

Long-term impact of cenobamate on cognition in patients with drug-resistant focal epilepsy: outcomes from an Expanded Access Program

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Tables

Supplementary Table S1. Cenobamate dose according to responder status at Month 18.

	≥50% responders at Month 18		Non-responders at Month 18	
	Month 6 (n=10)	Month 18 (n=10)	Month 6 (n=4)	Month 18 (n=4)
Cenobamate dose (mg)				
Mean (SD)	220 (42)	280 (82)	169 (63)	150 (71)
Median (range)	250 (150–250)	300 (150–400)	200 (75–200)	175 (50–200)

SD, standard deviation.

Supplementary Table S2. Change in total DDD ratio between baseline, Month 6 and Month 18 according to mechanism of action of concomitant ASMs.

Mechanism of action	Baseline	Month 6	Change from baseline at Month 6	P value*	Month 18	Change from baseline at Month 18	P value*	Change from Month 6 to Month 18	P value**
AMPAr (n=6)	0.6 (0.4)	0.4 (0.5)	-0.2 (0.2)	0.012	0.2 (0.5)	-0.4 (0.3)	0.017	-0.1 (0.2)	NS
Benzodiazepines (n=9)	0.8 (0.6)	0.3 (0.5)	-0.4 (0.6)	NS	0.4 (0.6)	-0.4 (0.7)	NS	0.1 (0.2)	NS
CCB (n=3)	0.9 (0.3)	0.8 (0.2)	-0.1 (0.1)	NS	0.8 (0.3)	-0.2 (0.3)	NS	0 (0.2)	NS
SCB (n=12)	1.8 (1)	1.3 (0.8)	-0.5 (0.5)	0.0038	0.7 (0.8)	-1.1 (0.7)	0.0003	-0.6 (0.6)	0.0052
SV2A (n=6)	1.8 (0.4)	1.6 (0.5)	-0.2 (0.3)	NS	1.3 (0.8)	-0.4 (0.7)	NS	-0.2 (0.4)	NS

P values are based on paired t-test: *vs baseline; **vs Month 6.

AMPAr, AMPA receptor antagonist (perampanel); benzo, benzodiazepines (clobazam, clonazepam, diazepam, phenobarbital); CCB, calcium channel blockers (ethosuximide, valproic acid); DDD, daily defined dose; NS, not significant; SCB, sodium channel blockers (carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, topiramate, zonisamide); SV2A, synaptic vesicle protein 2A modulators (brivaracetam and levetiracetam)

Supplementary Table S2. Change in cognitive parameter scores between baseline, Month 6 and Month 18, in patients with $\geq 50\%$ reduction in seizure frequency

		Baseline (n=10)	Month 6 (n=10)	Change from baseline at Month 6 (n=10)	P value*	Month 18 (n=10)	Change from baseline at Month 18 (n=10)	P value*	Change from Month 6 to Month 18 (n=10)	P value**
FCSRT (verbal episodic memory)										
TFR	Mean (SD)	5.2 (2.6)	6.6 (3.4)	1.4 (1.8)	0.034	7.1 (4.6)	1.9 (3.2)	NS	0.5 (3.2)	NS
	Median (range)	5 (2– 9)	7 (2– 11)	1 (-1– 4)		6.5 (2– 15)	1 (-3– 8)		1.5 (-7– 4)	
TR	Mean (SD)	5.3 (3.1)	8.1 (4.9)	2.8 (3.1)	0.018	9.4 (6.1)	4.1 (5.1)	0.032	1.3 (3.7)	NS
	Median (range)	4.5 (2– 11)	9.5 (2– 17)	2.5 (-1– 9)		9 (3– 18)	2.5 (-2– 15)		1 (-6– 6)	
DFR	Mean (SD)	6.9 (3.8)	6.8 (3.7)	-0.1 (2.7)	NS	6.3 (2.5)	-0.6 (2.7)	NS	-0.5 (2.2)	NS
	Median (range)	7 (2– 13)	7 (2– 13)	0 (-5– 5)		7 (3– 10)	0 (-6– 3)		-0.5 (-4– 3)	
DTR	Mean (SD)	10.2 (6.9)	10.5 (6.3)	0.3 (1.6)	NS	9.8 (6.1)	-0.4 (7.7)	NS	-0.7 (7.3)	NS
	Median (range)	8.5 (2– 18)	9 (2– 18)	0 (-1– 4)		9 (2– 18)	0 (-11– 13)		0 (-11– 11)	
Verbal fluency										
FAN	Mean (SD)	5.5 (3.2)	5 (2.4)	-0.5 (3.7)	NS	5.5 (3.2)	0 (2.4)	NS	0.5 (4.3)	NS
	Median (range)	4 (2– 11)	6 (2– 9)	-0.5 (-9– 4)		5 (2– 11)	0 (-5– 3)		1.5 (-5– 8)	
FP	Mean (SD)	7.6 (4.3)	6.5 (3.7)	-1.1 (1.9)	NS	6.1 (3.2)	-1.5 (2.8)	NS	-0.4 (2.5)	NS
	Median (range)	8.5 (2– 14)	8 (2– 12)	-1 (-5– 2)		7.5 (2– 10)	-1 (-7– 2)		0 (-5– 4)	
ROCF (Visuospatial episodic memory)										

