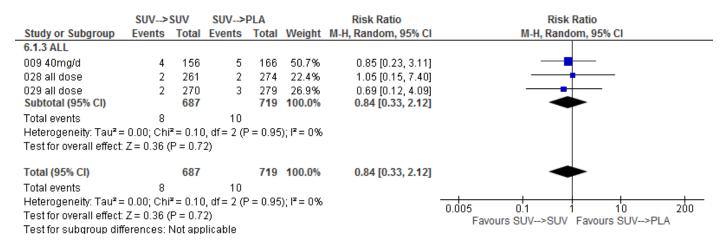
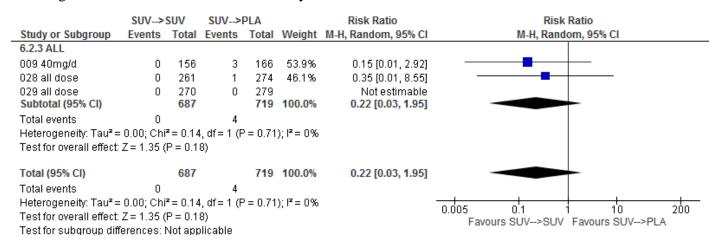
S3 Fig. Forest plots of study run-out phase outcomes.

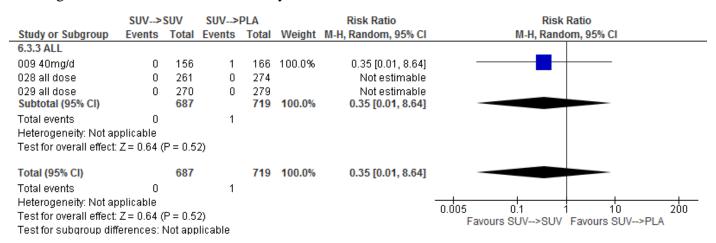
S3-1 Fig. Discontinuation due to all cause



S3-2 Fig. Discontinuation due to intolerability



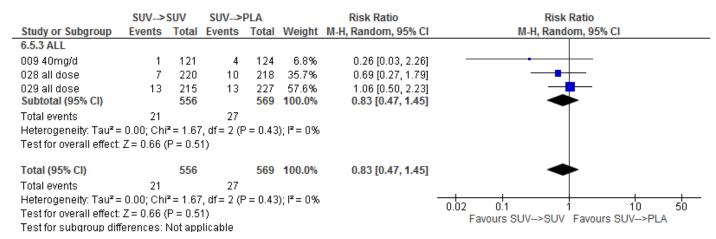
S3-3 Fig. Discontinuation due to inefficacy



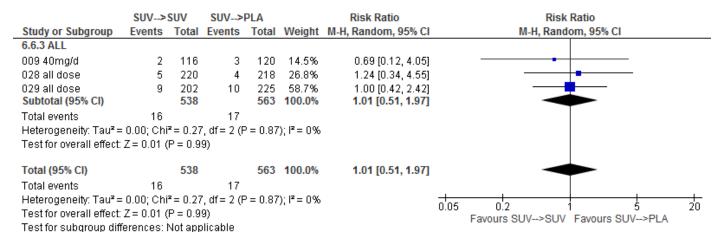
S3-4 Fig. Withdrawal (Tyrer Withdrawal Symptom Questionnaire) at Day 1

	SUV>	SUV	SUV>	PLA		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.4.3 ALL							
009 40mg/d	1	121	2	122	9.1%	0.50 [0.05, 5.49]	
028 all dose	5	223	5	226	34.6%	1.01 [0.30, 3.45]	-+ -
029 all dose	6	211	12	229	56.2%	0.54 [0.21, 1.42]	
Subtotal (95% CI)		555		577	100.0%	0.67 [0.33, 1.38]	•
Total events	12		19				
Heterogeneity: Tau ²	= 0.00; Chi	$i^2 = 0.68$	3, df = 2 (F)	P = 0.71); I ² = 0%		
Test for overall effec	t: $Z = 1.09$ (P = 0.2	8)				
Total (95% CI)		555		577	100.0%	0.67 [0.33, 1.38]	•
Total events	12		19				
Heterogeneity: Tau ²	= 0.00; Chi	$i^2 = 0.68$	3, df = 2 (F)	9 = 0.71); I ² = 0%		0.005 0.1 1 10 200
Test for overall effect	t: Z = 1.09 (P = 0.2	8)		0.005 0.1 1 10 200 Favours SUV>SUV Favours SUV>PLA		
Test for subaroup di	ifferences:	Not app	olicable				Tavouis COV - COV Tavouis COV LA

