ADONE

(**AD**D **ON** VS R**E**PLACEMENT)

Studio di superiorità randomizzato, in aperto, multicentrico per confrontare l'efficacia e la sicurezza di zonisamide come terapia aggiuntiva con zonisamide come terapia sostitutiva del secondo farmaco antiepilettico ad essere stato aggiunto in pazienti affetti da crisi focali.

Final statistical report

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Statistical analysis

Descriptive statistics are reported as count and percentage, mean, standard deviation (SD) or standard error (SE) or median, range (min-max) and inter-quartile range (IQR=1st quartile-3rd quartile). Univariate analysis was performed using the Wilcoxon Mann-Whitney, the Chi-square or the Fisher Exact tests according to the distribution of each variable for unpaired comparisons and using the Signed-Rank test for paired comparisons. The primary endpoint (retention time) was assessed using Kaplan-Meier curves and the two groups were compared with the log-rank test. The Kaplan Meier curves have been also used to assess retention time with events marked as lack of tolerability and lack of efficacy, with log-rank test used to compare groups. The multivariable Cox proportional hazard model have been performed on the primary endpoint with group (as independent variable) and age, gender, qolie-31 baseline scores and EPS baseline scores as confounders. For variables assessed serially during the follow-up the ANOVA for repeated measures or the ANOVA on ranks for repeated measures has been performed as appropriate. Missing data have been imputed using the last observation carried forward (LOCF) and the worst rank (WR) techniques and the results with both procedures (together with the results on the COMPLETERS population) are given. The incidence rate (IC) of the number of adverse events occurred in each group during the follow-up has been calculated and its 95% confidence interval (CI) was calculated according to the Poisson distribution. Statistical significance is set to alpha=0.05. All the statistical tests have been performed using the Statistical Analysis Software (SAS, version 9.2, Sas Institute Inc., Cary, NC, USA).

Results and comments (text)

All the demographic and clinical characteristics of the study sample are reported in table 1. The two groups are well balanced for the baseline variables except for the body mass index (BMI), that was significantly higher in the tri-therapy group (p=0.0043). The study sample included prevalently female patients (23, 59.0%), with non concomitant drugs (26, 66.7%), with a negative general examination (35, 89.7%) and a negative neurological examination (34, 87.2%). Thirty patients (76.9%) reported at least one seizure (in the 8 weeks before the baseline visit). The QoL score was similar in the two groups with an IQR of 58-69 and 45-70 respectively in the duo and tri-therapy arms. The most common type of seizure was the complex partial (32, 82.1%). Symptomatic and cryptogenic syndromes had virtually a 1:1 ratio (19 and 20 respectively) with the same distribution in both groups (p=1.0000). Six patients (15.4%) had a familiar epilepsy and the 50% of the study sample had taken at least 6 previous AEDs (min=1, max=13). During the study follow-up a total number of 7 patients were classified as "failures" (5 (31.3%) and 2 (8.7%) respectively in the duo-therapy and the tri-therapy groups, Fisher test p-value=0.1005). The Kaplan-meier survival curves on the primary endpoint are depicted in figure 1. The between curves log-rank test p-value was 0.0729. The mean (SE) retention time was respectively 152 (19) and 295 (15) days in the duo and tri-therapy groups. Table 2 reported estimates and HRs with 95% CI of all variables included in the full Cox model. Neither of the variables resulted significantly related to the primary endpoint, although group was close to the significance threshold (p=0.0734) with an excess of risk HR (95%CI)=4.76 (0.86-26.30) in the duo-therapy group. The same model with a stepwise selection procedure retained (as significant) only the EPS baseline score 0.67 (0.46-0.99), p=0.0471. Kaplan-Meier curves on the tolerability and efficacy outcomes are depicted in figure 2 and 3. Drug discontinuation due to lack of tolerability was reported only by 1 patient (duo-therapy arm), while drug discontinuation because of lack of efficacy was reported by a total number of 4 patients (3 (18.8%) and 1 (4.3%) respectively in

the duo-therapy and the tri-therapy groups). The log-rank p-values were respectively 0.1757 and 0.1523.

The between group differences in quality of life were assessed using the QoLIE-31 scale. There were no significant differences between the two groups nor at the baseline neither at the follow-up visit (table 3). The repeated measures ANOVA models did not find any significant effect of the group, the time and the interaction between time and group in neither of the populations analyzed (completers, LOCF and WR).

