STATISTICAL ANALYSIS REPORT

Project: CSDR RP1558/YODA 2016-1038

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LIST OF ABBREVIATIONS

AD	Aggregated data
ADF	Average daily frequency
AED	Anti-epileptic drug
ANCOVA	Analysis of covariance
CSDR	Clinical Study Data Request
CSR	Clinical Study Report
IPD	Individual patient data
LTG	Lamotrigine
LVT	Levetiracetam
OXC	Oxcarbazepine
PEACE	Pediatric Epilepsy Academic Consortium for Extrapolation
PGTCS	Primary generalized tonic clonic seizures
POS	Partial onset seizures
REML	Restricted maximum likelihood
TPM	Topiramate
YODA	Yale University Open Data Access (YODA) Project

1 INTRODUCTION

In the development of new drugs, pharmaceutical companies need to conduct clinical studies in the pediatric population for a medication that has been approved for the same indication in adults where the disease has similar characteristics and the same response to treatment is expected. To prove that the new treatment works in children, there needs to be a standard to which the new medication data can be compared to show it performs better than no treatment.

Clinical studies in the pediatric population are often more difficult to enroll than those conducted in adults; especially in the population of children younger than 4 years of age. Challenges in study design, ethical questions about exposing children to placebo, and logistics of pediatric subjects participating in a clinical trial contribute to the difficulty in enrollment. To limit the number of pediatric subjects exposed to placebo, it is proposed to perform a combined analysis of the placebo responses observed in completed studies in children with epilepsy (especially partial-onset seizures) to create a historical control for reference in future studies.

In 2015, the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE) initiative examined the concept of extrapolation of efficacy data from adults to pediatric subjects to show that if a pharmaceutical company's study data proved an anti-epileptic drug was efficacious in adults then the drug would be efficacious in children without conducting a placebo-controlled study due to the similarity of the disease between adults and children. Companies are still required to conduct studies to assess the safety of the subjects taking the investigational drug and measure the levels of the medication in a subject's system. The initiative was able to show that efficacy of anti-epileptic drugs in adults based on clinical trial data and drug concentration data, could be used to predict efficacy of anti-epileptic drugs in pediatric population.

Extrapolation from adult efficacy data to < 4 years old was not recommended due to limited data. Borrowing historical control data in the new clinical trials would possibly reduce the number of pediatric subjects required to be randomized to the placebo arm, and would minimize the exposure of a larger number of pediatric subjects with potentially life-threatening seizures to placebo. In addition, leveraging historical control placebo response may shorten development timelines, allowing quicker access to additional treatment options for epilepsy in the pediatric population.

2 OBJECTIVE

The goal of this project is to create an estimate of a historical control rate of pediatric subjects with POS with epilepsy using the data from several anti-epileptic drugs (eg, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate) that could be used as a comparator to future new anti-epileptic drugs.

2.1 Data sources

To obtain individual patient data (IPD), a research proposal was submitted to Clinical Study Data Request (CSDR) and The Yale University Open Data Access (YODA). Data were obtained on pediatric subjects randomized to the placebo arm of randomized controlled studies for AEDs that have been completed prior to 2017. Specifically, the clinical trial data met the following criteria were requested:

1. The study is randomized and placebo-controlled

2. The study has at least one of the following efficacy endpoints as primary with aggregate statistics reported:
    - Reduction in seizure frequency compared to baseline
    - Percent reduction in seizure frequency from baseline (responder status)
3. Information is available on the number of treatment arms in the study and subjects randomized to each arm and corresponding dosages
4. Study includes subjects <18 years of age
5. Specific indication (partial-onset seizures, generalized seizures)
6. Type of therapy: adjunctive or monotherapy

Of note, individual patient data (IPD) are confined in two data sharing systems, and only aggregated data (AD) can be exported out of the closed research environment.

2.2 Studies obtained

The studies obtained from CSDR and YODA are listed in Appendix 6.1. They are summarized by indication and age category as following:

Seizure Type	Age Category	Study Index*
Partial onset seizures (POS)	Children and adults	LTG1, LTG2, LVT1, LVT3, and TPM1
Partial onset seizures (POS)	Infants and young children*	LTG3*, LVT2, OXC1*, OXC2*, and TPM2
Primary generalized tonic clonic seizures (PGTCS)	Children and adults	LTG4 and LTG5
Lennox-Gastaut syndrome (LGS)	Children and adults	LTG6

LTG = Lamotrigine, LVT= Levetiracetam, OXC= Oxcarbazepine, and TPM= Topiramate.
*More information for the studies are listed in Appendix 6.1. There were few placebo-controlled parallel studies for < 4 years old. Studies using pseudo-placebo (OXC1 and OXC2) and response enrichment design (LTG3) were also requested.

3 EFFICACY VARIABLES

Two efficacy variables from the placebo group in each clinical trial will be analyzed:

- Percent (%) reduction in seizure frequency from baseline
- Percentages of patients who experienced a ≥50% reduction in seizure frequency from baseline (≥50% responder rate)

In older children and adults, seizure count data are collected through patient diaries over a few months. Because it is difficult to classify seizures and count seizures in young children, video-EEG (vEEG) is used to measure seizures in infants and neonates.

4 STATISTICAL METHODS

4.1 Analysis set

Only placebo treated subjects will be used in the analyses. Because of the study designs, placebo responses can't be adequately estimated from LGT3, OXC1, and OXC2 and will be excluded from the analysis.

The analysis set used for the primary efficacy endpoint in a clinical study report (CSR) will be used. For UCB-N1009 and JNJ-3001, subjects in the modified full analysis set will be used. For all the other studies, full analysis sets will be used.

Subjects were required to have baseline seizures per the protocols. Different rules were used to impute zero baseline seizure in CSR analyses. Because few subjects had zero baseline seizure, these subjects will be excluded from the analyses.

4.2 Analysis period

Baseline and double-blinded treatment period defined in each CSR will be used in the analyses.

4.3 Subject disposition

The number and percentages of subjects in the analysis set who completed or discontinued a study will be summarized by study. For subjects who discontinued, the reasons for discontinuation will also be summarized.

4.4 Baseline characteristics and covariates

The following baseline characteristics and covariates will be summarized by study using descriptive statistics:

Study level parameters

- Year of study start
- Seizure type of the study (POS, PGTCS, or LGS)
- Number of placebo subjects

Subject level parameters (if collected)

- Age or age category whichever is provided
- Gender
- Race
- Baseline seizure frequency
- Number of prior AEDs (≤2 vs. >2)
  - Prior AEDs are AEDs with start date prior to the date of first dose.
- For the POS studies, if collected: Historical Type IC seizures: Yes vs. No.