S3-5 Fig. Withdrawal (Tyrer Withdrawal Symptom Questionnaire) at Day 2



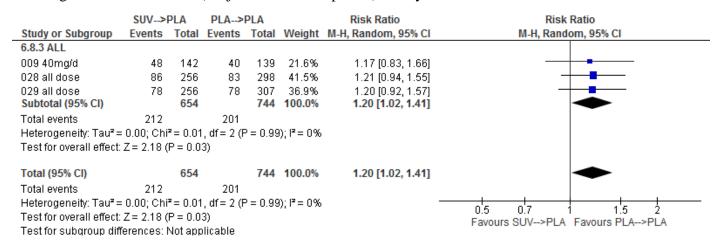
S3-6 Fig. Withdrawal (Tyrer Withdrawal Symptom Questionnaire) at Day 3



S3-7 Fig. Withdrawal (Tyrer Withdrawal Symptom Questionnaire) at Day 1-3

	SUV>SUV		SUV SUV>F		A Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.7.3 ALL							
009 40mg/d	8	129	8	129	20.4%	1.00 [0.39, 2.58]	
028 all dose	11	240	11	238	27.5%	0.99 [0.44, 2.24]	
029 all dose Subtotal (95% CI)	19	227 596	21	244 611	52.1% 100.0%	0.97 [0.54, 1.76] 0.98 [0.64, 1.51]	
Total events	38		40				
Heterogeneity: Tau ² =	= 0.00; Chi	z = 0.00	i, df = 2 (F	P = 1.00); I ² = 0%		
Test for overall effect:	Z = 0.08 (P = 0.9	4)				
Total (95% CI)		596		611	100.0%	0.98 [0.64, 1.51]	-
Total events	38		40				
Heterogeneity: Tau² =	= 0.00; Chi	z = 0.00	i, df = 2 (F	e 1.00); I² = 0%		02 05 1 2 5
Test for overall effect:	Z = 0.08 (P = 0.9	4)	0.2 0.5 1 2 5 Favours SUV>SUV Favours SUV>PLA			
Test for subgroup dif	ferences: I	Not app	licable				Tavouis GOV

S3-8 Fig. Rebound insomnia (subjective total sleep time) at Day 1



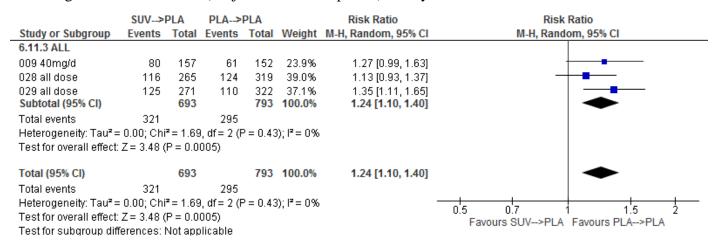
S3-9 Fig. Rebound insomnia (subjective total sleep time) at Day 2

	SUV>	SUV>PLA PLA>PLA				Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.9.3 ALL							
009 40mg/d	52	146	39	145	29.2%	1.32 [0.94, 1.87]	
028 all dose	61	243	74	302	40.2%	1.02 [0.76, 1.37]	
029 all dose	58	255	51	308	30.6%	1.37 [0.98, 1.93]	
Subtotal (95% CI)		644		755	100.0%	1.21 [1.00, 1.46]	
Total events	171		164				
Heterogeneity: Tau ^z	= 0.00; Chi	$i^2 = 2.04$	I, df = 2 (F	P = 0.38	6); I² = 2%		
Test for overall effect	t: Z= 1.97 (P = 0.0	5)				
Total (95% CI)		644		755	100.0%	1.21 [1.00, 1.46]	-
Total events	171		164				
Heterogeneity: Tau ^z	= 0.00; Chi	$i^2 = 2.04$	l, df = 2 (F	9 = 0.38	6); I² = 2%		0.5 0.7 1 1.5 2
Test for overall effect	t: Z = 1.97 (P = 0.0	5)				Favours SUV>PLA Favours PLA>PLA
Test for subgroup di	fferences:	Not app	olicable				Tavodis SOV-FI EX Tavodis I EX-FI EX

