Protocol A0081105

A randomized, double-blind, placebo-controlled, parallel group, multi-center trial of pregabalin as adjunctive therapy in pediatric and adult subjects with primary generalized tonic-clonic seizures

Statistical Analysis Plan (SAP)

Version: 4.0

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Date: 18 March 2019

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APPENDICES

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

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

Final Date: 04-Jan-2013 Version 1.0	1. This is the first SAP for protocol A0081105.	1. N/A
Amendment 1 Date: 21-Apr-2017 Version 2.0	2. Updated to the reference of the blinded sample size formula of Friede and Kieser (2011) to apply the latest methodology with considering covariate of continuous data under Section 2.2, References, and Appendix 6. 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. 3. Added the description to explain the procedure for final analysis and unblinding under Section 3.2. 4. Revised the analysis of pattern mixture model under Section 7, Reference, and Appendix 4. 5. Added to calculate odds ratio with 95% confidence interval of responder rate and added the explanation of SAS code for p-value calculation under Section 8.2.	2. To update the sample size re-estimation reference. 3. To match protocol procedure. 4. To replace multiple imputation analysis method consistent with A0081041 and A0081042. 5. To add detailed specification of the responder analysis with SAS code.

[redacted]

Amendment 2 Date: 01-Mar-2019 Version 3.0	1. Add the following equation in Section 6.1, Section 8.1, and Appendix 1 for additional presentation of percent reduction of treatment difference relative to placebo: $100\% \times \frac{[\exp(\text{LSMean(pregabalin)}) - 1] - [\exp(\text{LSMean(placebo)}) - 1]}{\exp(\text{LSMean(placebo)}) - 1}$ 2. Amended the seizure type for evaluation from partial seizures to PGTC seizures under Section 6.1.3.4. 3. Removed cognitive testing of safety endpoint under Section 6.2. 4. Added a sensitivity analysis with age group (5-16 years of age and 17-65 years of age) as a covariate in Section 8.1. 5. Added a supplemental analysis with treatment-by-age group (5-16 years of age and 17-65 years of age) interaction term in the ANCOVA model in Section 8.1. 6. Updated geographical region definition under Section 6.4 with consideration of enrollment by country based on SSR dataset, and updated the definition to remain consistent under Section 8.1. 7. Moved supplemental analysis detail from Section 7 to Section 8. 8. Updated a sensitivity analysis of pattern mixture model of multiple imputation under Section 8.1, Section 8.5 and Appendix 4. 9. Updated dependent variable of ranked ANCOVA and Wilcoxon-Mann Whitney test from "log-transformed 28 day seizure rate" to "change from baseline to double blind phase of log-transformed 28	1. This back transformation was requested by FDA for A0081042. It is added to be consistent with A0081042. 2. Correction, consistent with the protocol-specified population. 3. Cognitive testing was not included in the study protocol. 4. To differentiate results in pediatric vs adult population. 5. Specified in the protocol. 6. Based on actual enrollment. 7. Editorial changes. 8. Added more details with multiple imputation. 9. To be consistent with A0081042 analyses and to be able to adjust the model for any baseline seizure imbalance. 10. The plot is not necessary as the interaction is

[redacted]

	day seizure rate" under Section 8.1. 10. Removed the possibility of forest plot to evaluate interaction by age under Section 8.1. 11. Updated the analysis with Poisson and negative binominal models with considering baseline seizure count as a covariate and Pearson as the scale parameter (Poisson model only) under Section 8.1, Section 8.5 and Appendix 5. 12. Updated the analysis of the proportion of seizure-free days for each seizure type from logistic regression to ANCOVA analysis under Section 8.3. 13. Clarified the definition of proportion of subjects with PGTC seizure-freedom in Section 6.1.3.3. 14. Added clarification regarding seizure free days and proportion of seizure free days in Section 6.1.3.1. 15. Clarified the definition of number of 12 week adjusted seizure free days gained in Section 6.1.3.2. 16. Added contingency plan in case the primary analysis model fails due to covariates of region and age strata in Section 8.1. 17. Added a secondary analysis based on combined European Union and US 18. Added clarification of responder rate	analytically checked by ANCOVA model 11. To be consistent with A0081042 analyses, to adjust for baseline seizure imbalance in the model (Pearson as the scale parameter). 12. To correct an error in the analysis model in the previous SAP. 13. To be consistent with adult PGTC seizure-freedom definition used in past pregabalin studies. 14. To add detailed specifications. 15. To add detailed specifications. 16. To make analysis viable in case small numbers of subjects in certain region(s) and/or age strata cause any issue with analysis model. 17. Based on blinded number of subjects across countries, US enrolled only 5 subjects 18. Make the definition of responder rate more clear
Date: 18-Mar-2019	1. Revised responder definition in Appendix I	1. To make the definition of responder rate consistent with adult

[redacted]

Version 4.0		study's definition.

