Protocol A0081042

A DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER STUDY OF THE EFFICACY AND SAFETY OF PREGABALIN AS ADJUNCTIVE THERAPY IN CHILDREN 1 MONTH THROUGH <4 YEARS OF AGE WITH PARTIAL ONSET SEIZURES

Statistical Analysis Plan (SAP)

Version: 1 (Final) **Author:** PPD (inVentiv Health Clinical, LLC)
Date: 12-FEB-2014

Version **2 (Amendment 1) Final**
By PPD
Date: **03-Mar-2017**

Version **3 (Amendment 2) Final**
By PPD
Date: **09-Aug-2017**

Version **4 (Amendment 3) Final**
By PPD
Date **02-Mar-2018**

Version **5 (Amendment 4) Final**
By PPD
Date **06-Apr-2018**

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Status of the study when amendments were made: Study is still ongoing and blinded.

Amendment 1 Date: **03-Mar-2017** Version 2	1. The following statement added in Section 3.1 Blinded Sample size re-estimation section: Pfizer and FDA agreed on a proposed sample size of no more than 150 subjects. 2. Reference Section Changed: From: Kieser, M. and Friede, T. (2003). Simple Procedures for Blinded Sample Size Adjustment that Do Not Affect the Type I Error Rate. *Statistics in Medicine,* **32**: 3571-3581. To: Friede, T and Kieser, M. (2011). Blinded Sample Size Recalculation for Clinical Trials with Normal Data and Baseline Adjusted Analysis. *Pharmaceut. Statist.,* **10**: 8-13.	1. To add the cap on sample size of N=150 based on FDA agreement with Pfizer. For study A0081042, FDA agrees with Pfizer's study sample size cap proposal: Archive Record: US20020055 - pregabalin, Pediatric; Post Approval Commitment dated 14-Oct-2016. 2. To update the sample size re-estimation reference.
Amendment 2 Dated 09-Aug-2017 Version 3	1. <u>In the *Statistical Power and Sample Size* section the following statement was added</u> **<u>NOTE: Because the following sample size work occurred prior to study conduct and prior to review of blinded data, this section remains unchanged with respect to the constant 1/28 in the log transformation of the 24-hour seizure rate data and the differences between pregabalin and placebo.</u>** *2.* In sections 6.1.1, 6.4, 8.2.1, Appendix 1, and Appendix 2.2.1, the constant in the log transformation of 24 hour seizure data is changed from "1/28" to "1". 3. Appendix 2.1.1 Blinded Sample Size Re-estimation changed From: Δ is the planned difference (ie, 7 mg/kg/day and placebo) as specified in the protocol (ie, *-0.448*). To: Δ= -0.355 is the planned difference (ie, 7 mg/kg/day and placebo) for the sample	1. Pfizer and FDA agreed to change the transformation of the primary endpoint due to distributional properties of the endpoint as follows: Add the constant "1" rather than "1/28" to the $\log_e$ (24-hour seizure rate) both in the sample size re-estimation (SSRE) plan and the study statistical analysis plan for the primary analysis.

<table>
<tr><td></td><td>size re-estimation. The details for deriving this delta are in the SSRE plan.</td><td></td></tr>
<tr><td>Amendment 3

Dated 02-Mar-2018

Version 4</td><td>Table 2, pooling of region has changed from:

<table><tr><th>Region</th><th>Countries</th></tr><tr><td>North America</td><td>United States</td></tr><tr><td>Europe</td><td>Belgium, Bulgaria, Croatia, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Spain, United Kingdom</td></tr><tr><td>Asia Pacific</td><td>China, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand</td></tr><tr><td>Rest Of World</td><td>Israel, South Africa, Serbia, Turkey, Ukraine</td></tr></table>
To:

<table><tr><th>Region</th><th>Countries</th></tr><tr><td>Asia Pacific</td><td>China, Malaysia, Philippines, South Korea, Taiwan, Thailand</td></tr><tr><td>Rest of the world</td><td>Russia, Ukraine</td></tr><tr><td>North America + Europe + Middle East</td><td>United States, Belgium, Bulgaria, Germany, Spain, France, Greece, Hungary, Romania, Belarus, Israel, Lebanon, Serbia, Turkey</td></tr></table></td><td>In a blinded manner, due to enrolment and distribution of subjects in each country, region pooling needs adjustment to ensure that each region includes a minimally appropriate number of subjects for each treatment.</td></tr>
<tr><td></td><td>Section 8.1.1, 8.1.3 and 8.2.2 has been revised regarding region to reflect table 2 on the revised SAP.</td><td>Adjustment made to account for treatment representation. See previous note.</td></tr>
<tr><td></td><td>Appendix 2.2.3 also has been simplified regarding region pooling</td><td>See previous note.</td></tr>
<tr><td></td><td>Appendix 2.2.1 has been updated to add programming code for Multiple Imputation</td><td>Details added to aid in programming.</td></tr>
</table>

	algorithm.	
	Section 8.1.3 was updated to allow for the removing of any non-treatment factor, from the responder analysis (key secondary endpoint) model if that factor causes non-convergence of the model.	Allowance to remove factor added to ensure program can run.
	Section 8.2.1 (other analyses) and Appendix 2.2.2 were updated to use the appropriate off-set time (V-EEG monitoring time – evaluable time).	Corrected to match with the numerator count time used in the sensitivity analysis.
Amendment 4 Dated 06-Apr-2018 Version 5	Add the following equation in section 6.1.1, 8.2.1 & Appendix 1 for additional presentation of percent reduction of treatment difference relative to placebo $100\% \times \frac{\left[\exp\left(\text{LSMean}(\text{pregabalin})\right) - 1\right] - \left[\exp\left(\text{LSMean}(\text{placebo})\right) - 1\right]}{\exp\left(\text{LSMean}(\text{placebo})\right) - 1}$	Based on FDA recommendation (IND 49393: Pediatric Protocol A0081042 Statistical Analysis Plan), for percent reduction relative to placebo (back transformation estimated treatment difference) for the primary endpoint the SAP will be updated to add additional treatment difference relative to placebo estimation.

The changes in this SAP regarding the use of the constant "1" in the log transformation of the seizure rates supersede the references to "1/28" used in the protocol. In particular, the transformation used for the primary endpoint in the protocol is now replaced in the primary analysis by the transformation used in this SAP. This SAP serves as the final documentation of the transformation used for the primary endpoint and analysis – $\log_e$(double blind 24-hour EEG seizure rate +1).