	Baseline (n=10)	Month 6 (n=10)	Change from baseline at Month 6 (n=10)	P value*	Month 18 (n=10)	Change from baseline at Month 18 (n=10)	P value*	Change from Month 6 to Month 18 (n=10)	P value**
ROCF-COP									
Mean (SD)	10.7 (4.9)	10.2 (3.6)	-0.5 (2.8)	NS	11.8 (4)	1.1 (5.2)	NS	1.6 (5.2)	NS
Median (range)	11 (2– 18)	10.5 (5– 18)	0.5 (-6– 3)		10 (7– 18)	0 (-10– 7)		2.5 (-10– 9)	
ROCF-MCP									
Mean (SD)	7.2 (4.2)	10.1 (3.5)	2.9 (2.6)	0.007	10.1 (3.9)	2.9 (3.6)	0.03	0 (2.7)	NS
Median (range)	8 (1– 13)	10 (5– 15)	2.5 (0– 9)		9.5 (6– 16)	1.5 (-1– 9)		-0.5 (-3– 5)	
ROCF-T									
Mean (SD)	9.5 (4.5)	9.8 (4.2)	0.3 (2.4)	NS	10.1 (3.4)	0.6 (4)	NS	0.3 (4)	NS
Median (range)	9 (2– 16)	10 (2– 16)	0 (-5– 4)		10 (5– 17)	1 (-6– 7)		0.5 (-6– 7)	
IFS & DD/DI (frontal executive function and working memory)									
IFS									
Mean (SD)	20.5 (4.5)	19.1 (4)	-1.4 (3.4)	NS	21.6 (2.1)	1.1 (3.8)	NS	2.5 (3.5)	0.048
Median (range)	21.5 (11– 26)	19.2 (11– 26)	0 (-8.5– 3.5)		21.5 (18– 25)	-0.8 (-2– 8.5)		2.2 (-3– 8.5)	
DD									
Mean (SD)	6.9 (3)	6.4 (3)	-0.5 (1.8)	NS	7.2 (3.2)	0.3 (1.2)	NS	0.8 (2)	NS
Median (range)	7.5 (3– 11)	6 (3– 10)	0 (-5– 2)		9 (3– 10)	0 (-1– 2)		0 (-1– 6)	
DI									
Mean (SD)	8.7 (2.4)	7.6 (2.8)	-1.1 (2.1)	NS	8.1 (3.1)	-0.6 (2.9)	NS	0.5 (3.9)	NS
Median (range)	8.5 (5– 13)	7.5 (2– 13)	-1 (-5– 2)		7.5 (3– 13)	-0.5 (-6– 3)		0 (-5– 6)	
TMT (attention and executive function)									
TMT-A									
Mean (SD)	9 (5.9)	5.7 (3.5)	-3.3 (3.7)	0.02	7.6 (4)	-1.4 (4.1)	NS	1.9 (2.6)	0.043
Median (range)	11 (2– 17)	6 (2– 12)	-3 (-9– 1)		7.5 (2– 13)	0 (-10– 3)		2 (-1– 7)	