4.5 Calculation of the efficacy variables

For UCB-N1009 and JNJ-3001, average daily seizure frequency (ADF) will be analyzed. For all the other studies, 28-day seizure frequency will be analyzed. If 7-day seizure frequency was

reported in the CSR, 28-day seizure frequency will be calculated as (7-day seizure frequency ×4). Of note, percent reduction in seizure frequency from baseline remains unchanged.

The percent reduction in seizure frequency is calculated as:

% reduction = 100 × (1- treatment period seizure frequency/baseline seizure frequency)

Patients with at least a 50% reduction from the baseline in seizure frequency will be categorized as a responder.

4.6 Analysis of efficacy variables

4.6.1 Descriptive statistics of efficacy variables by study

The following descriptive statistics will be produced for percent reduction in seizure frequency: n, median, minimum, maximum, quartile 1, quartile 3, and 95% distribution-free confidence interval of the median.

The number and percentages of responders will be produced. Percentages will be displayed to one decimal place along with the Wald 95% confidence interval.

4.6.2 Meta-analysis

Meta-analysis will be performed to summarize diary-based seizure endpoints in POS studies (LTG1, LTG2, LVT1, LVT3, and TPM1). A two-stage approach will be used so that data from YODA and CSDR can be combined. The random-effects meta-analysis method will be used to account for between-trial heterogeneity (Higgins et al., 2009). SAS procedure Proc Mixed with restricted maximum likelihood (REML) will be used to estimate the parameters.

4.6.2.1 Percent reduction in seizure frequency from baseline

To normalize the data, change from baseline in log-transformed seizure frequency will be used to perform the meta-analysis.

chg_log = log (treatment period seizure frequency +1) – log (baseline seizure frequency +1)

The results will be converted back to the percent reduction. The % reduction in seizure frequency will be calculated as 100×(1-exp(chg_log)). The lower limit (LL) and upper limit (UL) of the 95% CI will be calculated 100× (1-exp(UL of chg_log)) and is 100× (1-exp(LL of chg_log)).

4.6.2.2 ≥50% responder

To normalize the data, responder rate on logit scale will be used to perform the meta-analysis:

LRR= logit(p) = log (odds) = log (p/1-p)

where p = %50 responder rate. The results will be converted back to the responder rate = exp(LRR)/1+exp(LRR).

4.6.3 Adjustments for covariates

The impacts of the following factors on the seizure frequency will be evaluated for each study:

- Baseline seizure frequency
- Age (if only categories are available, age is calculated as the median of a category).
- Number of prior AEDs: ≤2 vs. >2

- For the POS studies, if collected: Historical Type IC seizures: Yes vs. No

Analysis of covariance (ANCOVA) will be used on log-transformed seizure frequency data:

chg_log = β_0 + β_1× log (baseline seizure frequency+1) + β_2×age + β_3×number of prior AEDs + β_4× historical type IC seizures.

In addition, IPDs from LTG1, LTG2, LVT1, and LVT3 will be pooled and the impacts of the factors will be evaluated using the following model:

chg_log = β_0 + β_1× study + β_2× log (baseline seizure frequency+1) + β_3×age + β_4×number of prior AEDs.

Historical type IC seizures will not be included because the information was not collected in LVT1 and LVT3.

4.7 vEEG vs diary-based seizure counts in young children

It is difficult to classify seizures and count POS in young children and diary-based seizure data are inaccurate and highly variable in young children. FDA recommended the use of video-EEG (vEEG) to measure seizures in infants and neonates with POS. However, there is also considerable diversity among clinicians in the interpretation of the EEG and the video.

In TOPMATPEP3001, take-home records were given to the parents at Screening and subsequent visits. The types and numbers of seizures for each type were recorded at minimum of once a day. Seizure data then was transcribed into the CRF. The treatment period was 20 days and the 48-hour vEEG was measured at the end of the treatment period (Day 19-20 or early discontinuation).

In UCB-N1009, no seizure diary data were collected during the baseline (Day -8 to Day 0). The historical seizure counts during the 2-weeks prior to Day -8 will be used as the CRF seizure data baseline. Seizure counts observed by the hospital staff and family members were collected daily and reported on the CRF while the subjects were hospitalized during the 6-day treatment period. The 48-hour vEEG was measured at the end of the treatment period (Day 4-6 or at early discontinuation).

Daily POS frequency at baseline, during the treatment period, percent reduction from the baseline, and 50% responder rate based on vEEG and diary data will be summarized for TOPMATPEP3001 and UCB-N1009.

In addition, the relationship between daily POS frequency based on vEEG and diary will be investigated through a linear regression model, where diary daily POS frequency during the treatment period (or at the end of the treatment period while the vEEG was taken) is the outcome variable and the end of treatment vEEG daily POS frequency is the predictor variable:

log (Diary_ADF + 1) = β_0 + β_1× log (vEEG_ADF+1)

where Diary_ADF = average daily POS frequency based on dairy during the treatment period (or at the end of the treatment period while the vEEG was taken) and vEEG_ADF = average daily POS frequency based on vEEG during the treatment period.

The agreement between vEEG_ADF and Diary_ADF will also be evaluated using Altman and Bland plot (Giavarina, 2015). The difference between vEEG_ADF and Diary_ADF will be plotted against the mean of the two.

5 STUDY POPULATION RESULTS

5.1 Population analyzed

In principle, subjects in the full analysis set in each study are included in the analyses. For UCB-N1009 and JNJ-3001, subjects in the modified full analysis set are included. Subjects with zero baseline seizure count are also excluded.

5.2 Subject disposition

Subject disposition is provided by study in Table 5-1.

Table 5-1: Overview of subject disposition by study

Study	Disposition Type	Disposition	n (%)
JNJ-Study-YP (N=45)	Study Status	Completed Study	43 (95.6)
		Discontinued	2 (4.4)
	Discontinuation Reason	ADVERSE EVENT	1 (2.2)
		SUBJECT CHOICE	1 (2.2)
JNJ-topmatpep3001 (N=25)	Study Status	Completed Study	22 (88.0)
		Discontinued	3 (12.0)
	Discontinuation Reason	ADVERSE EVENT	1 (4.0)
		OTHER	2 (8.0)
GSK-105-040 (N=101)	Study Status	Completed Study	83 (82.2)
		Discontinued	18 (17.8)
	Discontinuation Reason	Adverse Event	6 (5.9)
		Consent Withdrawn	2 (2.0)
		Lack of Efficacy	8 (7.9)
		Protocol Violation	2 (2.0)
GSK-105-123 (N=89)	Study Status	Completed Study	76 (85.4)
		Discontinued	13 (14.6)
	Discontinuation Reason	Adverse Event	7 (7.9)
GSK-LAM100034 (N=120)	Study Status	Completed Study	106 (88.3)
		Discontinued	14 (11.7)
	Discontinuation Reason	Adverse event	1 (0.8)
		Non-compliance	1 (0.8)
		Other,specify	4 (3.3)
		Protocol violation	1 (0.8)
		Subject decided to withdraw from the study	7 (5.8)

