

Table e-2. Change from baseline in each total score for UPDRS Parts, MMSE, NPI-10, and ZBI at Week 12

	Baseline score			Change from baseline		
	Placebo (N = 55)	Zonisamide		Placebo	Zonisamide	
		25 mg (N = 48)	50 mg (N = 49)		25 mg	50 mg
	(mean ± SD [n])			(LSM ± SEM [<i>P</i> -value vs placebo])		
UPDRS Part 1	5.2 ± 2.7 (55)	5.2 ± 2.8 (48)	5.0 ± 2.3 (49)	0.1 ± 0.2	-0.2 ± 0.2 (0.262)	0.1 ± 0.2 (0.893)
UPDRS Part 2 (ON)	12.7 ± 6.3 (55)	13.3 ± 7.6 (48)	13.9 ± 6.6 (49)	-1.1 ± 0.4	-0.7 ± 0.5 (0.601)	-0.6 ± 0.5 (0.448)
UPDRS Part 3	31.4 ± 10.3 (55)	33.2 ± 13.4 (48)	32.4 ± 10.5 (49)	-2.1 ± 0.9	-4.4 ± 1.0 (0.099)	-6.2 ± 1.0 (0.003)
UPDRS Part 4	1.5 ± 1.8 (55)	1.8 ± 2.2 (48)	1.5 ± 1.5 (49)	-0.1 ± 0.1	0.0 ± 0.1 (0.598)	0.1 ± 0.1 (0.482)
UPDRS Parts 1-4	50.8 ± 16.5 (55)	53.5 ± 22.6 (48)	52.7 ± 16.6 (49)	-3.1 ± 1.3	-5.3 ± 1.4 (0.259)	-6.7 ± 1.4 (0.067)
MMSE	21.4 ± 4.7 (54)	22.1 ± 5.3 (44)	21.2 ± 3.9 (45)	-0.4 ± 0.4	-0.3 ± 0.4 (0.834)	0.5 ± 0.4 (0.138)
NPI-10	7.6 ± 8.5 (52)	6.4 ± 8.7 (45)	7.8 ± 8.3 (46)	0.0 ± 1.0	1.1 ± 1.1 (0.452)	0.1 ± 1.1 (0.900)
ZBI	25.3 ± 19.8 (52)	21.7 ± 16.8 (46)	23.3 ± 15.3 (47)	1.6 ± 1.1	2.0 ± 1.2 (0.793)	4.1 ± 1.2 (0.141)

For each UPDRS score, missing values at Week 12 were imputed using the LOCF method. Statistical analysis was performed by

ANCOVA, except for UPDRS Part 3 by ANCOVA with Fisher's least significant difference method for multiplicity adjustment.

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; NPI-10,

Neuropsychiatric Inventory-10; ZBI, Zarit Burden Interview; LOCF, last observation carried forward; LSM, least squares mean;

ANCOVA, analysis of covariance.

Table e-3. Change from baseline in each UPDRS Part 3 item score at Week 12 (LOCF)