To both the clinician's and the self-patients' perception the number of subjects improved during the study were non significantly different in the two arms 53.3% and 46.2% in the duo-therapy group and 60.9% and 68.2% in the tri-therapy group. Similar results were found comparing the subjects satisfied 46.2% and 59.1%. Comparable results were detected imputing data with the WR technique (table 4).

The EPS score at the end of the follow-up was significantly lower in the duo-therapy arm both comparing completers and the Intent-to-treat population (with the LOCF technique), p=0.0321 and p=0.0486 (see table 5). The signed-rank test (assessed on the completers population) reported a significantly decrease of EPS score in the duo-therapy group (p=0.0352), but not in the tri-therapy arm (p=0.9363). However, the repeated measure ANOVA on ranks did not highlight any significant interaction between the course of follow-up (time) and the treatment group.

Respectively 5 (31.3%) and 10 (43.5%) patients in the duo and tri-therapy groups experienced adverse event(s) during the follow-up (p=0.5166). The five patients in the duo-therapy who experienced adverse events registered a total number of 13 adverse events (described in table 6) (one patient one event, two patients two events and two patients three events); the ten patients in the tri-therapy group who experienced adverse events registered a total number of 17 events (five patients one event, three patients two events and two patients three events). The incidence rate (IR) of adverse events in the two groups was similar and around two/three AEs per month (p=0.8516).

Table 7 reported descriptive statistics about all laboratory, general examination and vital signs data at the baseline and the last visits in the two treatment arms.

Results (tables & figures)

Table 1. Demographic and clinical characteristics of the study sample

		Duo-therapy (n=16)	Tri-therapy (n=23)	p-value
Age (years)	Mean (SD)	44.4 (13.8)	47.4 (12.1)	0.3534
BMI	Mean (SD)	23.8 (3.7)	27.5 (4.4)	0.0043
Sex	M/F	4/12	12/11	0.1108
Concomitant drugs	Y/N	4/12	9/14	0.4946
General examination	Neg/Pos	15/1	20/3	0.6309
Neurological examination	Neg/Pos	15/1	19/4	0.6309
Seizures frequency	0	4 (25.0)	5 (21.7)	0.1106
	1-4	2 (12.5)	11 (47.8)	
	5-9	3 (18.8)	2 (8.7)	
	10+	7 (43.8)	5 (21.7)	
QoLIE-31	Mean (SD)	62.2 (15.5)	57.0 (15.0)	0.4493
EPS	≥10/<10	2/14	6/17	0.4318
Seizure type	Simple partial	4 (25.0)	9 (39.1)	0.4946
	Complex partial	14 (87.5)	18 (78.3)	0.6776
	Partial secondarily generalized	9 (56.3)	13 (56.5)	1.0000
	Generalized	-	2 (8.7)	0.5034
Syndrome	Symptomatic	8 (50.0)	11 (47.8)	1.000
	Cryptogenic	8 (50.0)	12 (52.2)	
Familiar with epilepsy	Y/N	2/14	4/19	1.000
Previous AEDs	Mean (SD)	5.4 (1.7)	6.0 (3.0)	0.6679