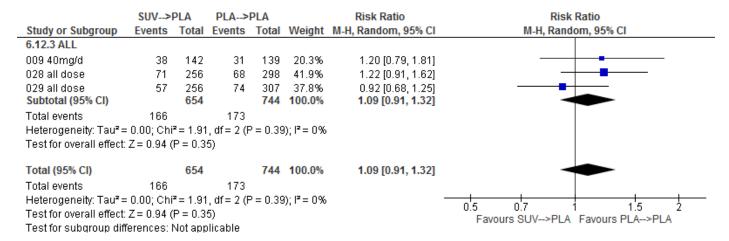
S3-10 Fig. Rebound insomnia (subjective total sleep time) at Day 3

	SUV>PLA		PLA>PLA		Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
6.10.3 ALL									
009 40mg/d	55	146	44	139	31.1%	1.19 [0.86, 1.64]			
028 all dose	62	253	64	294	34.3%	1.13 [0.83, 1.53]			
029 all dose Subtotal (95% CI)	72	255 654	57	300 733	34.6% 100.0%	1.49 [1.10, 2.02] 1.26 [1.05, 1.51]			
Total events 189 165 Heterogeneity: Tau² = 0.00; Chi² = 1.77, df = 2 (P = 0.41); I² = 0% Test for overall effect: Z = 2.53 (P = 0.01)									
Total (95% CI)	,	654	,	733	100.0%	1.26 [1.05, 1.51]	•		
Total events	189		165						
Heterogeneity: Tau ² =	: 0.00; Chi	$^{2} = 1.77$, df = 2 (F	o = 0.41); l² = 0%		0.5 0.7 1 1.5 2		
Test for overall effect:	Z = 2.53 (P = 0.0	1)	Favours SUV>PLA Favours PLA>PLA					
Test for subgroup differences: Not applicable									

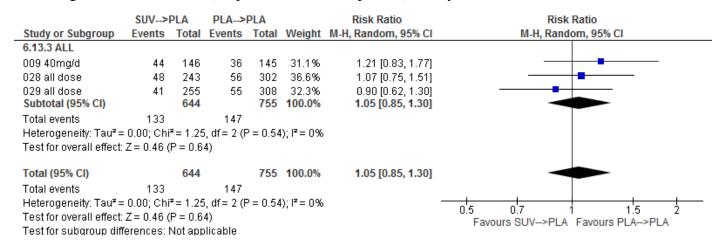
S3-11 Fig. Rebound insomnia (subjective total sleep time) at Day 1-3



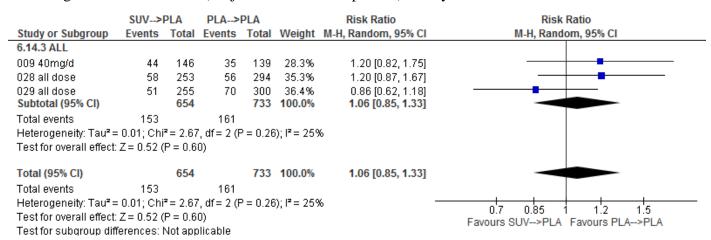
S3-12 Fig. Rebound insomnia (subjective time to sleep onset) at Day 1



S3-13 Fig. Rebound insomnia (subjective time to sleep onset) at Day 2



S3-14 Fig. Rebound insomnia (subjective time to sleep onset) at Day 3



S3-15 Fig. Rebound insomnia (subjective time to sleep onset) at Day 1-3

	SUV>	SUV>PLA PLA>PLA				Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
6.15.3 ALL									
009 40mg/d	64	157	55	152	24.5%	1.13 [0.85, 1.50]			
028 all dose	102	265	101	319	37.8%	1.22 [0.97, 1.52]	+		
029 all dose	92	271	114	322	37.7%	0.96 [0.77, 1.20]			
Subtotal (95% CI)	050	693	070	793	100.0%	1.09 [0.94, 1.26]			
Total events Heterogeneity: Tau ²	258 = 0.00; Chi	i² = 2.28	270 6, df = 2 (F	e = 0.32	2); I² = 129	%			
Test for overall effect	t: Z= 1.17 (P = 0.2	4)						
Total (95% CI)		693		793	100.0%	1.09 [0.94, 1.26]	-		
Total events	258		270						
Heterogeneity: Tau ²	= 0.00; Chi	i ^z = 2.28	6, df = 2 (F	9 = 0.32	2); I ^z = 129	%	0.7 0.85 1 1.2 1.5		
Test for overall effect	t: Z = 1.17 (P = 0.2	4)				0.7 0.85 1 1.2 1.5 Favours SUV>PLA Favours PLA>PLA		
Test for subgroup di	fferences:	Not app	licable				Tavodio COV TEXT Tavodio TEX		