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicized***. The current protocol version is dated 30 December 2013 (Original).

2.1. Study Design

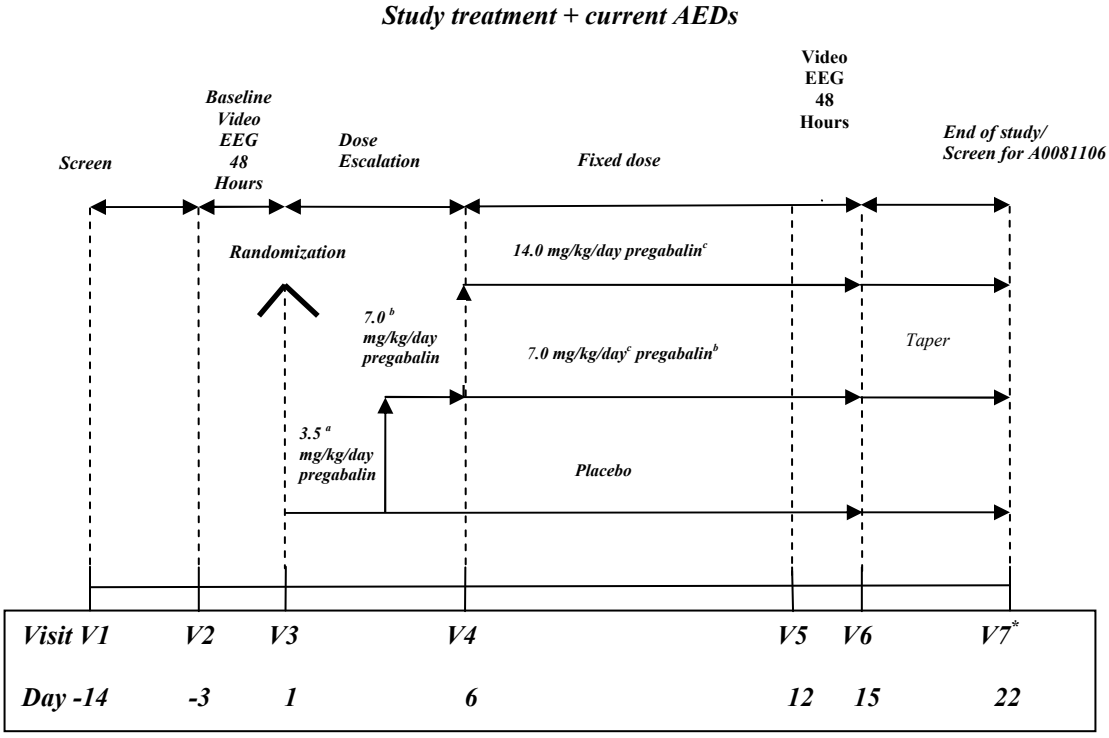
Study A0081042 is a double-blind, placebo-controlled, randomized, parallel group, multicenter study to evaluate efficacy and safety of two dose levels of pregabalin compared to placebo administered TID as adjunctive therapy in pediatric subjects 1 month (44 weeks gestational age) through <4 years of age with partial onset seizures with or without secondary generalization.

The study is composed of 4 phases:

- *Video-Electroencephalographic (EEG) baseline phase with a target minimum of 48 hours. To ensure that the target minimum of 48 hours of Video-EEG is obtained, the total duration of the Video-EEG baseline phase will be up to 72 hours.*
- *5 day double-blind dose escalation phase.*
- *9 day double-blind fixed dose treatment phase, which includes a Video-EEG evaluation over the final 3 days at the end of this 9-day phase with a target minimum of 48 hours and a total recording duration of up to 72 hours. For subjects who successfully complete the target 48 hour Video-EEG or must terminate the Video-EEG recording before the end of this 9-day phase, fixed dosing will continue until beginning the taper phase.*
- *7 day double-blind taper phase.*

The total double-blind treatment phase is 21 days.

Study Design Diagram:



** Eligible subjects may be assessed for screening into study A0081106 and complete end of study activities for A0081042 at Visit 7 (V7)*
[a] [3 mg/kg/day for subjects 1 to 3 months of age];
[b] [6 mg/kg/day for subjects 1 to 3 months of age];
[c] [12 mg/kg/day for subjects 1 to 3 months of age]

Statistical Power and Sample Size

NOTE: Because the following sample size work occurred prior to study conduct and prior to review of blinded data, this section remains unchanged with respect to the constant 1/28 in the log transformation of the 24-hour seizure rate data and the differences between pregabalin and placebo.

A total of approximately 123 subjects will be randomized in this study in a 2:2:1 ratio of placebo, Level 1 and Level 2. This randomization scheme will allow a sufficient number of patients to be studied at each dose level for safety, while providing adequate power of the study to detect a significant effect for dose Levels 1 and 2. Randomization of 123 subjects accounts for a 10% discontinuation rate, with a resulting sample size of the necessary 110 subjects (44 placebo, 44 Level 1, and 22 Level 2).

The sample size rationale is based on the observed difference in $\log_e$ (double-blind 24-hour seizure rate $+\frac{1}{28}$) between pregabalin and placebo. A difference in the least squares means between pregabalin and placebo was estimated to be -0.668 and -0.448 for 600- and 300 mg doses respectively, with a pooled standard deviation (SD) of 0.73. This difference and pooled SD was obtained from a meta analysis of the -34, -11, -09 study data in adult subjects with partial onset seizures.

For the purposes of this study, the same SD is also used to assess the power and sample size requirements for comparing each pregabalin group to placebo. While every effort will be put forth to minimize the variability in conducting this study, a larger than anticipated SD may actually be observed. To address this potential concern, a blinded sample size re-estimation procedure will be applied when approximately two thirds of the subjects that make up initial sample size have the opportunity to complete the study. Details of the sample size re-estimation procedure will be included in Appendix 2.1.1.

Table 1. Power Calculations and Sample Size Assumptions for the Primary Endpoint ($\log_e$ (24-hour seizure rate $+\frac{1}{28}$))

Comparison	*Log Transformed Difference from Placebo*	*Percent Difference from Placebo*	*Number of Pregabalin Subjects*	*Number of Placebo Subjects*	*SD (log transformed 24-hour seizure rate)*	*Power*
Expected difference[1] between Level 2	*-0.668*	*-48.7%*	*22*	*44*	*0.73*	*0.932*
Expected difference[1] between Level 1	*-0.448*	*-36.1%*	*44*	*44*	*0.73*	*0.812*

1 Expected difference is the observed difference between the specified pregabalin dose minus placebo based on a meta analysis of studies -009, -011, and -034 based on the log transformed 24-hour seizure rate.