M/F=Males/Females; Y/N=Yes/No; Neg/Pos=Negative/Positive

Figure 1. Kaplan Meier survival curves on the primary endpoint

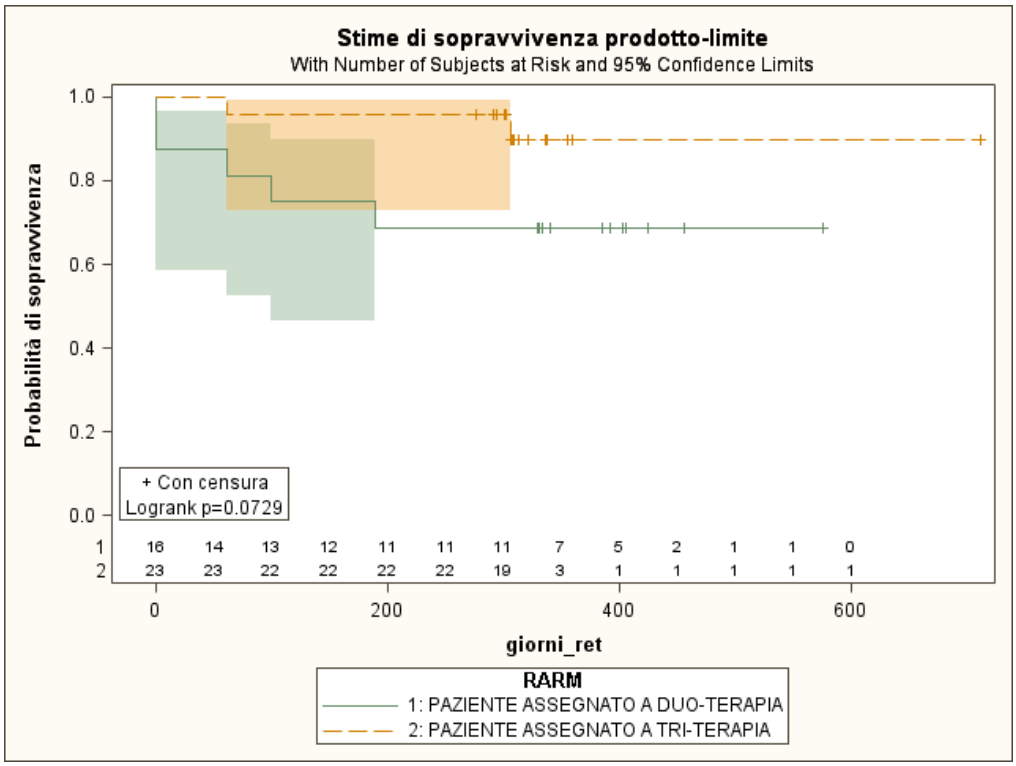

Table 2. Cox full model (primary endpoint)

		Estimate	HR (95% CI)	p-value
Group	Tri-therapy	(ref.)	1.00 (ref)	0.0734
	Duo-therapy	1.56	4.76 (0.86-26.30)	
Age	X	(ref)	1.00 (ref)	0.7104
	X+1	0.01	1.01 (0.95-1.09)	
Gender	F	(ref)	1.00 (ref)	0.3029
	M	0.91	2.48 (0.44-14.08)	
QoLIE 31	X	(ref.)	1.00 (ref)	0.9194
	X+1	-0.00	1.00 (0.94-1.06)	
EPS	X	(ref.)	1.00 (ref)	0.1431
	X+1	-0.37	0.69 (0.42-1.14)	

All independent variables complied with the PH assumption.

Figure 2. Kaplan Meier survival curves. Endpoint (tolerability)

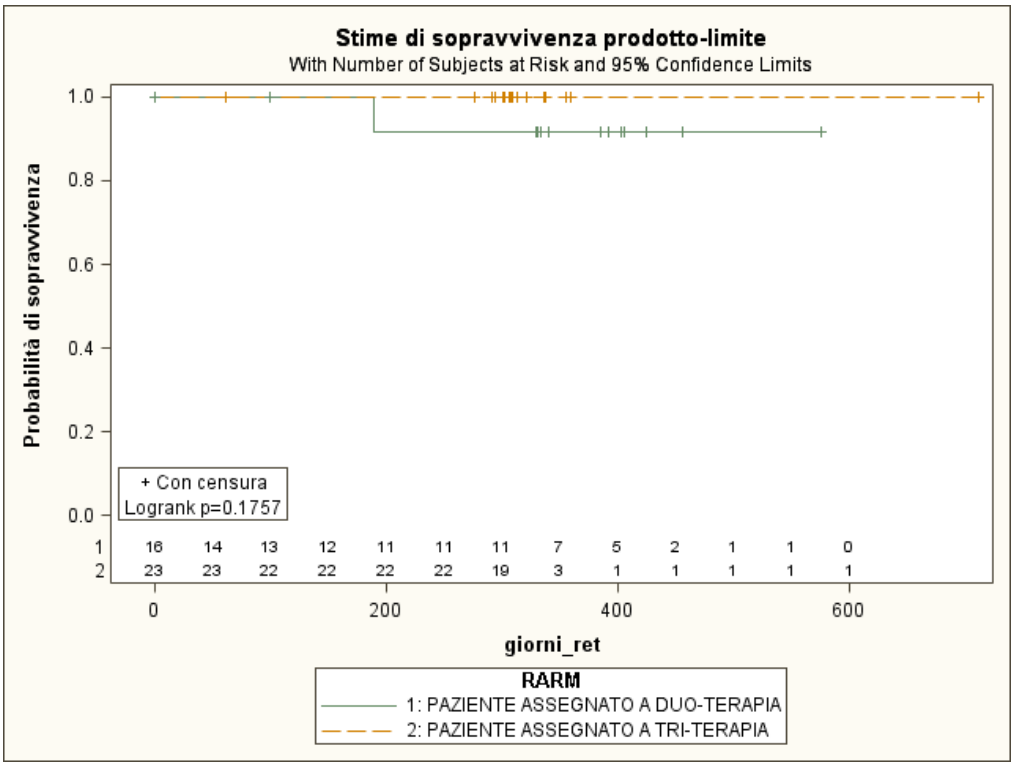

Figure 3. Kaplan Meier survival curves. Endpoint (efficacy)