Study	Disposition Type	Disposition	n (%)
GSK-LAM100036 (N=72)	Study Status	Completed Study	68 (94.4)
		Discontinued	4 (5.6)
	Discontinuation Reason	Adverse event	2 (2.8)
		Subject decided to withdraw from the study	2 (2.8)
GSK-LAM40097 (N=59)	Study Status	Completed Study	45 (76.3)
		Discontinued	14 (23.7)
	Discontinuation Reason	Adverse Event	2 (3.4)
		Lack of Efficacy	4 (6.8)
		Lost to Follow-Up	1 (1.7)
		Non-Compliance	6 (10.2)
		Other	1 (1.7)
UCB-N01009 (N=50)	Study Status	Completed Study	49 (98.0)
		Discontinued	1 (2.0)
	Discontinuation Reason	Withdrawal of consent	1 (2.0)
UCB-N01103 (N=34)	Study Status	Completed Study	29 (85.3)
		Discontinued	5 (14.7)
	Discontinuation Reason	Adverse event	2 (5.9)
		Lack of efficacy	1 (2.9)
		Lost to follow-up	1 (2.9)
		Protocol violation	1 (2.9)
UCB-N159 (N=96)	Study Status	Completed Study	82 (85.4)
		Discontinued	14 (14.6)
	Discontinuation Reason	Adverse Event	9 (9.4)
		Lack of Efficacy	2 (2.1)
		Lost to Follow-up	2 (2.1)
		Other	1 (1.0)

Note: The percentage for each discontinuation reason is based on the total number of subjects who discontinued.

5.3 Demographic and Baseline characteristics

The demographic and Baseline characteristics are summarized by study in Table 5-2.

Table 5-2: Summary of demographic and Baseline characteristics

Study	Year Start	Seizure Type	Parameter	Statistic	
JNJ-Study-YP	1994	POS	Age (Years)	n	45
				Mean	9.4
				SD	3.35
				Median	10.0
				Q1 - Q3	7.0 – 12.0
				Min - Max	3.0 – 17.0
			Baseline Seizure Frequency (28 Days)	n	45
				Mean	84.5
				SD	190.15
				Median	19.0
				Q1 - Q3	9.5 - 71.9
				Min - Max	2.0 - 1132.5
			Gender	F	20
				M	25
			Race	Non-White	2
				White	43
			Number of Prior AEDs	<=2	40
				>2	5
JNJ-topmatpep3001	2005	POS	Gender	F	14
				M	11
			Race	Non-White	6
				White	19
			Number of Prior AEDs	<=2	23
				>2	2
			Historical Type IC	No	16
				Yes	9
			Baseline Seizure Frequency (ADF)	n	25
				Mean	22.7
				SD	36.97
				Median	7.3
				Q1 - Q3	3.6 - 21.2

Study	Year Start	Seizure Type	Parameter	Statistic	
				Min - Max	1.0 - 148.7
GSK-105-040	1993	POS	Age (Years)	n	101
				Mean	8.8
				SD	3.62
				Median	9.4
				Q1 - Q3	6.0 - 11.8
				Min - Max	2.4 - 15.7
			Gender	F	45
				M	56
			Race	Non-White	16
				White	85
			Number of Prior AEDs	<=2	14
				>2	87
			Historical Type IC	No	47
				Yes	54
			Baseline Seizure frequency (28 Days)	n	101
				Mean	77.1
				SD	124.37
				Median	40.5
				Q1 - Q3	8.0 - 102.3
				Min - Max	1.0 – 812.0

Study	Year Start	Seizure Type	Parameter	Statistic	
GSK-105-123	1993	Lennox-Gastaut syndrome	Age (Years)	n	89
				Mean	12.0
				SD	5.86
				Median	11.2
				Q1 - Q3	7.6 - 15.6
				Min - Max	3.2 - 29.5
			Gender	F	44
				M	45
			Race	Non-White	6
				White	83
			Number of Prior AEDs	<=2	77
				>2	12
			Baseline Seizure Frequency (28 Days)	n	89
				Mean	143.6
				SD	293.83
				Median	54.0
				Q1 - Q3	21.2 - 113.9
				Min - Max	6.0 – 2371.0

Study	Year Start	Seizure Type	Parameter	Statistic	
GSK-LAM100034	2003	POS	Age (Years)	n	120
				Mean	37.6
				SD	14.32
				Median	36.5
				Q1 - Q3	26.5 - 49.5
				Min - Max	14.0 – 73.0
			Gender	F	57
				M	63
			Race	Non-White	38
				White	82
			Number of Prior AEDs	<=2	47
				>2	73
			Historical Type IC	No	80
				Yes	40
			Baseline Seizure frequency (28 Days)	n	120
				Mean	16.8
				SD	29.49
				Median	8.5
				Q1 - Q3	5.5 - 13.5
				Min - Max	3.5 – 200.0

Study	Year Start	Seizure Type	Parameter	Statistic	
GSK-LAM100036	2004	PGTCS	Age (Years)	n	72
				Mean	28.1
				SD	11.32
				Median	26.0
				Q1 - Q3	19.5 - 34.5
				Min - Max	13.0 – 74.0
			Gender	F	37
				M	35
			Race	Non-White	35
				White	37
			Number of Prior AEDs	<=2	37
				>2	35
			Historical Type IC		
			Age Category	>12 and <= 16	8
				> 16	64
			Baseline Seizure frequency (28 Days)	n	72
				Mean	3.7
				SD	3.99
				Median	2.5
				Q1 - Q3	2.0 - 3.5
				Min - Max	1.0 - 29.5

Study	Year Start	Seizure Type	Parameter	Statistic	
GSK-LAM40097	2000	PGTCS	Age (Years)	n	59
				Mean	24.9
				SD	13.79
				Median	25.0
				Q1 - Q3	14.0 - 39.0
				Min - Max	2.0 – 55.0
			Gender	F	26
				M	33
			Race	Non-White	31
				White	28
			Number of Prior AEDs	<=2	59
			Baseline Seizure frequency (28 Days)	n	59
				Mean	5.8
				SD	13.97
				Median	2.8
				Q1 - Q3	1.6 - 5.3
				Min - Max	0.8 - 107.4