		Baseline (n=10)	Month 6 (n=10)	Change from baseline at Month 6 (n=10)	P value*	Month 18 (n=10)	Change from baseline at Month 18 (n=10)	P value*	Change from Month 6 to Month 18 (n=10)	P value**
TMT-B										
	Mean (SD)	7.1 (5)	5.8 (3.4)	-1.3 (3.9)	NS	7.3 (2.6)	0.2 (3.7)	NS	1.5 (2.7)	NS
	Median (range)	6 (2– 18)	6 (2– 13)	0 (-12– 1)		6.5 (4– 12)	0.5 (-7– 5)		1 (-2– 5)	
5-Digit Test (speed of processing)										
5A										
	Mean (SD)	30.1 (23.9)	26.4 (25.9)	-3.7 (18.5)	NS	33.6 (25.1)	3.5 (11.6)	NS	7.2 (18.5)	NS
	Median (range)	25 (1– 70)	20 (1– 70)	2.5 (-45– 15)		30 (1– 70)	2.5 (-15– 20)		0 (-15– 40)	
5C										
	Mean (SD)	25.1 (27.2)	25.9 (30.1)	0.8 (7.2)	NS	30.2 (28.9)	5.1 (15.1)	NS	4.3 (19.9)	NS
	Median (range)	10 (1– 65)	10 (1– 70)	4 (-10– 10)		25 (1– 70)	0 (-10– 35)		0 (-15– 44)	
5E										
	Mean (SD)	30.6 (23)	24 (26.3)	-6.6 (20.5)	NS	30.6 (29.5)	0 (23.3)	NS	6.6 (17.3)	NS
	Median (range)	27.5 (1– 75)	16.5 (1– 75)	-10 (-30– 30)		22.5 (1– 80)	0 (-40– 35)		5 (-20– 30)	
5F										
	Mean (SD)	26.6 (24.4)	28.9 (25.9)	2.3 (37.4)	NS	46.2 (30.8)	19.6 (34.8)	NS	17.3 (20.6)	0.027
	Median (range)	22.5 (1– 70)	27.5 (1– 70)	-2.5 (-64– 65)		42.5 (10– 97)	17 (-55– 65)		7 (0– 62)	
5I										
	Mean (SD)	28.3 (25.6)	27 (24.9)	-1.3 (31.8)	NS	44.3 (30.1)	16 (39.5)	NS	17.3 (33)	NS
	Median (range)	22.5 (1– 75)	17.5 (1– 60)	-1 (-55– 58)		47.5 (3– 85)	15 (-45– 74)		16 (-52– 74)	
5L										
	Mean (SD)	29.1 (24.1)	26.3 (25.2)	-2.8 (21.4)	NS	27.6 (22.1)	-1.5 (12.7)	NS	1.3 (19.1)	NS
	Median (range)	27.5 (1– 60)	22.5 (1– 60)	-1 (-37– 45)		30 (1– 65)	-4.5 (-20– 20)		-1 (-25– 32)	

P values are based on paired t-test: *vs baseline; **vs Month 6.

DD, Digit direct; DFR, delayed free recall; DI, Digit inverse; DTR, delayed total recall; FAN, fluency-semantics; FP, fluency-phonometrics; IFS, INECO Frontal Screening; NS, not significant; ROCF, Rey-Osterrieth Complex Figure; ROCF-COP, ROCF-Copying; ROCF-MCP, ROCF-Copy from memory; ROCF-T; ROCF-Time; SD, standard deviation; TFR, total free recall; TMT, Trail-Making Test; TMT-A, TMT-attention; TMT-B, TMT-processing; TR, total recall.

Supplementary Table S4. Analysis of covariance for each cognitive parameter by 50% responder status, total DDD ratio change from baseline, and baseline.

Cognitive parameter	50% responder status	Total DDD ratio change from baseline	Baseline parameter value
FCSRT (verbal episodic memory)			
TFR	0.28	0.81	0.63
TR	0.63	0.19	0.98
DFR	0.45	0.63	0.01
DTR	0.70	0.57	0.08
Verbal fluency			
FAN	0.46	0.16	0.09
FP	0.45	0.87	0.01
ROCF (visuospatial episodic memory)			
ROCF COP	0.17	0.98	0.01
ROCF MCP	0.58	0.77	0.10
ROCFT	0.69	0.03	0.14
Frontal executive function and working memory			
IFS	0.17	0.69	0.00
DD	0.68	0.28	0.21
DI	0.89	0.65	0.07
TMT (attention and executive function)			
TMTA	0.97	0.51	0.02
TMTB	0.99	0.88	0.01
5-Digit Test (speed of processing)			
5A	0.58	0.76	0.75
5C	0.60	0.65	0.81
5E	0.89	0.63	0.11
5F	0.99	0.59	0.07
5I	0.98	0.28	0.27
5L	0.25	0.93	0.44