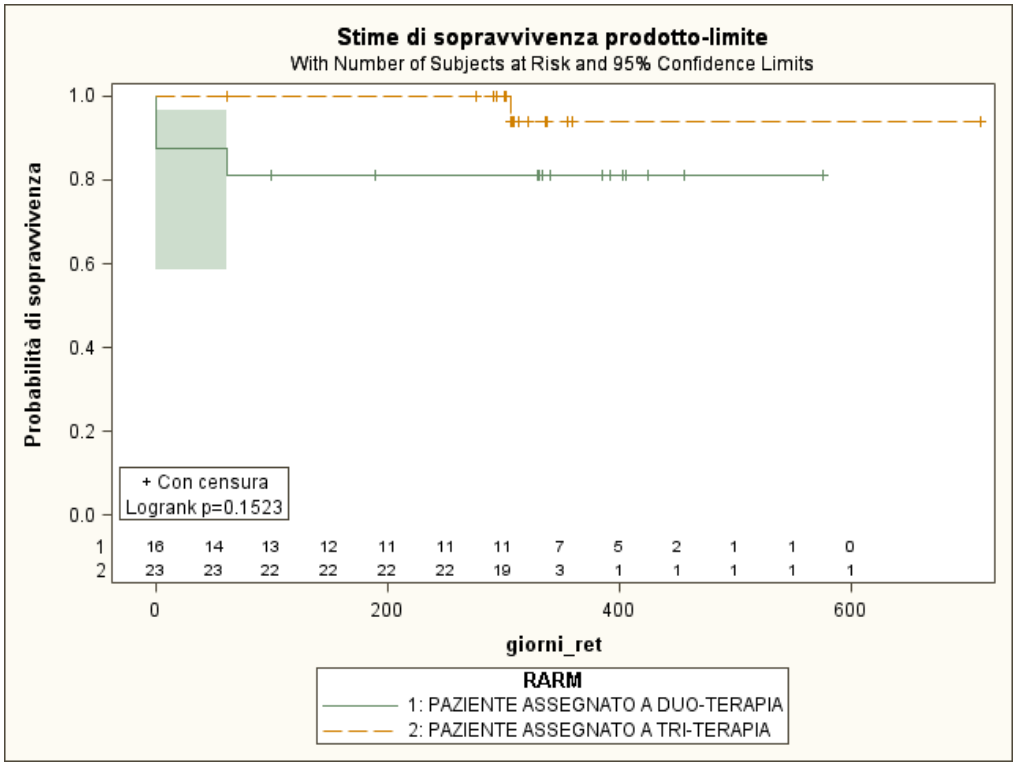

Table 3. QoLIE-31. Baseline and follow-up values and ANOVA repeated measure results.

	Duo-therapy Mean (SD)	Tri-therapy Mean (SD)	p-value
QoLIE 31 baseline	62.2 (15.5)	57.0 (15.0)	0.4539
QoLIE 31 follow-up	63.4 (12.6) (*****)	55.6 (13.6) (*)	0.2683
QoLIE 31 follow-up (LOCF)	62.1 (14.0)	56.3 (13.8)	0.3172
QoLIE 31 follow-up (WR)	57.7 (13.5)	54.4 (14.5)	0.8314
	COMPLETERS		
Effect	*F-value (df)*	*p-value*	
Group	1.89 (1,37.2)	0.1775	
Visit	0.02 (1,33.7)	0.8901	
Group*visit	0.10 (1,33.7)	0.7541	
	LOCF		
Effect	*F-value (df)*	*p-value*	
Group	1.59 (1,37)	0.2153	
Visit	0.05 (1,37)	0.8321	
Group*visit	0.02 (1,37)	0.8833	
	WR		
Effect	*F-value (df)*	*p-value*	
Group	1.09 (1,37)	0.3024	
Visit	2.16 (1,37)	0.1500	
Group*visit	0.16 (1,37)	0.6876	

Each * represents a missing value

Table 4. Clinical global impression.