Study	Year Start	Seizure Type	Parameter	Statistic	
UCB-N01009	2004	POS	Age (Years)	n	50
				Mean	1.8
				SD	0.76
				Median	1.8
				Q1 - Q3	1.0 - 2.5
				Min - Max	1.0 - 2.5
			Gender	Female	25
				Male	25
			Number of Prior AEDs	<=2	41
				>2	9
			Historical Type IC	No	50
			Age Category	>2 and <= 12	25
				<= 2	25
			Baseline Seizure frequency (1 Day)	n	50
				Mean	15.7
				SD	23.04
				Median	7.2
				Q1 - Q3	2.0 - 16.2
				Min - Max	1.0 - 98.0

Study	Year Start	Seizure Type	Parameter	Statistic	
UCB-N01103	2004	POS	Age (Years)	n	34
				Mean	9.9
				SD	3.53
				Median	9.0
				Q1 - Q3	6.5 - 12.0
				Min - Max	4.5 - 15
			Gender	Female	17
				Male	17
			Number of Prior AEDs	<=2	33
				>2	1
			Historical Type IC	No	34
			Baseline Seizure frequency (28 Days)	n	34
				Mean	32.8
				SD	85.48
				Median	5.5
				Q1 - Q3	1.6 - 20.6
				Min - Max	0.8 - 401.3

Study	Year Start	Seizure Type	Parameter	Statistic	
UCB-N159	1998	POS	Age (Years)	n	96
				Mean	9.4
				SD	3.51
				Median	9.0
				Q1 - Q3	7.0 - 11.0
				Min - Max	4.0 – 16.0
			Gender	F	50
				M	46
			Number of Prior AEDs	<=2	60
				>2	36
			Historical Type IC	No	66
				Yes	30
			Baseline Seizure frequency (28 Days)	n	96
				Mean	74.6
				SD	204.55
				Median	21.5
				Q1 - Q3	9.9 - 56.5
				Min - Max	2.0 - 1866.5

Note: if a parameter isn't presented for a study, the parameter wasn't collected or removed from the anonymized data.

6 EFFICACY RESULTS

6.1 Percent reduction in seizure frequency

6.1.1 Summary of percent reduction in seizure frequency by study

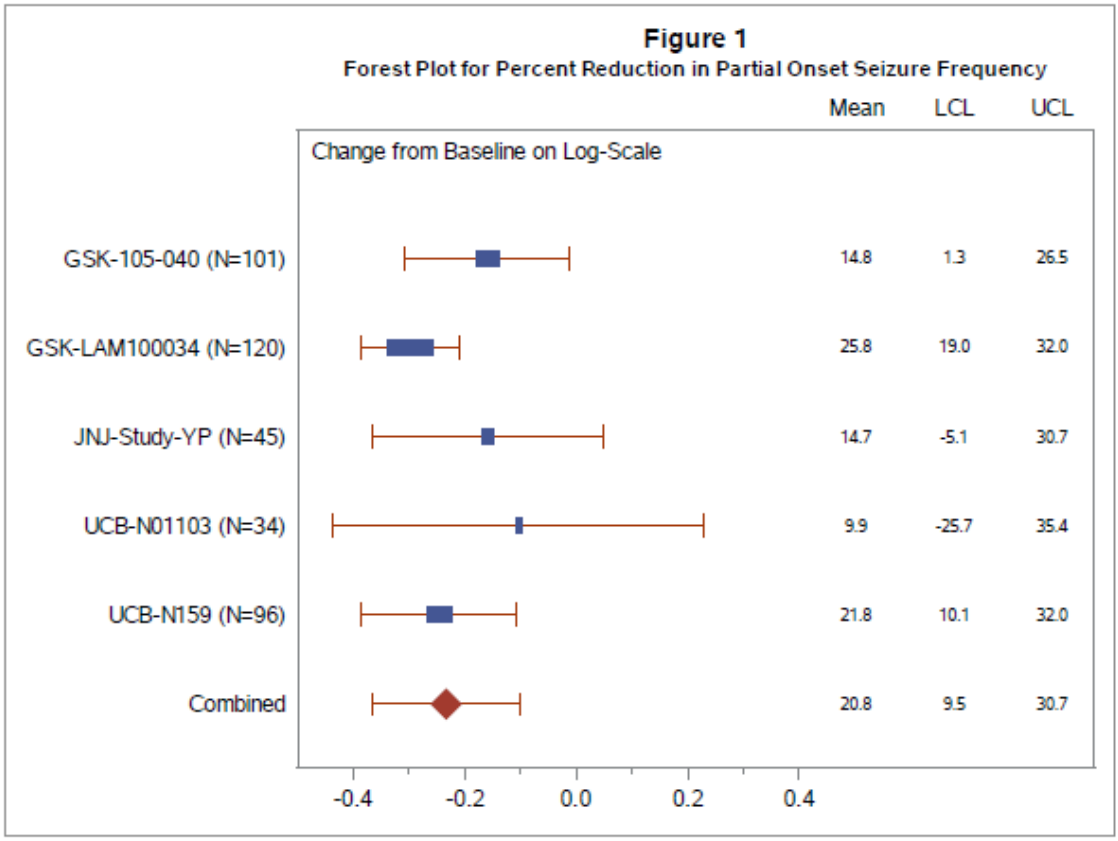
The percent of reduction in seizure frequency from Baseline during the Treatment Period is summarized by study in Table 6.1.

Table 6-1: Summary of percent reduction in seizure frequency from Baseline during the Treatment Period.

Study	N	Median	Q1	Q3
JNJ-Study-YP	45	10.5	-17.4	42.6
JNJ-topmatpep3001	25	35.6	-75.9	93.5
GSK-105-040	101	5.7	-33.4	41.8
GSK-105-123	89	7.2	-14.6	39.1

Study	N	Median	Q1	Q3
GSK-LAM100034	120	24.5	1.3	47.6
GSK-LAM100036	72	32.1	4.2	67.4
GSK-LAM40097	59	34.2	-35.4	71.2
UCB-N01009	50	7.1	-42.3	35.1
UCB-N01103	34	26.5	-108.5	62.7
UCB-N159	96	16.3	-17.6	42.0

6.1.2 Meta-analysis of percent reduction in seizure frequency



6.2 50% Responder Rate (RR)