	Baseline score			Change from baseline		
	Placebo (N = 55)	Zonisamide		Placebo	Zonisamide	
		25 mg (N = 48)	50 mg (N = 49)		25 mg	50 mg
	(mean ± SD [n])			(LSM ± SEM [P-value vs placebo])		
18. Speech	1.31 ± 0.60 (45)	1.36 ± 0.82 (42)	1.41 ± 0.55 (41)	-0.06 ± 0.07	-0.10 ± 0.07 (0.721)	-0.01 ± 0.07 (0.583)
19. Facial expression	1.58 ± 0.75 (52)	1.98 ± 0.91 (48)	1.75 ± 0.79 (48)	-0.12 ± 0.08	-0.18 ± 0.09 (0.644)	-0.27 ± 0.09 (0.200)
20. Tremor at rest*	1.79 ± 1.97 (28)	2.09 ± 2.58 (22)	1.83 ± 1.81 (29)	0.26 ± 0.28	-0.82 ± 0.32 (0.013)	-0.46 ± 0.28 (0.071)
21. Action or postural tremor*	1.86 ± 1.20 (42)	1.81 ± 1.39 (37)	1.79 ± 1.14 (38)	-0.46 ± 0.16	-0.41 ± 0.17 (0.834)	-0.67 ± 0.17 (0.362)
22. Rigidity*	7.46 ± 3.33 (54)	7.89 ± 3.78 (47)	8.04 ± 3.14 (47)	-0.77 ± 0.30	-1.00 ± 0.32 (0.592)	-1.70 ± 0.32 (0.033)
23. Finger taps*	3.43 ± 1.66 (53)	3.43 ± 1.53 (46)	3.46 ± 1.49 (48)	-0.38 ± 0.17	-0.59 ± 0.18 (0.405)	-0.83 ± 0.18 (0.072)
24. Hand movements*	2.83 ± 1.35 (53)	2.98 ± 1.60 (45)	2.93 ± 1.32 (44)	-0.44 ± 0.16	-0.56 ± 0.18 (0.610)	-0.63 ± 0.18 (0.422)
25. Rapid alternating movements of hands (pronate/supinate)*	3.41 ± 1.65 (54)	3.33 ± 1.46 (46)	3.60 ± 1.64 (47)	-0.32 ± 0.18	-0.60 ± 0.19 (0.300)	-0.85 ± 0.19 (0.048)
26. Leg agility*	2.82 ± 1.36 (55)	3.15 ± 1.70 (46)	3.04 ± 1.33 (47)	0.01 ± 0.19	-0.09 ± 0.21 (0.718)	-0.52 ± 0.20 (0.057)
27. Arising from chair	1.33 ± 1.05 (40)	1.58 ± 1.06 (33)	1.03 ± 0.87 (37)	0.03 ± 0.13	-0.09 ± 0.15 (0.554)	-0.01 ± 0.14 (0.837)
28. Posture	1.52 ± 0.73 (52)	1.60 ± 0.71 (47)	1.53 ± 0.80 (47)	0.09 ± 0.07	-0.16 ± 0.08 (0.023)	-0.17 ± 0.08 (0.015)
29. Gait	1.54 ± 0.61 (52)	1.59 ± 0.83 (46)	1.43 ± 0.74 (49)	-0.02 ± 0.07	-0.08 ± 0.08 (0.573)	-0.07 ± 0.08 (0.575)
30. Postural stability	1.53 ± 0.70 (51)	1.64 ± 0.97 (44)	1.43 ± 0.81 (46)	-0.02 ± 0.11	-0.05 ± 0.12 (0.868)	-0.34 ± 0.12 (0.047)
31. Body bradykinesia/hypokinesia	1.78 ± 0.74 (54)	2.04 ± 0.91 (47)	1.88 ± 0.67 (49)	-0.11 ± 0.08	-0.14 ± 0.08 (0.789)	-0.21 ± 0.08 (0.392)

*Summary of scores for all areas of body evaluated. Patients who had a score of 0 or data missing at all the evaluation time points were excluded from the analysis population. Statistical analysis was performed by ANCOVA. Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; LOCF, last observation carried forward; LSM, least squares mean; ANCOVA, analysis of covariance.

Table e-4. Change from baseline in each score for MMSE item at Week 12

	Baseline score			Change from baseline		
	Placebo (N = 55)	Zonisamide		Placebo	Zonisamide	
		25 mg (N = 48)	50 mg (N = 49)		25 mg	50 mg
	(mean ± SD [n])			(LSM ± SEM [P-value vs placebo])		
1. Orientation to time	3.30 ± 1.54 (54)	3.70 ± 1.69 (44)	3.44 ± 1.29 (45)	-0.17 ± 0.15	0.04 ± 0.17 (0.359)	-0.07 ± 0.17 (0.657)
2. Orientation to place	4.24 ± 0.91 (54)	4.09 ± 1.20 (44)	4.07 ± 1.05 (45)	-0.05 ± 0.12	0.01 ± 0.13 (0.756)	-0.18 ± 0.13 (0.452)
3. Registration	2.96 ± 0.19 (54)	2.80 ± 0.59 (44)	2.89 ± 0.32 (45)	-0.11 ± 0.06	0.04 ± 0.06 (0.084)	0.02 ± 0.06 (0.119)
4. Attention and calculation	1.74 ± 1.57 (54)	1.91 ± 1.63 (44)	1.69 ± 1.35 (45)	0.18 ± 0.18	-0.08 ± 0.20 (0.334)	0.44 ± 0.19 (0.309)
5. Recall	1.67 ± 1.08 (54)	1.89 ± 1.04 (44)	1.33 ± 1.17 (45)	0.01 ± 0.13	-0.13 ± 0.14 (0.433)	0.07 ± 0.14 (0.760)
6. Naming	1.98 ± 0.14 (54)	1.93 ± 0.33 (44)	2.00 ± 0.00 (45)	-0.01 ± 0.02	0.02 ± 0.03 (0.390)	-0.03 ± 0.03 (0.701)
7. Repetition	0.96 ± 0.19 (54)	0.98 ± 0.15 (44)	0.98 ± 0.15 (45)	-0.03 ± 0.03	-0.06 ± 0.03 (0.413)	0.00 ± 0.03 (0.513)
8. Comprehension	2.44 ± 0.82 (54)	2.61 ± 0.65 (44)	2.47 ± 0.76 (45)	-0.17 ± 0.10	-0.11 ± 0.12 (0.697)	0.05 ± 0.11 (0.148)
9. Reading	0.93 ± 0.26 (54)	0.93 ± 0.25 (44)	0.98 ± 0.15 (45)	-0.10 ± 0.03	-0.03 ± 0.04 (0.175)	-0.04 ± 0.04 (0.263)
10. Writing	0.65 ± 0.48 (54)	0.70 ± 0.46 (44)	0.78 ± 0.42 (45)	0.02 ± 0.05	-0.05 ± 0.05 (0.351)	0.05 ± 0.05 (0.682)
11. Drawing	0.57 ± 0.50 (54)	0.52 ± 0.51 (44)	0.62 ± 0.49 (45)	0.04 ± 0.05	0.18 ± 0.06 (0.068)	0.09 ± 0.06 (0.512)