	CGI	Duo-therapy	Tri-therapy	p-value
Clinician	Improved/worsened	8/7 (*)	14/9	0.6456
Satisfaction	Satisfied/NotSatisfied	6/7 (***)	13/9 (*)	0.4579
Patient	Improved/worsened	6/7 (***)	15/7 (*)	0.1987
ClinicianWR	*Improved/worsened*	*8/8*	*14/9*	*0.5007*
SatisfactionWR	*Satisfied/NotSatisfied*	*6/10*	*13/10*	*0.2424*
PatientWR	*Improved/worsened*	*6/10*	*15/8*	*0.0877*

Each * represents a missing value

Table 5. EPS baseline and follow-up values and ANOVA (on ranks) repeated measure results.

	Duo-therapy Median (range)	Tri-therapy Median (range)	p-value
EPS baseline	6 (2-12)	7 (3-17)	0.2628
EPS follow-up	4 (1-10) (******)	7 (2-17) (**)	0.0321
EPS follow-up (LOCF)	5 (1-10)	7 (1-17)	0.0486
EPS follow-up (WR)	7 (1-17)	8 (2-17)	0.9316
	COMPLETERS		
Effect	**F-value (df)**	**p-value**	
Group	3.85 (1,36.6)	0.0575	
Visit	3.98 (3,33.8)	0.0157	
Group*visit	0.68 (3,33.8)	0.5687	
	LOCF		
Effect	**F-value (df)**	**p-value**	
Group	2.97 (1,37)	0.0930	
Visit	0.03 (3,37)	0.9938	
Group*visit	0.59 (3,37)	0.6225	
	WR		
Effect	**F-value (df)**	**p-value**	
Group	0.32 (1,37)	0.5740	
Visit	0.03 (3,37)	0.9937	
Group*visit	0.59 (3,37)	0.6246	

Each * represents a missing value

Table 6. Adverse events

AE description	Duo-therapy	Tri-therapy
Behavior disorders	x	
Bronchitis		x
Bronchopneumonia	x	
Cough		x
Diarrhea		xx
Fever		x
Flu		x
Focal status epilepticus	**x**	
Gastroenteritis	**x**	
Headache	x	x
Herpes virus infection		x
Hypertension	x	
Lack of appetite		x
Low back pain		x
Lower limb edema		xx
Nausea		x
Shoulder algia	x	
Shoulder trauma		x
sleepiness		xxx
Tooth abscess	xx	
Unknown	x	
Varicella	x	
Weight loss	x	
Total # of AEs*	13	17
IR (95% CI) per month	2.17 (1.15-3.71)*	2.83 (1.65-4.54)**

In **bold** SAE; * 161.6 person-months; ** 235.6 person-months

Table 7. Laboratory data, general and neurological examination and vital signs

				Duo-therapy	Tri-therapy
Lab data	**Bicarbonate**	Baseline	N/A	9/2	18/1
		Follow-up	N/A	7/0	12/1
	Calcium	Baseline	N/A	14/0	17/2
		Follow-up	N/A	9/1	18/2
	Chlorine	Baseline	N/A	12/2	20/1
		Follow-up	N/A	6/3	12/5
	Phosphate	Baseline	N/A	10/3	16/4
		Follow-up	N/A	6/3	11/6
	Potassium	Baseline	N/A	14/0	22/0
		Follow-up	N/A	10/0	19/1
	Sodium	Baseline	N/A	11/3	22/0
		Follow-up	N/A	8/2	18/2
	Platelets	Baseline	N/A	16/0	21/2
		Follow-up	N/A	8/2	16/4
	Erythrocytes	Baseline	N/A	14/2	20/3
		Follow-up	N/A	9/1	17/3
	Leukocytes	Baseline	N/A	14/2	19/4
		Follow-up	N/A	8/2	14/6
	White blood cell count	Baseline	N/A	14/2	17/5
		Follow-up	N/A	8/2	13/6
	Hematocrit	Baseline	N/A	12/4	19/4
		Follow-up	N/A	8/2	17/3
	Hemoglobin	Baseline	N/A	13/3	19/4
		Follow-up	N/A	8/2	17/3
	Bilirubin	Baseline	N/A	15/0	20/2
		Follow-up	N/A	10/0	18/2
	Phosphatase	Baseline	N/A	13/2	20/0
		Follow-up	N/A	9/1	17/3
	Alt	Baseline	N/A	16/0	21/2
		Follow-up	N/A	9/1	15/5
	Ast	Baseline	N/A	16/0	22/1
		Follow-up	N/A	10/0	15/5
	Ggt	Baseline	N/A	11/5	15/7
		Follow-up	N/A	7/3	10/9
	Albumin	Baseline	N/A	14/0	20/2
		Follow-up	N/A	10/0	18/2
	Ldh	Baseline	N/A	12/2	19/1
		Follow-up	N/A	10/0	16/4
	Cpk	Baseline	N/A	15/0	18/2
		Follow-up	N/A	9/1	14/4
	Azotemia	Baseline	N/A	14/0	20/1
		Follow-up	N/A	8/2	12/6
	Cholesterol	Baseline	N/A	6/9	14/7
		Follow-up	N/A	5/5	10/9
	Creatinine	Baseline	N/A	11/3	23/0
		Follow-up	N/A	10/0	18/2
	Uric acid	Baseline	N/A	13/2	19/3
		Follow-up	N/A	9/1	12/7
	Glycemia	Baseline	N/A	14/1	22/1
		Follow-up	N/A	9/1	19/1