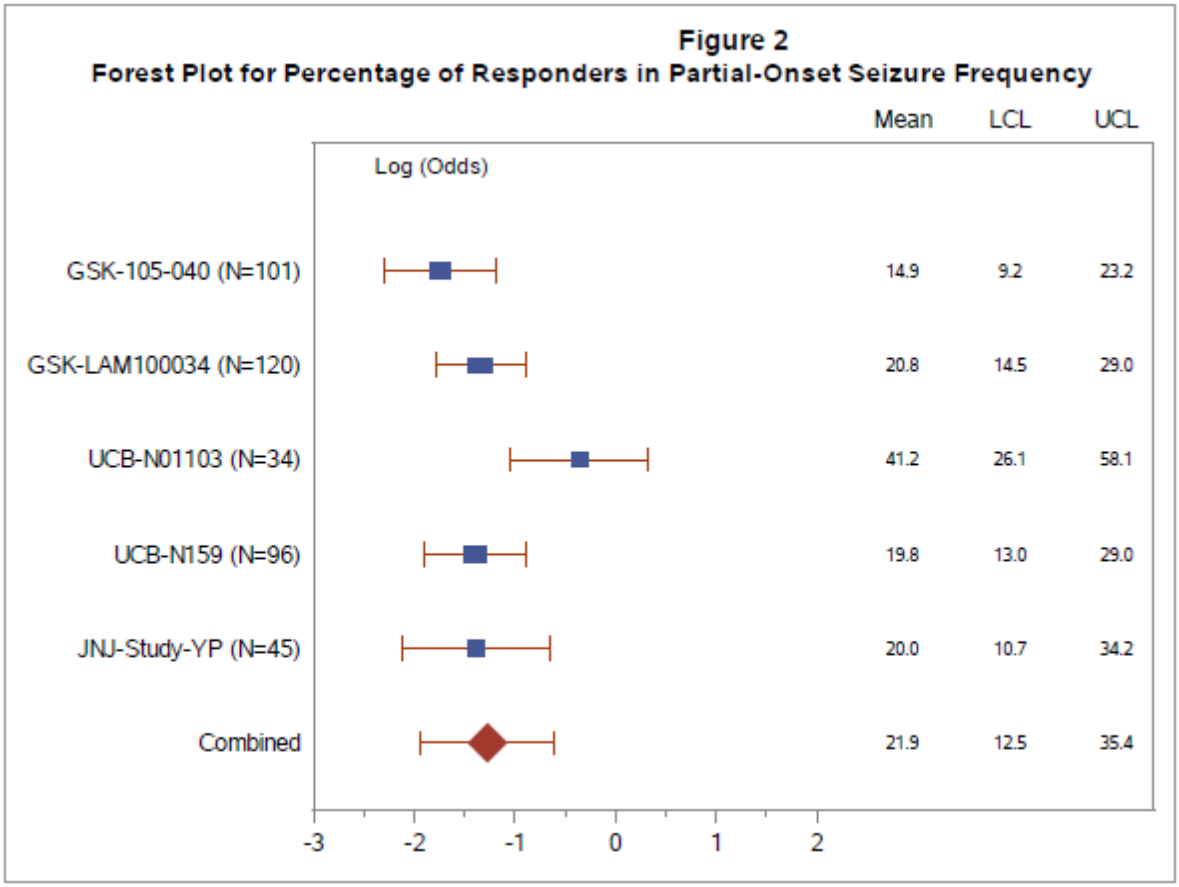
6.2.1 Summary of 50% RR by study

The 50% responder rates are summarized in Table 6-4 by study.

Table 6-2: Responder rates by study.

Study	N	n (%)
JNJ-Study-YP	45	9 (20.0)
JNJ-topmatpep3001	25	11 (44.0)
GSK-105-040	101	15 (14.9)
GSK-105-123	89	14 (15.7)
GSK-LAM100034	120	25 (20.8)
GSK-LAM100036	72	23 (31.9)
GSK-LAM40097	59	23 (39.0)
UCB-N01009	50	10 (20.0)
UCB-N01103	34	14 (41.2)
UCB-N159	96	19 (19.8)

6.2.2 Meta-analysis of 50% RR



6.3 Impact of covariates on reduction in seizure frequency

The impact of age, historical Type IC, and number of prior AEDs to reduction in seizure frequency were evaluated using multivariate ANCOVA by study. The estimates and p-values are presented in Table 6-3. The two smallest p-values are observed for prior AEDs in GSK-LAM100034 and UCB-N159. Only 1 p-value is < 0.05 (bolded).

Table 6-3: ANCOVA results for reduction in seizure frequency

study	Covariate	Estimate	P-value
GSK-105-040	Age	-0.03	0.15
	Historical Type IC seizures Yes	-0.20	0.18
	Baseline Seizure Frequency (Log-scale)	-0.06	0.32
	Prior AEDs >2	0.01	0.96
GSK-LAM100034	Age	0.00	0.66
	Historical Type IC seizures Yes	0.04	0.66
	Baseline Seizure Frequency (Log-scale)	0.00	0.99
	Prior AEDs >2	0.21	**0.02**
UCB-N01009	Age	0.02	0.85
	Baseline Seizure Frequency (Log-scale)	-0.03	0.75
	Prior AEDs >2	-0.09	0.70
UCB-N01103	Age	0.02	0.75
	Baseline Seizure Frequency (Log-scale)	-0.09	0.51
	Prior AEDs >2	1.66	0.11
UCB-N159	Age	0.02	0.25
	age	0.02	0.25
	Historical Type IC seizures Yes	0.11	0.49
	Baseline Seizure Frequency (Log-scale)	-0.06	0.25
	Prior AEDs >2	0.28	0.06
JNJ-Study-YP	Age	-0.02	0.59
	Baseline Seizure Frequency (Log-scale)	-0.05	0.51
	Prior AEDs >2	-0.07	0.86
JNJ-topmatpep3001	Age	-1.86	0.11
	Historical Type IC seizures Yes	0.20	0.74
	Baseline Seizure Frequency (Log-scale)	-0.18	0.51
	Prior AEDs >2	-0.69	0.46

The impacts of age and number of prior AEDs are also performed by pooling similar studies in POS subjects. Historical Type IC wasn't included in the model because the 2 LEV studies didn't collect the information. Prior AEDs >2 is statistically significant suggesting subjects with >2 prior AEDs have smaller reduction in seizure frequency from Baseline as compared to subjects with ≤ 2 prior AEDs.

Table 6-4: ANCOVA results for pooled POS studies

Covariate	Estimate	P-value
Age	0.00	0.72
Baseline Seizure Frequency (Log-scale)	-0.05	0.11
Prior AEDs >2	0.23	**0.01**

6.4 Agreement between vEEG and diary seizure counts at the end of the Treatment Period

The agreement between vEEG and diary seizure counts at the 48-hr end of Treatment Period was evaluated. The R-square of the linear regression is low in both JNJ 3001 and UCB N1009 suggesting a lacking of correlation.