Level 1 and Level 2 doses are anticipated to result in exposure that approximates 300 mg/day and 600 mg/day, respectively, achieved in adults.

In order to address the primary analysis comparison between placebo and the Level 2 dose group, a sample size of 44 subjects in the placebo group and 22 subjects in the Level 2 dose group will provide at least 90% power to detect a true difference of -0.668 using a two-sided test at the 0.05 level of significance with a standard deviation of 0.73.

In order to address the primary analysis comparison between placebo and the Level 1 dose group, a sample size of 44 in each of these two groups will provide at least 80% power to detect a true difference of -0.448 using a two-sided test at the 0.05 level of significance with a standard deviation of 0.73.

Randomization will be stratified by subject age (Stratum 1: <1 year of age; Stratum 2: 1-2 years of age; Stratum 3: >2 years of age). Subjects in each age stratum within the site will be randomized to either placebo or 1 of 2 fixed doses of pregabalin divided TID, Dose Level 1: pregabalin 7 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age] or Dose Level 2: pregabalin 14 mg/kg/day [12 mg/kg/day for subjects 1 to 3 months of age] in a 2:2:1 ratio. Every reasonable effort will be made to enroll a minimum of 10 subjects in each of the 3 age strata.

2.2. Study Objectives

Primary Efficacy Objective

- *The primary objective of this study is to evaluate the efficacy of two dose levels of pregabalin compared to placebo as an adjunctive treatment in reducing the frequency of partial onset seizures in pediatric subjects 1 month through <4 years of age.*

Secondary Efficacy Objective

- *To evaluate the efficacy of pregabalin compared to placebo on the frequency of partial onset seizures as determined by responder rate in pediatric subjects 1 month through <4 years of age.*

- *To assess the safety and tolerability of pregabalin in pediatric subjects 1 month (44 weeks gestational age) through <4 years of age with partial onset seizures.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

3.1. Blinded Sample Size Re-estimation

While every effort will be put forth to minimize the variability in conducting this study, a larger than anticipated SD may actually be observed. To address this potential concern, a blinded sample size re-estimation procedure will be applied when approximately two thirds of the subjects that make up initial sample size have the opportunity to complete the study (ie, no ongoing subjects will be included in this sample size re-estimation procedure).

The blinded sample size re-estimation procedure for this study will not allow for a reduction in the planned sample size of 123 subjects, however Pfizer and FDA agreed on a proposed sample size of no more than 150 subjects*. The procedure will be conducted by a statistician who is not associated with the study during its conduct or during the final analysis. There*

will be no penalty applied to the final analysis p-values or confidence intervals for assessing treatment difference from placebo due to this blinded sample size re-estimation procedure. Details of the sample size re-estimation procedure will be included in Appendix 2.1.1.

3.2. Interim Safety Analyses

Two Interim Safety Analyses (ISA) will be conducted to assess safety. The timing of the first interim analysis will be when approximately the first one-third of the subjects enrolled (randomized) *have had an opportunity to complete the study. The second ISA will be performed when approximately two-thirds of the subjects have had an opportunity to complete the study. A charter to delineate the safety parameters to be assessed and the general procedures to govern the ISA will be the subject of a separate document.*

The ISA will involve the descriptive review of deaths, SAEs, and discontinuations due to AEs.

Since the ISA may include a review of the seizure data and the primary efficacy endpoint is a function of seizures, if the study is stopped for safety purposes then futility will be declared for efficacy. This strong rule does not require any type I error (alpha) spending penalty for the primary efficacy analysis.

This study will use an External Data Monitoring Committee (EDMC). The DMC will be responsible for conducting these unblinded ISAs and *for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter.* An E-DMC Charter will specify the details of how the safety interim analyses are to be conducted, and how communications between the sponsor and the E-DMC will take place through open and closed meeting sessions. Additionally, the Charter will address the confidentiality of the interim safety information and appropriate measures will be taken to minimize bias so that the integrity of the study is protected. *The recommendations made by the DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.*

3.3. Unblinding and Final Analysis

Blinding codes should only be used for an individual subject and the blind broken only in an emergency situation or when it is critical to guide treatment and care of a given subject for reasons of subject safety. At the initiation of the study, the study site will be instructed on the method for breaking the blind for an individual subject. The method will be either a manual or electronic process. When breaking the blind is required the investigator should contact Pfizer before breaking the blind if possible. When the blinding code is broken for a subject, the reason must be fully documented and entered on the subject's case report form.

Final analyses will be conducted after the database is released.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There will be 2 pair-wise comparisons of interest:

- Level 1: 7.0 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age] – Placebo and,
- Level 2: 14 mg/kg/day [12 mg/kg/day for subjects 1 to 3 months of age] – Placebo.

For the primary analysis which assesses the double blind 24-hour EEG seizure rate, the following step-wise testing procedure will be applied:

- *Step 1: Test the difference between the Level 2 group and placebo.*
  - H_{01}: $\mu_{Level\ 2} - \mu_{Placebo} = 0$
  - H_{a1}: $\mu_{Level\ 2} - \mu_{Placebo} \neq 0$
- *Step 2: Test the difference between the Level 1 group and placebo.*
  - H_{02}: $\mu_{Level1} - \mu_{Placebo} = 0$
  - H_{a2}: $\mu_{Level1} - \mu_{Placebo} \neq 0$

4.2. Statistical Decision Rules

Each dose of pregabalin will be compared to placebo in a pair-wise manner using a sequential step-wise testing procedure to control for multiplicity of testing such that the experiment-wise type I error rate will not exceed the 5% level of significance. *If* H_{01} *is rejected ($p \leq 0.05$) then move to step 2, otherwise claim no difference and stop. If* H_{02} *is rejected ($p \leq 0.05$) then claim a difference for all the comparisons, otherwise claim differences between 14 mg/kg/day and placebo only.*

All other endpoints *inferences will be performed at the nominal level, and may not control the type I experiment wise error rate at 0.05.*

5. ANALYSIS SETS

5.1. Full Analysis Set (mITT)

The efficacy analyses will be performed on the modified intent to treat (mITT) population which consists of randomized subjects who took at least one dose of study drug during the double-blind treatment phase, have a baseline with at least one partial onset seizure identified by Video-EEG and a follow-up Video-EEG. Video-EEG assessments must include at least 24 hours of evaluable monitoring to be eligible for the mITT population. This will be the primary efficacy population.