	Proteins	Baseline	N/A	15/0	20/1
		Follow-up	N/A	9/0	19/1
	Ph urine	Baseline	N/A	14/2	19/4
		Follow-up	N/A	6/0	16/3
	Ph specific weight	Baseline	N/A	14/2	22/1
		Follow-up	N/A	5/1	15/4
	Ph proteins	Baseline	N/A	14/2	21/2
		Follow-up	N/A	6/0	12/7
Gen examination	**Head**	Baseline	N/A	16/0	20/3
		Follow-up	N/A	10/0	21/1
	Cardiovascular	Baseline	N/A	14/2	22/1
		Follow-up	N/A	9/1	22/0
	Respiratory	Baseline	N/A	15/1	23/0
		Follow-up	N/A	10/0	22/0
	Abdominal	Baseline	N/A	16/0	23/0
		Follow-up	N/A	10/0	22/0
	Urogenital	Baseline	N/A	15/0	23/0
		Follow-up	N/A	10/0	22/0
	Musculoskeletal	Baseline	N/A	15/1	21/2
		Follow-up	N/A	10/0	21/1
	Dermatologic	Baseline	N/A	15/1	22/1
		Follow-up	N/A	9/1	21/1
	Lymphatic	Baseline	N/A	16/0	22/1
		Follow-up	N/A	10/0	22/0
	Other	Baseline	N/A	15/1	19/0
		Follow-up	N/A	9/0	18/1
Vital signs	**Weight**	Baseline	Median (IQR)	60 (58-78)	76 (70-86)
		Follow-up	Median (IQR)	60 (57-78)	76.5 (68-87)
	Systolic BP	Baseline	Median (IQR)	120 (115-125)	120 (120-125)
		Follow-up	Median (IQR)	120 (120-120)	120 (115-130)
	Diastolic BP	Baseline	Median (IQR)	80 (70-80)	80 (80-80)
		Follow-up	Median (IQR)	80 (70-80)	77.5 (70-80)
	Cardiac Freq	Baseline	Median (IQR)	76 (70-80)	72 (70-76)
		Follow-up	Median (IQR)	74 (70-78)	72 (70-75)
	Temperature	Baseline	Median (IQR)	36.2 (36.0-36.5)	36.0 (36.0-36.5)
		Follow-up	Median (IQR)	36.0 (36.0-36.0)	36.0 (36.0-36.4)
	Resp Freq	Baseline	Median (IQR)	15 (12-20)	12 (12-17)
		Follow-up	Median (IQR)	16.5 (12-24)	13.5 (12-17)
	Consciousness	Baseline	N/A	15/0	23/0
		Follow-up	N/A	10/0	22/0

N/A=Normal/Abnormal

Conclusions

The results obtained suggest, but do not prove with statistical significance, the efficacy on retention time of Zonisamide as an add-on treatment. The mean retention time in the experimental arm was almost doubled respect that observed in the control group (295 days vs. 152 days). Data on QoL and safety were fully comparable and only two serious adverse events occurred during the follow-up (in the duo-therapy arm). Comparing the proportion of patients improved, the clinical global impression scale suggested a beneficial effect of the add-on therapy without any significant result, while the EPS scale reported highest (worst) value of its score in the experimental arm.