Figure 6-1:

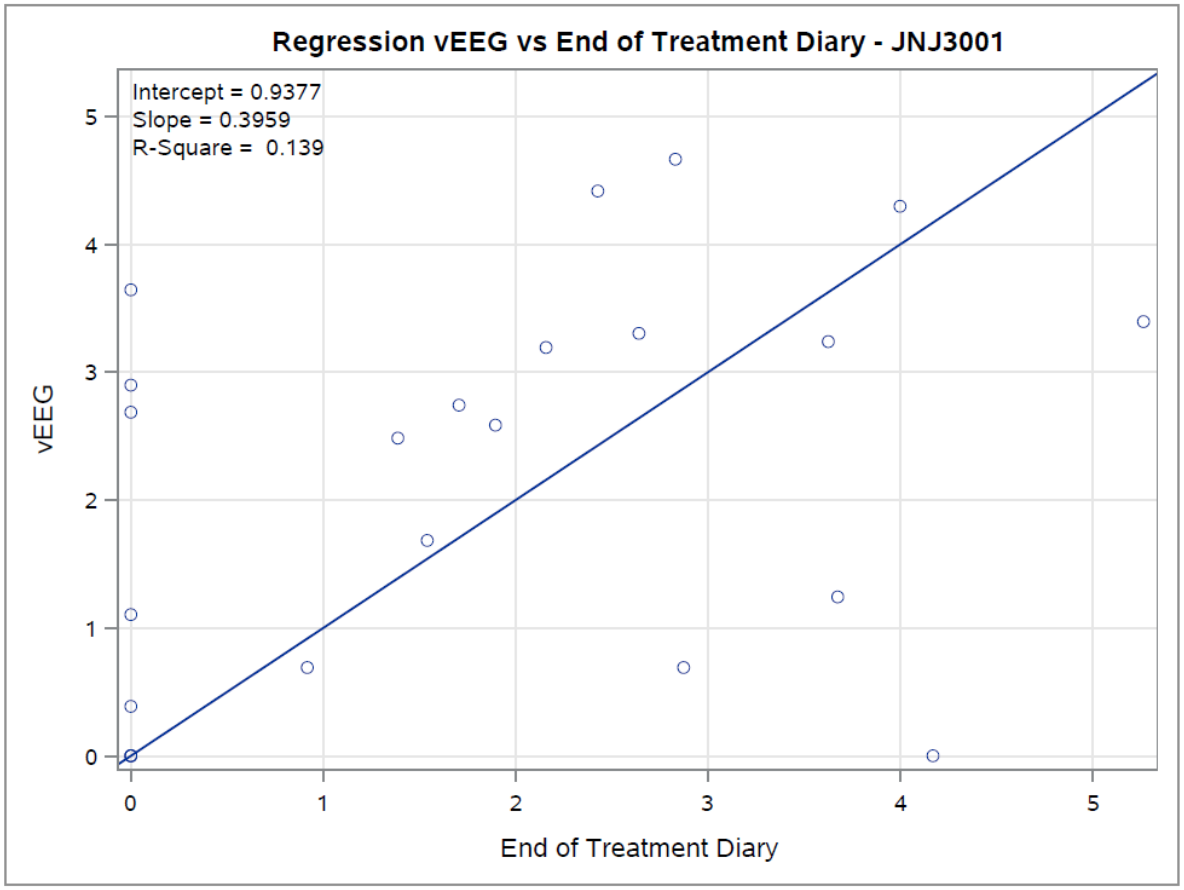
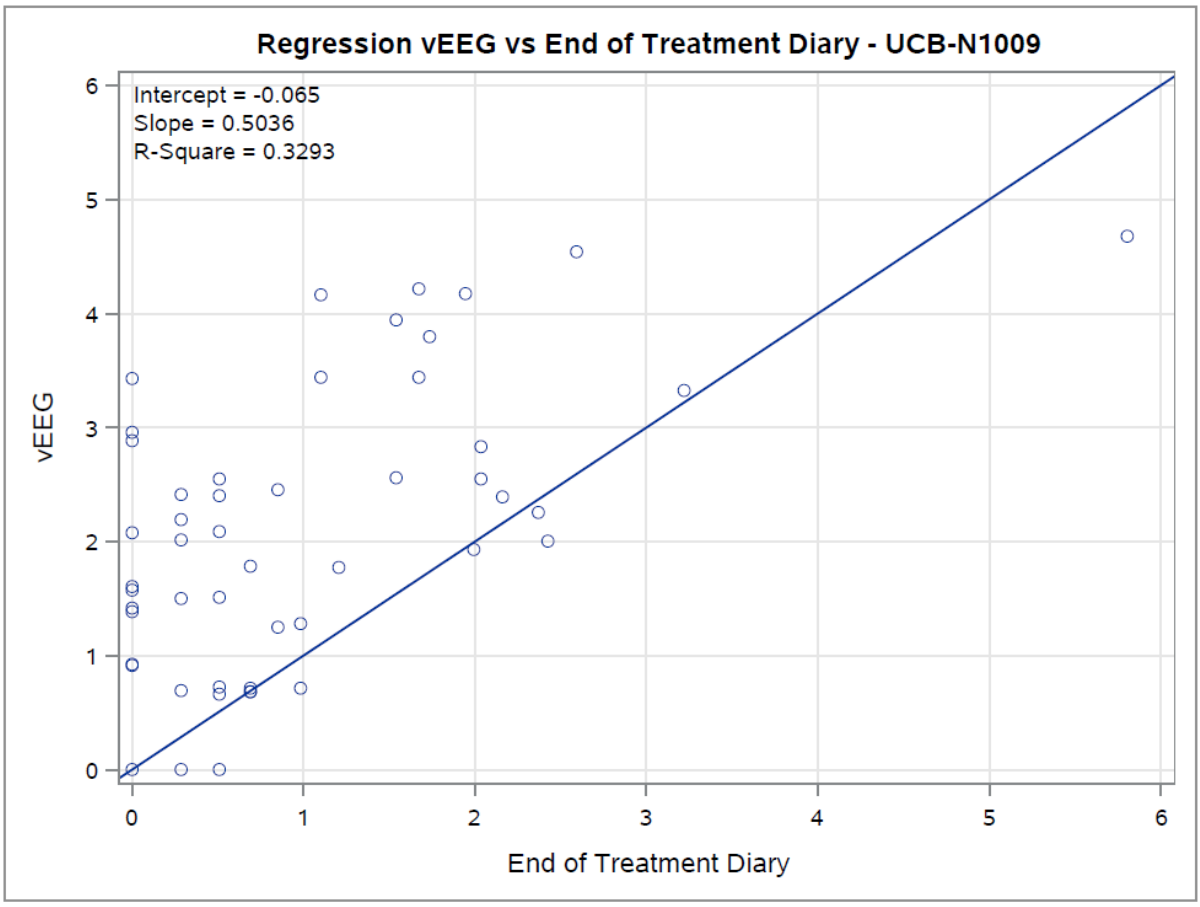

Regression vEEG vs End of Treatment Diary - JNJ3001
Intercept = 0.9377
Slope = 0.3959
R-Square = 0.139
vEEG
End of Treatment Diary
0
1
2
3
4
5

Figure 6-2:



The B&A plot suggest that dairy seizure counts tend to be smaller than vEEG seizure counts.