5.2. 'Per Protocol' Analysis Set

None. Protocol Deviations will be addressed (See Section 5.6) but no PP analyses are planned.

5.3. Safety Analysis Set

The primary analysis set for safety will be the safety population which will include subjects who took at least one dose of the investigational product.

5.4. Other Analysis Sets

5.4.1. ITT Analysis Set

Sensitivity analyses include evaluation of missing data, so the ITT population will include additional subjects not included in mITT, those without a follow-up Video-EEG. The intent to treat (ITT) population will consist of randomized subjects who took at least one dose of study drug during the double-blind treatment phase and have a baseline with at least one partial onset seizure identified by Video-EEG.

5.5. Treatment Misallocations

If a subject was:

- Randomized but not treated, then they are by definition excluded from the efficacy and safety analyses as actual treatment is missing.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but will be reported under the treatment they actually received for all safety analyses.
- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will reported under the treatment they actually received for all safety analyses.

5.6. Protocol Deviations

The list of protocol deviations will be compiled prior to database closure and study unblinding. All deviations will be reviewed and decisions for handling each of the deviations will be made prior to unblinding of the study.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

6.1.1. Primary Efficacy Endpoint

- *The primary endpoint will be the log transformed double blind 24 hr seizure rate for all partial onset seizures collected at Visit 6 (48 hour Video-EEG assessment phase) during the double blind phase as determined by the central reader. This 24-hour seizure rate will be calculated as follows for the double-blind period:*

$$\text{Double Blind 24-hr EEG seizure rate} = \frac{\#\text{ of seizures in double blind 48-hr assessment phase}}{\#\text{ of hours of Video-EEG monitoring}} \times 24$$

- *When the log-transformation is used, the quantity* 1 *is added to the double blind 24-hr EEG seizure rate for all subjects to account for any possible "0" seizure incidence. This will result in the following primary efficacy measure: $\log_e$ (double blind 24-hr EEG seizure rate +*1*). Results will be reported as "percent change in seizures" relative to placebo. For example, a difference between one of the pregabalin doses and placebo of -0.400 on the log transformed scale for the double blind 24-hr seizure rate, translates into a 33% reduction in the double blind 24-hour EEG seizure rate of the pregabalin group from the placebo group (ie, 100%*[exp$^{-0.400}$-1]=-33%]).*

- An additional back transformation will be calculated for percent reduction in seizures for each pregabalin treatment group relative to placebo for presentation in the CSR as follows: $100\% \times \frac{[\exp(\text{LSMean(pregabalin)})-1]-[\exp(\text{LSMean(placebo)})-1]}{\exp(\text{LSMean(placebo)})-1}$

- *A minimum of 24 hours of evaluable Video-EEG will be required to utilize the EEG. In cases where there is less than 24 hours of evaluable Video-EEG, the seizure rate will be set to missing.*

- *The baseline 24-hr EEG seizure rate will be calculated in the same respective manner.*

6.1.2. Secondary Efficacy Endpoints

Responder Rate, defined as subjects who have a ≥50% reduction from baseline in partial seizure rate during the double-blind 48 hour Video-EEG phase. Subjects meeting this criterion will be considered responders.

6.2. Safety Endpoints

The evaluation of safety will include adverse event (AE) data (occurrence, nature, intensity, and relationship to study drug), assessment of clinical laboratory data and the results of physical examinations, vital signs, weight, neurological examinations, and electrocardiograms (ECGs).

6.2.1. Adverse Events

All AEs occurring during the course of the study will be coded using the MedDRA coding dictionary.

All AEs (serious and non-serious) reported during the course of this study from the first day of study treatment through and including 999 calendar days after the last administration of the study drug will be considered treatment emergent AEs (TEAEs). Only AEs captured in this study will be included, and not AEs captured in the 1-year open label safety study.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 8.2.3.1).

6.2.2. Prior and Concomitant Treatments and Medications

Concomitant and prior medications, defined as medications stopped, ongoing or started on or after the first day of study treatment up to the last dose of study treatment, will be summarized, using the WHO-drug coding dictionary. In addition, concomitant and prior non-drug treatments/procedures will be summarized using the MedDRA coding dictionary.

CCI [redacted]

6.4. Covariates

Log-transformed 24-hour seizure rate [$\log_e$(24-hour seizure rate$_b$ + 1)] at baseline will be utilized as a covariate in the linear model used in the primary analysis, and for parametric sensitivity analyses utilizing a similar model. Regarding a non-parametric analysis of covariance based on the rank transformed data, ranked Log-Transformed 24-hour seizure rate at baseline will also be utilized as covariate.

Additional terms considered in the primary analysis and included in the responder rate analysis are age strata and geographic region. Because it is anticipated that this study will have many investigator centers having very few subjects in each treatment group, age strata, and geographic region combination; a pre-specified pooling will take place (See Appendix 2.2.3).

Age strata will be defined as Stratum 1: <1 year of age; Stratum 2: 1-2 years of age; Stratum 3: >2 years of age.

Region pooling will be defined as follows (Upon closing of the randomization, region determinations will be further evaluated-See Appendix 2.2.3):

Table 2. **Description of Stratifying Factors and Their Levels**

Region	Countries
Asia Pacific	China, Malaysia, Philippines, South Korea, Taiwan, Thailand
Rest of the world	Russia, Ukraine
North America + Europe + Middle East	United States, Belgium, Bulgaria, Germany, Spain, France, Greece, Hungary, Romania, Belarus, Israel, Lebanon, Serbia, Turkey

7. HANDLING OF MISSING VALUES

Due to the use of Video-EEG assessments to collect seizure data (at baseline and the end of the double blind period), subjects who discontinue from the study may have no post-baseline efficacy data. If there is missing post-baseline 24-hour seizure rate for more than 5% of any treatment group, then multiple imputation techniques will be applied to the primary analysis model. Specific details are provided in Appendix 2.2.1.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

The mITT population will be used in the analyses of the primary efficacy endpoint, and for all other efficacy endpoints. The Safety population will be used in the analyses of the safety data.

8.1. Statistical Methods

8.1.1. Analyses for Continuous Data

ANCOVA methods will use a linear model with treatment, age stratum, and geographical region (as defined in *Table 2* above) as fixed factor effects, and baseline as a continuous covariate. This linear model will include both dose groups of pregabalin.

- Least square means will be calculated using the observed marginal distribution. Two-sided 95% confidence intervals of the difference between the least square means will be calculated by using the appropriate least square means and their standard errors.