2. INTRODUCTION

Protocol A0081105 is a randomized, double-blind, parallel-group, placebo-controlled, multi-center trial in subjects 5 to 65 years of age with PGTC seizures. This study will evaluate the efficacy of 2 dose levels of pregabalin [Dose Level 1: pregabalin 5 mg/kg/day (maximum 300 mg/day) or Dose Level 2: pregabalin 10 mg/kg/day (maximum 600 mg/day), administered BID] compared with placebo.

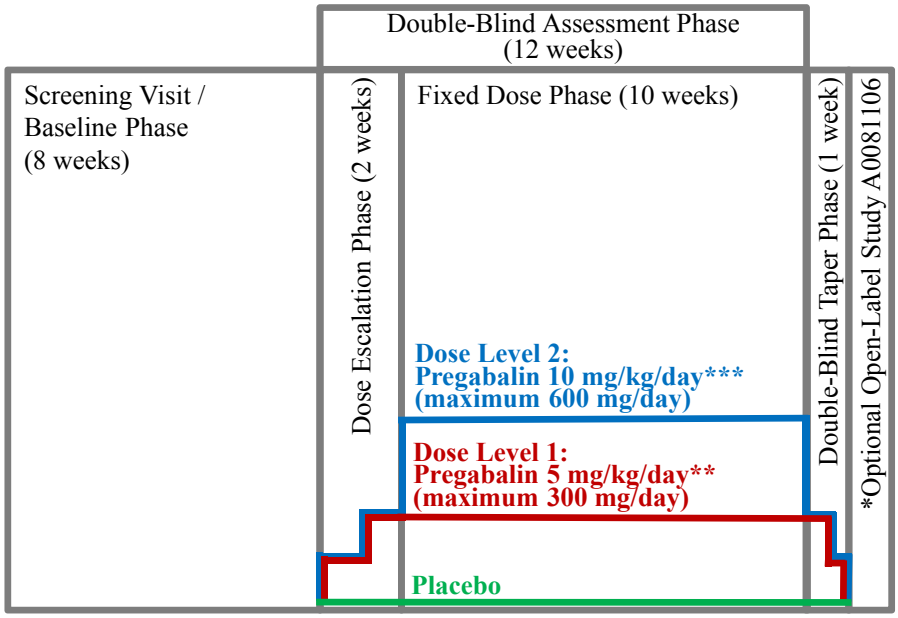
2.1. Study Design

This study will consist of an 8-week baseline phase, a 12-week double-blind assessment phase (including a 2-week double-blind dose escalation phase and a 10-week double-blind fixed dose phase), and a 1-week double-blind taper phase. Eligible subjects will be randomly assigned to receive double-blind treatment with 1 of 2 dose levels of pregabalin or placebo. Study drug treatments are to be taken orally twice daily (BID) in equally divided doses for 12 weeks during the double-blind assessment phase and then 1 week double-blind taper. Subjects who complete the double-blind phase of this trial may be eligible for screening for a 1-year open-label pregabalin safety study.

A total sample size of 168 subjects (ie, 56 subjects per group) is needed to have been randomized, received treatment and had a baseline and post baseline efficacy assessment. Randomization will be stratified by site and subject age (Stratum 1: 5-7 years of age; Stratum 2: 8-11 years of age; Stratum 3: 12-16 years of age; Stratum 4: 17-65 years of age). Subjects in each age stratum within site will be randomized to a fixed dose of either placebo, Dose Level 1: pregabalin 5 mg/kg/day (maximum 300 mg/day) or Dose Level 2: pregabalin 10 mg/kg/day (maximum 600 mg/day) in a 1:1:1 ratio. Approximately 30% of planned enrollment (approximately 50 subjects) will be subjects <17 years of age. Every reasonable effort will be made to enroll a minimum of 12 subjects in each of the 4 age strata.

[redacted]

Study Design Diagram:



Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Week	-8	-4	0	1	2	3	6	9	12	13
Day	-56	-28	1	8	15	22	43	64	85	92
Window (days)	±3	±3	0	±3	±3	±3	±3	±3	±3	±3

Randomization

*Eligible subjects may be assessed for a 1-year open-label pregabalin safety study (Study A0081106) and complete end of study activities for A0081105 at Visit 10 (V10).

** Dose Level 1: 7 mg/kg/day for pediatric subjects <30 kg and 300 mg/day for subjects ≥17 years of age.

*** Dose Level 2: 14 mg/kg/day for pediatric subjects <30 kg and 600 mg/day for subjects ≥17 years of age.

Phone visits are also scheduled for Study Days 3, 10, 17, and 89 (each with a ±3 day window).