Figure 6-3:

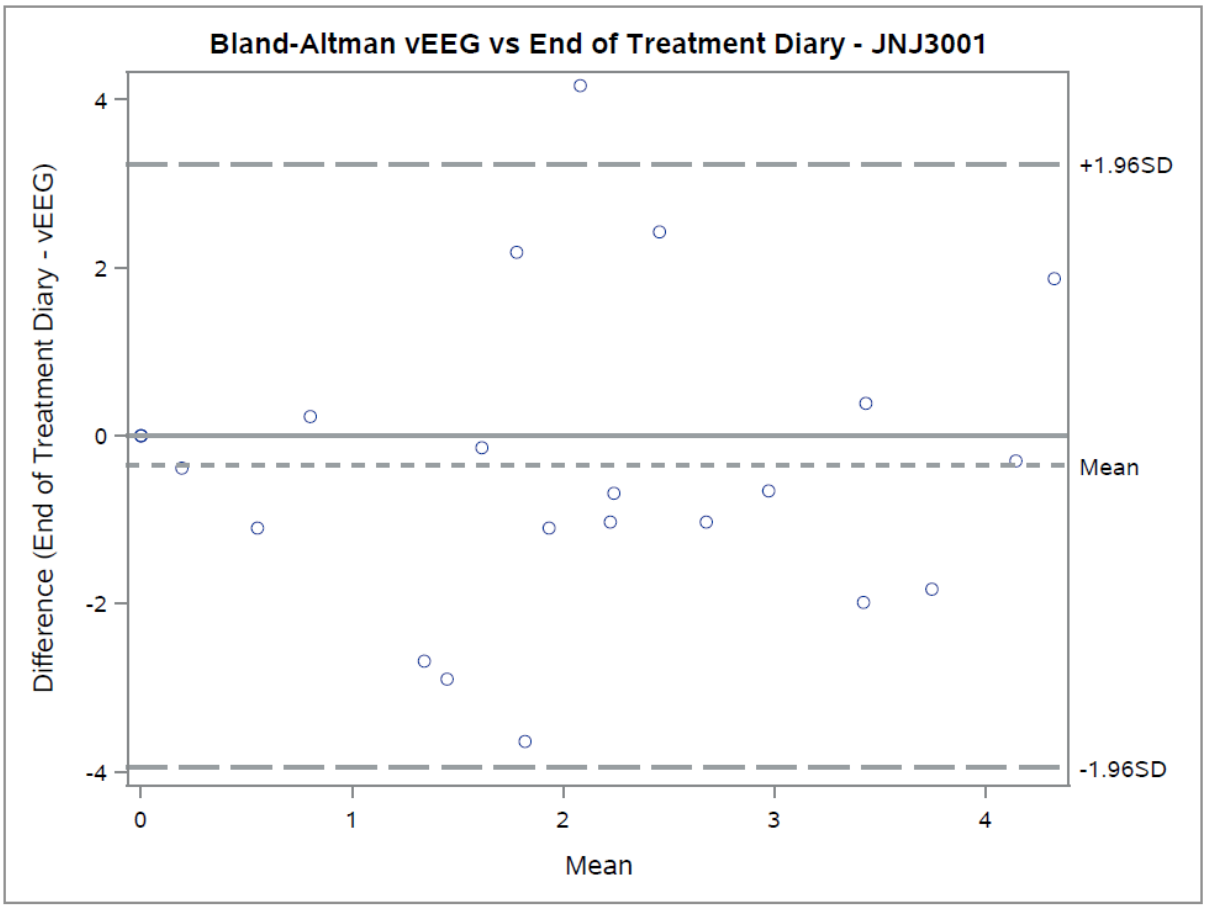
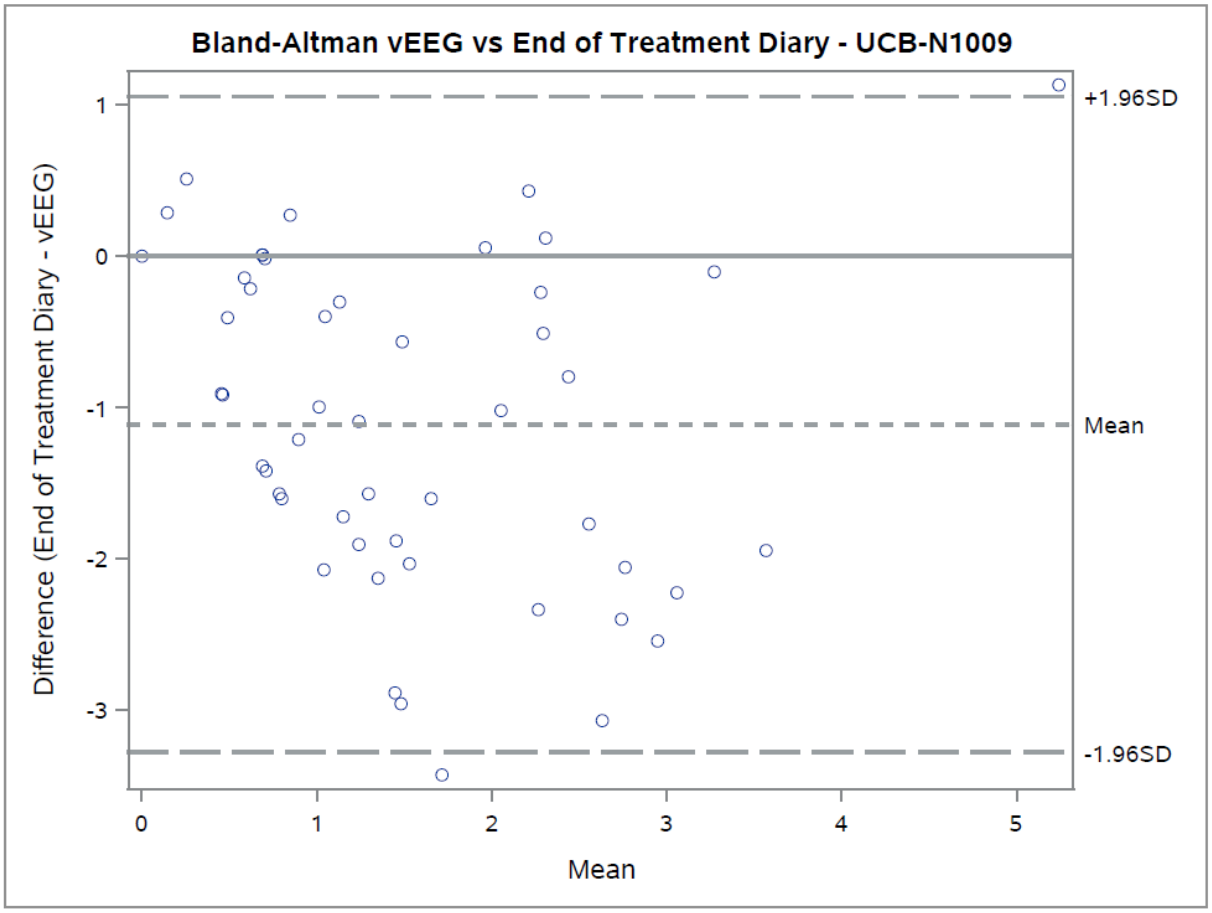