Sensitivity analyses will include non-parametric analyses including analysis of covariance based on the rank transformed data, and a Wilcoxon-Mann Whitney test; and handling of missing data using multiple imputation methods (See Appendix 2.2.1).

8.1.2. Analyses for Count Data

A generalized linear model assuming a Poisson distribution and canonical log link function will be applied to the raw seizure counts (McCullagh and Nelder, 1989 and Stokes et al., 2000).[2,3] Further details will be provided in Appendix 2.2.2.

8.1.3. Analyses for Binary Endpoints

A logistic regression model via maximum likelihood estimation with the following covariates will be performed:

- *treatment group, as a fixed effect;*
- *age stratum, as a fixed effect;*
- *geographical region (as defined in Table 2 above) by pooling of investigator centers, as a fixed effect. If any non-treatment factor causes non-convergence of the model, that factor will be dropped from the model.*

Comparisons will be performed for each pregabalin dose relative to placebo using a maximum likelihood tests and confidence intervals. The definitive statistical summary for treatment group comparisons will be the odds ratios.

8.2. Statistical Analyses

8.2.1. Analysis of Primary Endpoints

The primary analysis will be performed on the primary endpoint, $\log_e$ (double blind 24-hour EEG seizure rate +1), using a linear model with treatment, age stratum, and geographical region (as defined in Table 2 above) as fixed factor effects, and $\log_e$ (baseline 24-hour EEG seizure rate +1) as a continuous covariate. This linear model will include both dose groups of pregabalin. This analysis will be applied for all subjects who satisfy mITT criteria and for data of observed case.

Each dose of pregabalin and placebo will be compared using a sequential step-wise testing procedure. For this analysis, the following steps will be applied*:*

- *Step 1: Test the difference between the Level 2 group and placebo.*
  - H_{01}: $\mu_{Level\ 2} - \mu_{Placebo} = 0$
  - H_{a1}: $\mu_{Level\ 2} - \mu_{Placebo} \neq 0$
- *Step 2: Test the difference between the Level 1 group and placebo.*
  - H_{02}: $\mu_{Level1} - \mu_{Placebo} = 0$
  - H_{a2}: $\mu_{Level1} - \mu_{Placebo} \neq 0$

If H_{01} *is rejected ($p \leq 0.05$) then move to step 2, otherwise claim no difference and stop.If* H_{02} *is rejected ($p \leq 0.05$) then claim a difference for all the comparisons, otherwise claim differences between 14 mg/kg/day and placebo only.*

Least square means will be calculated using the observed marginal distribution. Two-sided 95% confidence intervals of the difference between the least square means will be calculated by using the appropriate least square means and their standard errors. Results will be reported as "percent reduction in seizures" relative to placebo. For example, a difference between one of the pregabalin doses and placebo of -0.400 on the log transformed scale for the 24-hour seizure rate, translates into a 33% reduction in the 24-hour seizure rate of the pregabalin group from the placebo group (ie, 100%[exp$^{-0.400}$-1]= -33%].*

An additional back transformation will be calculated for percent reduction in seizures for each pregabalin treatment group relative to placebo for presentation in the CSR as follows: $100\% \times \frac{[\exp(\text{LSMean(pregabalin)})-1]-[\exp(\text{LSMean(placebo)})-1]}{\exp(\text{LSMean(placebo)})-1}$

Sensitivity Analysis

The same analysis as the primary, except for missing data imputation and analysis set, will be performed as a sensitivity analysis. In this analysis, a multiple imputation technique for missing data will be applied for the ITT population. This sensitivity analysis will only be applied for the ITT analysis set, and all other efficacy analyses will be applied for the mITT analysis set.

A non-parametric analysis of covariance based on the rank transformed data will be performed and evaluated for efficacy results in combination with the primary analysis.

A Wilcoxon-Mann Whitney test will also be performed and reported for the primary endpoint.

Other Supplemental Analyses

The primary analysis of the primary endpoint will be evaluated for violations to model assumptions based on descriptive statistics, box plots and residual plots.

The change from baseline in 24-hour seizure rate, with and without log-transformation, will be analyzed descriptively for each treatment group using tables and plots.

A *generalized linear model assuming a Poisson distribution and canonical log link function will be applied to the raw seizure counts* (McCullagh and Nelder, 1989 and Stokes et al., 2000).[2,3] *The model will have an off-set parameter for the amount of* evaluable *time (ie, log$_e$(*time monitored*)) the subject was* with V-EEG. *Over-dispersion will be investigated, and if it appears to exist for this model, then the scale parameter will be set to the deviance in the Poisson model, and a negative binomial will be also be explored in addition to analyzing the data with a quasi-likelihood function. This analysis will assume missing completely at random, and will assess seizure frequency in relation to the amount of time each subject was at risk relative to their* evaluable hours of V-EEG monitoring. *In addition, this analysis will not be subject to any potential extrapolation of applying the 24 hour seizure rate.* Further details will be provided in Appendix 2.2.2.

8.2.2. Analysis of Secondary Endpoints

A secondary efficacy parameter is Responder Rate, defined as subjects who have a ≥50% reduction from baseline in partial seizure rate during the double-blind 48 hour Video-EEG period. Subjects meeting this criterion will be considered responders.

Subjects who do not meet the favorable responder definition will be considered non-responders. The dichotomized Responder variable will be analyzed using a logistic regression model via maximum likelihood estimation with the following covariates:

- *treatment group, as a fixed effect;*
- *age stratum, as a fixed effect;*
- *geographical region (as defined in Table 2 above) by pooling of investigator centers, as a fixed effect. If any non-treatment factor causes non-convergence of the model, that factor will be dropped from the model.*

Comparisons will be performed for each pregabalin dose relative to placebo using a maximum likelihood tests and confidence intervals. The definitive statistical summary for treatment group comparisons will be the odds ratios.

The responder outcomes will be summarized descriptively by treatment group using counts and percentages.

8.2.3. Analysis of Safety Data

All subjects with at least 1 dose of study medication will be included in the safety analyses. Baseline assessments are done at Day 1 (Visit 3). If Visit 3 data is missing the last available observation prior to start of study treatment is considered as baseline.

No inferential safety analyses are planned. Pfizer safety reporting standards will be utilized for all safety endpoints.

In addition, a summary of the number of days in the study will be presented for each treatment group.

8.2.3.1. Adverse Events

All AEs occurring during the course of the study will be coded using MedDRA coding dictionary.

