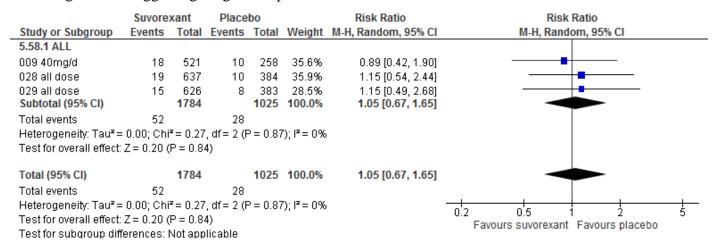
S2-15 Fig. Abnormal dream

	Suvore	xant	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.56.1 ALL							
028 all dose	12	637	3	384	58.4%	2.41 [0.68, 8.49]	
029 all dose Subtotal (95% CI)	12	626 1263	2	383 767	41.6% 100.0%	3.67 [0.83, 16.31] 2.87 [1.10, 7.52]	
Total events	24		5				
Heterogeneity: Tau ² :	= 0.00; Chi	$^{2} = 0.18$, df = 1 (F	P = 0.67	7); I² = 0%	ı	
Test for overall effect	t: Z= 2.15 (P = 0.0	3)				
Total (95% CI)		1263		767	100.0%	2.87 [1.10, 7.52]	-
Total events	24		5				
Heterogeneity: Tau ² :	= 0.00; Chi	z = 0.18	, df = 1 (F	P = 0.67	7); I ^z = 0%	1	005 00
Test for overall effect	t: Z = 2.15 (P = 0.03	3)				0.05 0.2 1 5 20 Favours suvorexant Favours placebo
Test for subgroup dit	fferences:	Not app	licable				i avouis suvoiexailt. Pavouis piacebo

S2-16 Fig. Suicidal ideation



S2-17 Fig. Events suggesting drug-abuse potential



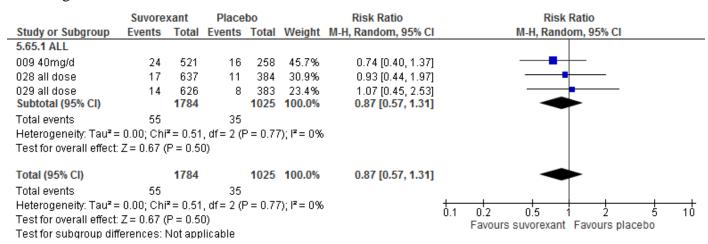
S2-18 Fig. Fall

	Suvore	xant	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.60.1 ALL							
009 40mg/d	12	521	8	258	54.7%	0.74 [0.31, 1.79]	
028 all dose	5	637	5	384	28.0%	0.60 [0.18, 2.07]	
029 all dose	7	626	2	383	17.3%	2.14 [0.45, 10.25]	_
Subtotal (95% CI)		1784		1025	100.0%	0.84 [0.44, 1.62]	•
Total events	24		15				
Heterogeneity: Tau ²	= 0.00; Chi	$i^2 = 1.74$	f = 2 (F)	P = 0.42	2); $I^2 = 0\%$)	
Test for overall effec	t: $Z = 0.52$ (P = 0.6	0)				
Total (95% CI)		1784		1025	100.0%	0.84 [0.44, 1.62]	•
Total events	24		15				
Heterogeneity: Tau ²	= 0.00; Chi	$i^2 = 1.74$	f = 2 (F)	P = 0.43	2); $I^2 = 0\%$,	0.005 0.1 1 10 200
Test for overall effect	t: Z = 0.52 (P = 0.6	0)				Favours suvorexant Favours placebo
Test for subaroup di	ifferences:	Not app	licable				1 avours suverexame 1 avours praceso