Bland-Altman vEEG vs End of Treatment Diary - JNJ3001
Difference (End of Treatment Diary - vEEG)
4
2
0
-2
-4
+1.96SD
Mean
-1.96SD
0
1
2
3
4
Mean

Figure 6-4:



7 CONCLUSIONS

In patients 4 years or older, the estimated percent reduction in seizure frequency on placebo is 20.8 (95% CI: 9.5 – 30.2); the estimated 50% responder rate is 21.9 (95% CI: 12.5-35.4). The results suggest a potentially large variability in placebo response.

Among the covariates evaluated, number of prior AEDs (≤2 vs >2) has p-values < 0.05 indicating a smaller percent reduction in seizure frequency in subjects with >2 prior AEDs.

In patients < 4 years old, vEEG gave higher seizure counts as compared to diary. Although the measurements are in general agreement but the correlation between the 2 measurements is lacking.

8 REFERENCES

Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. Journal of the Royal Statistical Society Series A (Statistics in Society). 2009; 172(1):137-159.

Giavarina D. Understanding Bland Altman analysis. Biochem Med (Zagreb). 2015; 25(2): 141–151.

9 APPENDICES

9.1 Clinical trials with individual patient data.

Study Index	Seizure Type/ Therapy	Age/Number of Subjects in Placebo Group	Study Design (Year of the Study)	Study Duration	Seizure Freq Endpoint	Publication/ ClinicalTrials.gov registry number	Individual Patient Data Source
Lamotrigine							
LTG1	POS/ Add-on	2-16 yrs/ITT=101	Double blinded, placebo-controlled, parallel group (1994-1997)	8-week baseline period; 6-week escalation period; 12-week maintenance period	weekly seizure frequency	Duchowny, 1999	CSDR (GSK-105-040)
LTG2	POS/ Add-on	≥ 13 yrs /ITT=120	Double blinded, placebo-controlled, parallel group (2004-2006)	8-week baseline period; 7-week escalation period; 12-week maintenance period	weekly seizure frequency	Naritoku, 2007 NCT00113165	CSDR (GSK-LAM100034)
LTG3	POS/ Add-on	1-24 mths /ITT=19	Double blinded, placebo-controlled, responder-enriched design. Subjects who achieved a response during the OL period were randomized to either continued LTG treatment or a gradual withdrawal of LTG (2000-2003).	8 weeks DB period	28-day seizure frequency The primary endpoint was proportion of subjects meeting the pre-defined escape criteria.	NCT00043875	CSDR (GSK-LAM20006)
LTG4	PGTCS/ Add-on	>=13 yrs/ ITT=73	Double blinded, placebo-controlled, parallel group (2004-2008)	8-week baseline period; 7-week escalation period; 12-week maintenance period	weekly seizure frequency	Biton, 2010 NCT00104416	CSDR (GSK-LAM10036)

LTG5	PGTCS/ Add-on	2-55 yrs/ ITT=59	Double blinded, placebo-controlled, parallel group (2001-2004)	8-week baseline period; 7-week (> 12 yrs) or 12-week (2-12 yrs) escalation period; 12-week maintenance period	28-day seizure frequency	Biton, 2005 NCT00043901	CSDR (GSK-LAM40097)
LTG6	Lennox-Gastaut syndrome	3-25 yrs/ ITT=90	Double blinded, placebo-controlled, parallel group	4-week baseline; 6-week escalation period; 10-week maintenance period	weekly seizure frequency	Motte, 1997	CSDR (GSK-105-123)
Levetiracetam							
LEV1	POS/ Add-on	4-16 yrs / ITT=97	Double blinded, placebo-controlled, parallel group (1999-2003)	8-week baseline period; 4-week escalation period; 10-week maintenance period	weekly seizure frequency	Glauser, 2006 NCT00615615	CSDR (UCB-N159)
LEV2	POS/ Add-on	1 - 48 months/mITT= 51	Double blinded, placebo-controlled, parallel group (2004-2007)	48-h inpatient baseline video-EEG and a 5-day inpatient treatment period (1-day up-titration; 48-h evaluation video-EEG in the last 2 days)	vEEG daily seizure frequency	Pina-Garza, 2009 NCT00175890	CSDR (UCB-N1009)
LEV3	POS/ Add-on	4-16 yrs/ITT=34	Double blinded, placebo-controlled, parallel group (2004-2007)	4-week historical baseline; 1-week baseline; 4-week titration; 8-week maintenance	weekly seizure frequency	Levisohn, 2009 NCT00105040	CSDR (UCB-N1103)
Oxcarbazepine							
OXC1	POS/ Mono	1 mths – <17 yrs/ITT=46	Rater blinded, two doses, parallel group (2002-2004)	5-day treatment period	vEEG daily seizure frequency The primary efficacy is based on time	NCT0050934	CSDR (NOVARTIS-CTRI476E2339)

					to meeting one of the exit criteria starting from the first dose of OXC on Day 3.		
OXC2	POS/ Add-on	1 mths – < 4 yrs/ITT=64 (2002-2004)	Rater blinded, two doses, parallel group	9-day treatment period	vEEG daily seizure frequency	Pina-Garza, 2005 NCT00050947	CSDR (NOVARTIS-CTRI476E2340)
Topiramate							
TPM1	POS/ Add-on	2-16 yrs / n=45	Double blinded, placebo-controlled, parallel group	8-week baseline period followed by a 16-week double-blind treatment period	28-day seizure frequency	Elterman, 1999	Yoda (JNJ-Study-YP)
TPM2	POS/ Add-on	1-24 mths/n=37	Double blinded, placebo-controlled, parallel group	3-day screening phase during which the 48-hour baseline vEEG was performed, a 20-day double-blind treatment phase, a 1-year open-label extension	vEEG daily seizure frequency	Novotony, 2010 NCT00113815	Yoda (JNJ-Study-TOPMATPEP3001)