All AEs (serious and non-serious) reported during the course of this study from the first day of study treatment through and including 999 calendar days after the last administration of the study drug will be considered treatment emergent AEs (TEAEs). Only AEs captured in this study will be included, and not AEs captured in the 1-year open label safety study.

An overall summary of treatment-emergent AEs will be provided. Treatment-emergent AEs will also be summarized by system organ class, preferred term, severity, and relationship to study drug. Summaries and listings of all AEs, SAEs and treatment-related AEs will be

presented in accordance with the current Pfizer Standard Operating Procedures (SOPs) and Best Practices.

The 3-tier Approach for summarizing AEs will be implemented, and events (MedDRA PTs) will be classified into the following tier definitions:

Tier 1: None

Tier 2: Targeted Medical Events (TMEs) identified in the Lyrica Safety Review Plan

- Point estimates and confidence intervals for the risk difference. Risk Difference is computed as Level 1 versus Placebo and as Level 2 versus Placebo.
- AEs will be arranged sorted in descending point estimate of the risk measure.

Tier 3: Standard safety output (no new outputs-see above).

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

8.2.3.2. Laboratory Data (Hy's Law)

A listing of subjects who meet the criteria for Hy's law will be presented.

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

- Subjects with AST or ALT and total bilirubin baseline values within the normal range *who subsequently present with AST or ALT ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 X ULN or not available.*
- *For subjects with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:*
    - *For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).*

- ***Concurrent with***
    - *For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal* ***or*** *≥3 times the upper limit of normal (whichever is smaller).*

8.2.4. Summary of Efficacy Analyses

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Output	Missing Data	Interpretation
Log_e (24-hour seizure rate +1) (DB Phase)	mITT	ANCOVA	Treatment, age strata, region and log-BL log-BL = Log_e (24-hour seizure rate +1) at baseline	Log-Scale - LS mean and 95% CI by treatment group, - LS mean difference from placebo, SE, 95% CI and p-value Original (Back Transformed) - LS Mean and 95% CI by treatment group - "Percent Change in Seizures" Relative to Placebo	OC	Primary Analysis
Log_e (24-hour seizure rate +1) (DB Phase)	ITT	ANCOVA	Treatment, age strata, region and log-BL	Log-Scale - LS mean and 95% CI by treatment group, - LS mean difference from placebo, SE, 95% CI and p-value Original (Back Transformed) - LS Mean and 95% CI by treatment group - "Percent Change in Seizures" Relative to Placebo	MI	Sensitivity Analysis
Log_e (24-hour seizure rate +1) (DB Phase)	mITT	Rank ANCOVA	Treatment, age strata, region and ranked log-BL	Log-Scale - Median by treatment group - LS mean difference from placebo, SE, 95% CI and p-value	OC	Sensitivity Analysis
Log_e (24-hour seizure rate +1) (DB Phase)	mITT	Wilcoxon-Mann Whitney Test		Log-Scale N, Mean, SD, Median, Min, Max, 25%, 75%, Test Statistics and p-value	OC	Sensitivity Analysis
Log_e (24-hour seizure rate +1)	mITT	Descriptive		N, Mean, SD, Median, Min,	OC	Evaluation for

Endpoint	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Output	Missing Data	Interpretation
(BL, DB and Chg. from BL)		Statistics		Max, 25%, 75%, Skewness and Kurtosis		violations to model assumption
Log_e (24-hour seizure rate +1) (BL, DB and Chg. from BL)	mITT	*Plot*		Box Plot and Histogram of endpoint by Treatment Group	OC	Evaluation for violations to model assumption
Log_e (24-hour seizure rate +1) (DB Phase)	mITT	ANCOVA (*Plot*)	Treatment, age strata, region and log-BL	Residual Plot of Primary Analysis	OC	Evaluation for violations to model assumption
Responder Rate	mITT	Logistic Regression	Treatment, age strata, and region	Odds Ratio, 95% CI and p-value	OC	Secondary Endpoint
Responder Rate	mITT	Descriptive Statistics		N^1, n^2 and %	OC	Secondary Endpoint
Raw Seizure Count	mITT	GLM	Assumption of a Poisson distribution and canonical log link function	Goodness of Fit, maximum likelihood estimates, least squares means, and p-values	OC	Supplemental Analysis

BL: Baseline, DB: Double Blind, OC: Observed Case, MI: Multiple Imputation, GLM: Generalized Linear Model

1: N is number of mITT subjects.
2: n is number of responder subjects.

9. REFERENCES

1. Friede, T and Kieser, M. (2011). Blinded Sample Size Recalculation for Clinical Trials with Normal Data and Baseline Adjusted Analysis. *Pharmaceut. Statist.,* **10**: 8-13.

2. McCullagh, P. and Nelder, J.A. (1989). *Generalized Linear Models*, Second Edition, New York: Chapman & Hall/CRC.

3. Stokes, M.E., Davis, C.S., and Koch, G.G. (2000). *Categorical Data Analysis Using the SAS System*, Second Edition, Cary, NC: SAS Institute.

10. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Endpoint	Derivation
24-hour seizure rate at baseline (b) phase (Count/24 hours)	24-hour seizure $rate_b$= [(# of $seizures_b$) ÷ (#of $hours_b$ of Video- EEG monitoring)] × 24
24-hour seizure rate at double-blind treatment (t) phase (Count/24 hours)	24-hour seizure $rate_t$= [(# of $seizures_t$) ÷ (#of $hours_t$ of Video- EEG monitoring)] × 24
Primary endpoint: Log_e of 24-hour seizure rate at double-blind treatment phase	Log_e (24-hour seizure ratet +1)
Log transformed baseline 24-hour seizure rate	Log_e (24-hour seizure rate +1) at baseline
"Percent reduction in seizures" relative to placebo	Example: A difference between one of the pregabalin doses and placebo of -0.400 on the log transformed scale for the 24-hour seizure rate translates into a 33% reduction in the 24-hour seizure rate of the pregabalin group from the placebo group (ie, 100%*[$exp^{-0.400}$ -1]= -33%) An additional back transformation will be calculated for the percent reduction in seizures for each pregabalin treatment group relative to placebo for presentation in the CSR as follows: $100\% \times \frac{[\exp(\text{LSMean(pregabalin)})-1]-[\exp(\text{LSMean(placebo)})-1]}{\exp(\text{LSMean(placebo)})-1}$
Change from baseline in 24-hour seizure rate	Change = 24-hour seizure $rate_t$ -24-hour seizure $rate_b$.
Percent change from baseline in 24-hour seizure rate for calculation of responders	% Change = [24-hour seizure $rate_t$ -24-hour seizure $rate_b$)/24-hour seizure $rate_b$] × 100
Responders	≥50% reduction in the 24-hour seizure rate from baseline during the double-blind 48 hour Video EEG period, then response = 1 (responder) otherwise response = 0 (non-responder)

