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Online resource 1: Supplementary tables

Table 1: Summary statistic of patient demographics

	Drug		
	LCM	**CBZ**	**Total**
N (%)	443 (50.2)	440 (49.8)	883 (100.0)
Age (yrs)			
Mean (CV%)	42.0 (42.6)	41.8 (41.3)	41.9 (41.9)
Median (range)	40.0 (16.0 - 87.0)	41.0 (16.0 - 85.0)	40.0 (16.0 - 87.0)
IQR	25.5 - 55.0	26.0 - 55.0	26.0 - 55.0
Weight (kg)			
Mean (CV%)	72.6 (22.2)	73.2 (21.6)	72.9 (21.9)
Median (range)	71.0 (35.6 - 130.0)	71.0 (37.2 - 136.1)	71.0 (35.6 - 136.1)
IQR	61.0 - 83.0	61.6 - 82.2	61.0 - 83.0
Time since diagnosis of epilepsy (yrs)			
Mean (CV%)	0.3 (715.6)	0.3 (539.5)	0.3 (630.9)
Median (range)	0.1 (0.0 - 37.9)	0.1 (0.0 - 21.9)	0.1 (0.0 - 37.9)
IQR	0.0 - 0.1	0.0 - 0.1	0.0 - 0.1
Number of seizures in the past 3 months			
Mean (CV%)	12.4 (319.8)	10.2 (279.1)	11.3 (305.3)
Median (range)	3.0 (1.0 - 450.0)	2.0 (0.0 - 300.0)	2.0 (0.0 - 450.0)
IQR	1.0 - 6.0	2.0 - 5.0	1.0 - 6.0
Number of seizures in the past 3 months (categorical) (N,%)			
<=1	122 (27.5)	105 (23.9)	227 (25.7)
2-6	216 (48.8)	238 (54.1)	454 (51.4)
7-50	80 (18.1)	80 (18.2)	160 (18.1)
>50	25 (5.6)	17 (3.9)	42 (4.8)
Time since diagnosis of epilepsy (categorical) (N,%)			
<=1yr	434 (98.0)	432 (98.2)	866 (98.1)
>1yr	9 (2.0)	8 (1.8)	17 (1.9)
Number of antiepileptic drugs taken before entering the study (N,%)			
none	398 (89.8)	403 (91.6)	801 (90.7)
>=1	45 (10.2)	37 (8.4)	82 (9.3)
Sex (N,%)			
Female	200 (45.1)	209 (47.5)	409 (46.3)
Male	243 (54.9)	231 (52.5)	474 (53.7)
Race (N,%)			
White	378 (85.3)	365 (83.0)	743 (84.1)
Black	5 (1.1)	2 (0.5)	7 (0.8)
Asian	49 (11.1)	57 (13.0)	106 (12.0)
Other	7 (1.6)	13 (3.0)	20 (2.3)

	Drug		
	LCM	**CBZ**	**Total**
Missing	4 (0.9)	3 (0.7)	7 (0.8)
Geographical region of study centers (N,%)			
Western Europe	159 (35.9)	126 (28.6)	285 (32.3)
Eastern Europe	177 (40.0)	200 (45.5)	377 (42.7)
Asia	47 (10.6)	55 (12.5)	102 (11.6)
Australia	22 (5.0)	10 (2.3)	32 (3.6)
North America	35 (7.9)	43 (9.8)	78 (8.8)
South America	3 (0.7)	6 (1.4)	9 (1.0)

Percentages shown in parenthesis; IQR: Interquartile range; CV: Coefficient of variation

Table 2: Summary of seizure events

	Drug		
	LCM	**CBZ**	**Total**
N (%)	443 (50.2)	440 (49.8)	883 (100.0)
Time in trial until end of treatment or dropout (days)			
Mean (CV%)	330.2 (43.7)	319.6 (49.2)	324.9 (46.4)
Median (range)	384.0 (0.5 - 706.0)	384.0 (0.5 - 671.0)	384.0 (0.5 - 706.0)
IQR	252.0 - 390.0	211.5 - 389.0	223.0 - 390.0
Number of seizure-days during trial			
Mean (CV%)	4.4 (276.2)	4.1 (345.3)	4.3 (309.8)
Median (range)	0.0 (0.0 - 140.0)	0.0 (0.0 - 161.0)	0.0 (0.0 - 161.0)
IQR	0.0 - 3.0	0.0 - 2.0	0.0 - 2.0
Number of seizure-days (categorical) (N,%)			
0	232 (52.4)	255 (58.0)	487 (55.2)
1	67 (15.1)	66 (15.0)	133 (15.1)
2	23 (5.2)	31 (7.0)	54 (6.1)
3	21 (4.7)	16 (3.6)	37 (4.2)
4	13 (2.9)	7 (1.6)	20 (2.3)
5	15 (3.4)	8 (1.8)	23 (2.6)
6	9 (2.0)	4 (0.9)	13 (1.5)
7	1 (0.2)	4 (0.9)	5 (0.6)
8	3 (0.7)	6 (1.4)	9 (1.0)
9	5 (1.1)	3 (0.7)	8 (0.9)
>=10	54 (12.2)	40 (9.1)	94 (10.6)
Last dose step (N,%)			
1	313 (70.7)	322 (73.2)	635 (71.9)
2	86 (19.4)	86 (19.5)	172 (19.5)
3	44 (9.9)	32 (7.3)	76 (8.6)