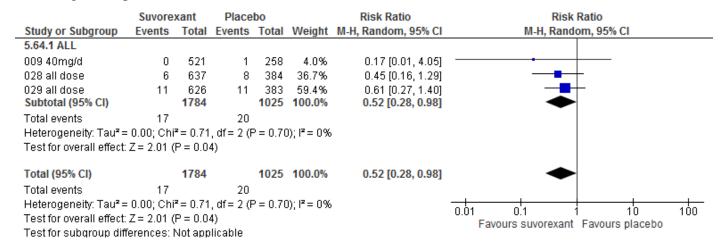
S2-19 Fig. Headache

	Suvore	xant	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.63.1 ALL							
009 40mg/d	43	521	22	258	33.1%	0.97 [0.59, 1.58]	
028 all dose	43	637	23	384	33.3%	1.13 [0.69, 1.84]	- •
029 all dose Subtotal (95% CI)	48	626 1784	22	383 1025	33.6% 100.0%	1.33 [0.82, 2.18] 1.13 [0.85, 1.51]	
Total events	134 - 0.00: Obi	z_ 0.00	67) – 0 66	:\· IZ = 000		
Heterogeneity: Tau ² : Test for overall effect			. ,	-= 0.00	o), i= U%		
Total (95% CI)		1784		1025	100.0%	1.13 [0.85, 1.51]	-
Total events	134		67				
Heterogeneity: Tau ² :	= 0.00; Chi	z = 0.83	df = 2 (F)	P = 0.66	S(t) = 0%		0.2 0.5 1 2 5
Test for overall effect	Z = 0.87 (P = 0.3	B)				Favours suvorexant Favours placebo
Test for subgroup dif	ferences: I	Not app	licable				Tavours suvorexant. Tavours praceso

S2-20 Fig. Dizziness



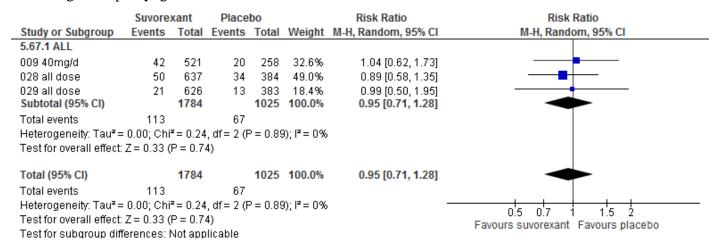
S2-21 Fig. Back pain



S2-22 Fig. Dry mouth

	Suvore	xant	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.66.1 ALL							
009 40mg/d	26	521	4	258	32.5%	3.22 [1.14, 9.13]	
028 all dose	10	637	4	384	26.6%	1.51 [0.48, 4.77]	
029 all dose	16	626	6	383	40.9%	1.63 [0.64, 4.13]	-
Subtotal (95% CI)		1784		1025	100.0%	1.99 [1.10, 3.61]	•
Total events	52		14				
Heterogeneity: Tau ² =	: 0.00; Chi	² = 1.23	df = 2 (F)	P = 0.54	l); l² = 0%		
Test for overall effect:	Z = 2.27 (P = 0.02	2)				
Total (95% CI)		1784		1025	100.0%	1.99 [1.10, 3.61]	•
Total events	52		14				
Heterogeneity: Tau ² =	0.00; Chi	² = 1.23	df = 2 (F)	P = 0.54	i); I² = 0%		0.05 0.2 1 5 20
Test for overall effect:	Z = 2.27 (P = 0.02	2)		0.05 0.2 1 5 20 Favours suvorexant Favours placebo		
Test for subgroup diff	ferences: I	Not app	licable				i avouis suvoiexain. Favouis piacebo

S2-23 Fig. Nasopharyngitis



S2-24 Fig. Motor vehicle accidents/violations

	Suvore	xant	nt Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
5.61.1 ALL							
009 40mg/d	2	521	0	258	6.8%	2.48 [0.12, 51.49]	
028 all dose	11	637	9	384	59.8%	0.74 [0.31, 1.76]	——
029 all dose	11	626	3	383	33.4%	2.24 [0.63, 7.99]	
Subtotal (95% CI)		1784		1025	100.0%	1.16 [0.52, 2.60]	*
Total events	24		12				
Heterogeneity: Tau² =	0.08; Chi	² = 2.33	df = 2 (F)	P = 0.31); $I^2 = 149$	%	
Test for overall effect:	Z = 0.36 (P = 0.73	2)				
Total (95% CI)		1784		1025	100.0%	1.16 [0.52, 2.60]	•
Total events	24		12				
Heterogeneity: Tau ² =	0.08; Chi	² = 2.33	df = 2 (F)	P = 0.31); $I^2 = 149$	%	3005
Test for overall effect:	Z = 0.36 (P = 0.72	2)				0.005 0.1 1 10 200 Favours suvorexant Favours placebo
Test for subgroup diff	erences: l	Not app	licable				ravouis suvoiexaiit ravouis piacebo