Appendix 2. STATISTICAL METHODOLOGY DETAILS

Appendix 2.1. Further Details of Interim Analyses

Appendix 2.1.1. Blinded Sample Size Re-estimation

The sample size re-estimation formula of Friede and Keiser (2011)[1] for this study is the following:

$$N = \frac{(1+\gamma)^2}{\gamma}(z_{1-\alpha/2} + z_{1-\beta})^2 \frac{(1-\rho^2)\sigma_Y{}^2}{(\Delta^*)^2}$$

where,

$N=N_A + N_B$, $N_B= \gamma^* N_A$ and z_p is the p-quantile of the standard normal distribution; $z_{1-\alpha/2}$ is a percentile from a standard normal cdf with $\alpha/2=0.025$; $\gamma=1$ assumes equal sample sizes; for this study the two groups are placebo and 7 mg/kg/day which are in 1:1 ratio.

$z_{1-\beta}$ is a percentile from a standard normal cdf with $\beta=0.20$;

ρ = correlation between primary endpoint and baseline;

$\sigma^2 = (1-\rho^2)\sigma_Y{}^2$

$\tilde{s}^2$ is the unbiased estimate of σ^2, which can be shown to equal the residual variance.

Δ= -0.355 is the planned difference (ie, 7 mg/kg/day and placebo) for the sample size re-estimation. The details for deriving this delta are in the SSRE plan.

The Guenther adjustment for equal sample sizes per group, leads to the final computation:

$$N_G = N + \frac{(z_{1-\alpha/2})^2}{2}$$

$n^* = N_G/2$; where n^* is the number of subjects per group (rounded to the nearest integer) for Pregabalin 7 mg/kg/day and placebo. Since the randomization ratio for this study is 2:2:1 for (Placebo: pregabalin 7 mg/kg/day: pregabalin 14 mg/kg/day), the number of subjects for pregabalin 14 mg/kg/day will be $n^*/2$, and 2.5 x n^* is the total subjects.

The pooled blinded estimate of the variance, $\tilde{s}^2$, will be based in a blinded manner without making any correction for possible treatment group differences after the 1st approximately 2/3 of the planned 123 subjects have had the opportunity to complete the study. Since baseline 24-hour seizure rate, age strata, and geographical region are important pre-specified modeling terms that explain sources of variability in the data, the estimate $\tilde{s}^2$ will take into consideration these three modeling terms as the mean squared error. While this pooled estimate of the variance under the null hypothesis will be biased upwards, this bias is negligible when the overall sample is reasonably large. The proposed blinded sample size re-estimation procedure will only allow for a new sample size (n_{New}) to be increased beyond

the initial targeted sample size ($n_{Initial}$). The n_{New} is estimated to keep at least the power of 0.8 for comparison of between Dose Level 1 and Placebo when estimated SD is larger than initial SD. In addition, the n_{New} is also estimated to keep the randomization ratio of Placebo, Dose Level l, Dose Level 2 in 2:2:1. The proposed blinded sample size re-estimation procedure will only allow for a new sample size (n_{New}) to be increased beyond the initial targeted sample size ($n_{Initial}$), but not beyond the pre-determined maximum sample size (n_{Max}=150).

Appendix 2.2. Further Details of the Statistical Methods

Appendix 2.2.1. Analysis Strategy Using Multiple Imputations

Multiple imputation procedure is used under the assumption of missing at random (MAR) data. The goal of the imputation strategy is to produce a completed dataset. This dataset has two time points, baseline and on study. The pattern of missing data is implicitly, monotone. It is likely that little or no data is missing at baseline. In general, let Y be the response data [$\log_e$(double blind 24-hour EEG seizure rate +1)] where that part of $\mathbf{Y}$ which is missing is denoted by $\mathbf{Y}_{mis}$, and that part of $\mathbf{Y}$ which is observed is denoted by $\mathbf{Y}_{obs}$. A data pattern is said to have a missing monotone data pattern when the variable $\mathbf{Y}_j$ for an individual subject is missing at time point j, and all subsequent variables for that individual are also missing for $\mathbf{Y}_k$ in which k>j. In this data there are only two assessment time points, baseline and the on-study measurement.

The three steps for conducting statistical inferences using a multiple imputation procedure consist of the following:

Imputation step: Missing data are filled in m times to generate m complete data sets, where m >1; for this study, m will take on the value 5.

Analysis step: The m complete data sets are analyzed using standard procedures.

Combination step: The results from the m complete data sets are combined for the final statistical inference.

The imputation step is perhaps the most critical, since it relies upon assumptions regarding the missing data mechanism. The goal of the imputation is to account for the relationships between the unobserved and observed variables, while taking into account the uncertainty of the imputation. The MAR assumption is key to the validity of multiple imputations. Use of this assumption allows the analyst to generate imputations ($\mathbf{Y}_{\{1\},}\mathbf{Y}_{\{2\},}$ . . .$\mathbf{Y}_{\{m\}}$) from the distribution $f(\mathbf{Y}_{mis}|\mathbf{Y}_{obs})$, since after conditioning on $\mathbf{Y}_{obs}$, the missingness is assumed to be due to chance and is considered ignorable. In this application, we will use the regression method in which the variable Y_j with missing values is fitted with non-missing observations as the dependent variables. This allows for the following regression model to be employed:

$\mathbf{Y}_0 = \beta_{0;}$ and $\mathbf{Y}_1 = \beta_0 + \beta_1 * \mathbf{Y}_1$.

The fitted model has parameter estimates (b_0, b_1) and the associated covariance matrix $s^2_j V_j$, where V_j is the usual $X^T X$ matrix from the intercept and variable $\mathbf{Y}_1$.

For each imputation, new parameters (β^*_0, β^*_1; and σ^{*2}) are drawn from a posterior predictive distribution of the missing data. The missing values of Y_j are then replaced with the predicted values using the following equation:

$$\beta^*_0 + \beta^*_1 * y_1 + z_i * \sigma^{*2}$$

where y_1 is the covariate value for the first variable and z_i a simulated standard normal deviate for the i^{th} individual.

The next step is to carry out the analysis of interest for each of the *m* imputed complete-observation datasets, storing the parameter vector and standard error estimates.