Percentages shown in parenthesis; IQR: Interquartile range; CV: Coefficient of variation

Table 3: Parameter estimates for dropout model on N01061 data

Parameter	Description	Estimate	90% CI[a]
$\lambda 1$ (1/day)[b]	Hazard from t=0 to breakpoint (BP) 1	0.00104	0.000641 - 0.00169
$\lambda 2$ (1/day)[b]	Hazard from BP1 to BP2	0.00611	0.00431 - 0.00867
$\lambda 3$ (1/day)[b]	Hazard from BP2 to BP3	0.00116	0.000879 - 0.00152
$\lambda 4$ (1/day)[b]	Hazard from BP3 to BP4	0.000521	0.000401 - 0.000678
$\lambda 5$ (1/day)[b]	Hazard from BP4 to end	0.00319	0.00191 - 0.00531
BP1 (day)	Breakpoint 1	20	19.1 - 20.8
BP2 (day)	Δ(BP2-BP1)	9.19	7.66 - 10.7
BP3 (day)	Δ(BP3-BP2)	90.7	84.6 - 96.7
BP4 (day)	Δ(BP4-BP3)	336	314 - 357
Coeff_SEX	Effect of sex=female on hazard	0.562	0.319 - 0.806
HR_SEX[b]	Hazard ratio female vs. male	1.75	1.38 - 2.24
Coeff_TYPE	Effect of LEV on hazard	-0.343	-0.586 to -0.0992
HR_TYPE[b]	Hazard ratio LEV vs. CBZ	0.71	0.557 - 0.906

HR: Hazard ratio

[a] Asymptotic confidence interval derived from NONMEM standard errors

[b] Parameter back-transformed to normal scale as: exp(x)

Table 4: Parameter estimates of the seizure model developed on N01061 data

Parameter	Description	Estimate	90% CI[a]
$\lambda 1$ (1/day)[b]	λ for the time to 1st event	0.000641	0.000395 - 0.000998
p1	Weibull shape parameter 1st event	0.558	0.518 - 0.613
$\lambda 2$ (1/day)[b]	λ for the 2nd+ event	0.00786	0.00496 - 0.0124
p2	Weibull shape parameter 2nd+ event	0.968	0.859 - 1.17
NSP3M(≤1)~λ1	Effect of NSP3M ≤1 on ln(λ1)	-1.41	-2.14 to -0.868
NSP3M(7-50)~ λ1	Effect of NSP3M 7-50 on ln(λ1)	2.11	1.59 - 2.62
NSP3M(>50)~λ1	Effect of NSP3M >50 on ln(λ1)	2.42	1.35 - 3.61
NSP3M(≤1)~λ2	Effect of NSP3M ≤1 on ln(λ2)	-0.631	-1.66 - 0.274
NSP3M(7-50)~λ2	Effect of NSP3M 7-50 on ln(λ2)	1.39	0.806 - 1.99
NSP3M(>50)~λ2	Effect of NSP3M >50 on ln(λ2)	3.11	2.15 - 3.94
AUC_LEV~λ1	Slope of AUC-ln(λ1) for LEV 1st event	-0.00446	-0.00705 to -0.00198
AUC_CBZ~λ1	Slope of AUC-ln(λ1) for CBZ 1st event	-0.0174	-0.0259 to -0.00867
AUC_LEV~λ2	Slope of AUC-ln(λ1) for LEV 2nd+ event	-0.000715	-0.00154 to -0.00019
AUC_CBZ~λ2	Slope of AUC-ln(λ1) for CBZ 2nd+ event	-0.00615	-0.0154 to -0.00153
TYPE_LEV~λ1	Effect of LEV on 1st event	0.815	0.332 - 1.32
IIV ln(λ2) (SD)	Inter-individual variability ln(λ2)	2.19	1.95 - 2.39

SD: Standard deviation

[a] 5th-95th percentiles of 500 bootstrap replicates

[b] Parameter back-transformed to normal scale as: exp(x)

AUC was centered around the typical value in the first dose level (LEV: 249 h.mg/L, CBZ: 132 h.mg/L)