Statistical analysis was performed by ANCOVA. Abbreviations: MMSE, Mini-Mental State Examination; LSM, least squares mean; ANCOVA, analysis of covariance.

Table e-5. Change from baseline in each score for NPI-10 item at Week 12

	Baseline score			Change from baseline		
	Placebo (N = 55)	Zonisamide		Placebo	Zonisamide	
		25 mg (N = 48)	50 mg (N = 49)		25 mg	50 mg
	(mean ± SD [n])			(LSM ± SEM [P-value vs placebo])		
A. Delusions	0.85 ± 1.85 (52)	0.67 ± 1.77 (45)	0.43 ± 1.38 (46)	-0.27 ± 0.17	0.18 ± 0.19 (0.076)	0.07 ± 0.18 (0.179)
B. Hallucinations	1.67 ± 2.38 (52)	1.58 ± 2.26 (45)	1.28 ± 2.16 (46)	0.33 ± 0.24	0.32 ± 0.26 (0.977)	0.05 ± 0.26 (0.440)
C. Agitation/aggression	0.40 ± 1.05 (52)	0.40 ± 1.01 (45)	0.65 ± 1.51 (46)	0.19 ± 0.20	0.09 ± 0.22 (0.731)	0.26 ± 0.21 (0.821)
D. Depression/dysphoria	0.87 ± 1.74 (52)	0.93 ± 2.20 (45)	0.63 ± 1.12 (46)	-0.41 ± 0.18	0.10 ± 0.20 (0.061)	-0.24 ± 0.19 (0.521)
E. Anxiety	1.12 ± 2.18 (52)	0.51 ± 1.46 (45)	1.15 ± 2.87 (46)	0.03 ± 0.23	0.26 ± 0.25 (0.517)	-0.13 ± 0.25 (0.626)
F. Elation/euphoria	0.12 ± 0.47 (52)	0.00 ± 0.00 (45)	0.00 ± 0.00 (46)	0.15 ± 0.14	0.03 ± 0.15 (0.549)	0.00 ± 0.14 (0.476)
G. Apathy/indifference	1.56 ± 2.29 (52)	1.84 ± 3.07 (45)	2.65 ± 3.43 (46)	-0.52 ± 0.35	-0.05 ± 0.37 (0.356)	0.66 ± 0.37 (0.022)
H. Disinhibition	0.04 ± 0.28 (52)	0.04 ± 0.21 (45)	0.07 ± 0.33 (46)	0.15 ± 0.11	0.18 ± 0.12 (0.868)	0.07 ± 0.12 (0.632)
I. Irritability/lability	0.40 ± 1.19 (52)	0.22 ± 0.85 (45)	0.24 ± 0.99 (46)	0.36 ± 0.13	-0.07 ± 0.14 (0.025)	-0.06 ± 0.14 (0.026)
J. Aberrant motor behavior	0.54 ± 1.59 (52)	0.22 ± 1.06 (45)	0.70 ± 2.21 (46)	-0.19 ± 0.16	-0.14 ± 0.17 (0.831)	-0.22 ± 0.17 (0.909)

Statistical analysis was performed by ANCOVA. Abbreviations: NPI-10, Neuropsychiatric Inventory-10; LSM, least squares mean; ANCOVA, analysis of covariance.

Table e-6. Adverse events (Safety population)

Number of patients	Placebo (N=58)	Zonisamide		
		25 mg (N=51)	50 mg (N=49)	Total ^a (N=100)
Neurologic and psychiatric adverse events, n (%)				
Somnolence	2 (3.4)	1 (2.0)	1 (2.0)	2 (2.0)
Cognitive disorder	0 (0.0)	1 (2.0)	1 (2.0)	2 (2.0)
Dysgeusia	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.0)
Dyskinesia	1 (1.7)	0 (0.0)	1 (2.0)	1 (1.0)
Headache	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Radial nerve palsy	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Syncope	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Hallucination	1 (1.7)	1 (2.0)	1 (2.0)	2 (2.0)
Agitation	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Apathy	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Depression	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Insomnia	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.0)
Abnormal behavior	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.0)
Delusion	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hallucination, visual	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety disorder	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric symptoms	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)

^aAdverse events in both zonisamide groups combined.