Finally, the results are combined using results from Rubin (1987) to calculate estimates of the within imputation and between imputation variability. These statistics account for the variability of the imputations and assuming that the imputation model is correct, provide consistent estimates of the parameters and their standard errors. The imputation model need not be exactly correct and the MI will provide these consistent estimates. The following are additional information and suggested code that can be used for MI:

In this appendix, we will assume that data are stored in a SAS dataset, with the following variables. Note that the variable names/labels are suggestions only and the actual names/labels and code levels should be consistent with current sponsor reporting standards.

SUBJID: subject identification number.

REGION and AGE_STRATA.

TRT: Treatment group (Placebo, Pregabalin 7.0 mg/kg/day, Pregabalin 14.0 mg/kg/day).

LN_BSZRT: A $\log_e$ transformed baseline seizure rate $\log_e$(Baseline 24-hour seizure rate_b +1).

LN_SZRATE: A $\log_e$ transformed double-blind seizure rate $\log_e$(Double blind 24-hour seizure rate_t +1).

IMPSTAT: Impstat = 1 if DC due to AE, death, or insufficient clinical response. Impstat = 2 otherwise.

MISS: Miss = 1 if ln_szrate is missing. Miss = 0 otherwise.

In order to impute missing data at the singular time point and based on the definition of the link function, first prepare an input dataset, making sure that it will contain only the intended donor and recipient patterns. Separate the input dataset **<efficacy>** into two datasets: IMP, containing all placebo subjects and those subjects from the pregabalin arms that have missing LN_SZRATE [Miss=1] and Impstat=1; and REST, containing the rest of the subjects from the pregabalin arms (those with non-missing LN_SZRATE [Miss=0] or Impstat=2).

title1 'Pattern Imputation based on reason for DC';

```
*these sets are exhaustive and mutually exclusive;
data IMP REST;
  set <efficacy>;
  if trt ne “Placebo” and (impstat = 2 or   miss = 0) then output REST;
  if trt =   “Placebo” or   (impstat = 1 and miss = 1) then output IMP;
run;
```

Call PROC MI to impute missing data at the time point using dataset IMP as input.

```
*order of variables matters in proc mi;
proc mi data = IMP out = impout nimpute=100 seed = 233;
  class region age_strata;
  var region age_strata ln_bszrt ln_szrate;
  monotone regression(ln_szrate = ln_bszrt region age_strata);
run;
```

Call PROC MI to impute missing data at the time point using dataset REST as input.

```
*impute like randomized trt for active who are 'ignorably missing';
proc mi data = REST out = restout nimpute=100 seed = 238 ;
  class region age_strata trt ;
  var region age_strata trt ln_bszrt ln_szrate ;
  monotone regression(ln_szrate = trt ln_bszrt region age_strata) ;
run;
```

Assemble back a dataset containing all subjects.

```
*fully imputed integrated dataset;
data main ;
 set impout restout ;
run ;
proc sort data = main ;
 by _imputation_ trt ;
run ;
```

```
*Analysis of imputed data sets;
* Confirm the ordering of the trt variable for specifying the vector.  Here it is assumed
Placebo, Pregabalin 7.0 mg/kg/day, and Pregabalin 14.0 mg/kg/day ;
proc glm data=main;
 by _imputation_ ;
 class region age_strata trt ;
 model ln_szrate = trt region age_strata ln_bszrt ;
 lsmeans trt / diff=control('Placebo') tdiff pdiff cl;
 estimate ‘Pregabalin 7.0 mg/kg/day vs Placebo’ trt -1 1 0 ;
 estimate ‘Pregabalin 14.0 mg/kg/day vs Placebo’ trt -1 0 1 ;
 ods output lsmeans=lsm diffs=lsdiff estimates=estdiffs ;
run ;
```

```
quit ;

*integrated summary of results of imputed datasets, please note the degree of freedom
(XXX) should come from MSE of GLM model above;
proc mianalyze parms(classvar=full)=lsm  edf=XXX;
  class trt ;
  modeleffects trt ;
run ;
proc sort data = estdiffs ;
  by parameter _imputation_ ;
run ;
proc mianalyze data=estdiffs edf=XXX;
  by parameter ;
  modeleffects estimate ;
  stderr stderr ;
run ;
```

Appendix 2.2.2. Analysis Strategy Using a Poisson Model

Poisson Distributions often arise from a Counting process

- Seizure counts as a random variable Y
  The expected value of the seizure counts is $E(Y) = \mu$
  The variance of the seizure counts is $Var(Y) = \mu$

Generalized Linear Model for Seizure Counts with equal duration

- $g(\mu) = \ln(\mu) = \alpha+X\beta$
  Distribution is Poisson
  Link function $g(\mu)$ is the natural log
  In other words $\mu = \exp(\alpha+X\beta)$

Incorporating exposure/V-EEG monitoring time (T) in the Model

- Off-setting the exposure/V-EEG monitoring time by ln(T)
- $\ln(\mu/T) = \alpha+X\beta$
- $\mu = T \cdot \exp(\alpha+X\beta)$
- Adjust for unequal exposure/V-EEG monitoring times among treatment groups

Exposure/V-EEG monitoring time, T, is based on observed V-EEG monitoring time (evaluable hours).

If the 'Criteria For Assessing Goodness Of Fit' section of the output indicates that the value/df for both deviance and Pearson Chi-Square statistics is numerically much higher than 1 (ie, value/df >1.5), then Poisson model is not quite adequate to describe the counts of seizures. This lack of fit is termed over-dispersion, and it indicates that the data contains more variability than what the model is explaining. While the maximum likelihood estimators for the fixed effect from the Poisson model are still consistent when over-dispersion is present, the variance is biased downward. Thus, statistical tests may lead to higher type I error rates (ie, p-values are smaller than what they should be) if over-dispersion was not present.

If over-dispersion is determined based on the threshold criteria above, a common statistical strategy of fitting quasi-likelihood and negative binomial models will be employed. A scale parameter (Scale=deviance, the dispersion parameter is estimated by the deviance divided by its degrees of freedom) will be specified to fit the overdispersed Poisson and negative binomial distributions, if warranted.

Appendix 2.2.3. Pooling

Pooling of sites will be determined prior to unblinding of the study. Any investigator center having less than 2 subjects in any given treatment group or efficacy outcome category within each strata will be defined as a 'small' center. The pooling of small centers will be based on the total number of subjects randomized at each center. Small centers will be pooled to large centers within the same country. When there are only small centers within a given country, small centers will be pooled to large centers within the same region.