2.2. Statistical Power and Sample Size

A total sample size estimate of 168 subjects allows for the evaluation of efficacy using the primary endpoint, $\log_e$ (28-day seizure rate + 1), for making comparisons between placebo vs. 5 mg/kg/day pregabalin (maximum 300 mg/day; Dose Level 1), and placebo vs. 10 mg/kg/day (maximum 600 mg/day; Dose Level 2) pregabalin groups for the treatment period of the study. The following sample size assumptions and corresponding power calculations are provided in Table 1 below. This sample size will also allow for a general assessment of safety and tolerability.

[redacted]

Table 1. Power Calculations and Sample Size Assumptions with 56 Subjects per Group for the Primary Endpoint (loge (28-day seizure rate + 1)

Comparison	*Log Transformed Difference from Placebo*	*Percent Difference from Placebo*	*SD (log transformed 28 day seizure rate)*	*Power*
Expected difference[1] between 600 mg/day and placebo	*-0.534*	*-41.4%*	*0.73* *0.67*	*0.970* *0.984*
Expected difference[1] between 300 mg/day and placebo	*-0.358*	*-30.1%*	*0.73* *0.67*	*0.742* *0.800*

[1] *Expected difference is 80% of the observed difference between the specified pregabalin dose minus placebo based on a meta-analysis of Studies 1008-009, 1008-011, and 1008-034 based on the log transformed 28 day seizure rate, with 300 mg/day only in Study 1008 -034.*

The primary statistical analysis will model the log transformed 28 day seizure rate, and compare each dose of pregabalin to placebo in a step-wise manner, starting with the highest dose of pregabalin. Since there is a significant dose response of pregabalin, the power to detect expected differences for each pregabalin dose relative to placebo will be different. Hence, this step-wise testing procedure will provide maximum power as well as control for multiplicity of testing at the desired 0.05 level of significance for the primary analysis.

Based on a meta-analysis of double-blind placebo controlled adult adjunctive therapy studies (Studies 1008-009, 1008-011, and 1008-034) using the log transformed 28 day seizure rate, the expected differences from placebo (ie, the difference in the observed least squares means after adjusting out the study-to-study differences and site clustering within study effects) were -0.668 (-48.7%) and -0.448 (-36.1%) for 600 mg/day (Dose Level 2) and 300 mg/day (Dose Level 1), respectively. This study is powered on 80% of these estimated treatment differences; -0.534 (-41.4%) and -0.358 (-30.1%) for 600 mg/day (Dose Level 2) and 300 mg/day (Dose Level 1), respectively.

A meta-analysis of Studies 1008-009, 1008-011, and 1008-034 was used to estimate a pooled standard deviation of 0.73 on the log transformed 28 day seizure rate scale, with a 95% confidence interval of [0.70, 0.76]. For the purposes of this study, a smaller standard deviation of 0.67 was used to assess the power and initial sample size requirements for comparing the 2 pregabalin group to placebo. The rationale for assuming the smaller SD of 0.67 is based on the Study 1008-034 data which included all three treatment groups of interest (i.e., placebo, 300 mg/day, and 600 mg/day). This study had a point estimate for the standard deviation of 0.72 and a 95% confidence interval for the standard deviation of [0.67, 0.77].

To ensure that the sample size is reasonably sufficient using an assumed pooled standard deviation of 0.67 on the $\log_e$ scale, in order to provide at least 80% power to detect a

[redacted]

*treatment difference of 0.358 on the log_e scale a blinded sample size re-estimation procedure (*Friede and Keiser, 2011)[3] *based upon a* residual variance of ANCOVA *under the null hypothesis will be applied when approximately the first 110 subjects in total have had 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 56 subjects per group or an increase in sample size greater than 65 subjects per group (195 subjects total). This represents the sample size required to provide 80% power to detect a treatment difference of -0.358 on the log scale with a standard deviation of 0.72. The sample size also allows for operational feasibility. Details regarding the statistical methodology of the blinded sample size re-estimation procedure will be documented in* Appendix 6. *This blinded sample size re-estimation procedure will be conducted by a statistician who is not associated with the conduct or final analysis of the study.*

There will be no penalty applied to the p-values or confidence intervals for assessing treatment difference from placebo due to this blinded sample size re-estimation procedure.

2.3. Study Objectives

Primary Objective:

- *To demonstrate superior efficacy of pregabalin compared to placebo for treatment of PGTC seizures as measured by the 28 day seizure rate.*

Safety Objectives:

- *To assess the safety and tolerability of pregabalin relative to placebo in pediatric and adult subjects with PGTC seizures.*

Secondary Objectives:

- *To demonstrate superior efficacy of pregabalin compared to placebo for PGTC seizures as determined by responder rate.*

Exploratory Efficacy Objectives:

- *To demonstrate superior efficacy of pregabalin compared to placebo as determined by seizure-free days for PGTC, myoclonic, tonic/atonic, absence, and clonic seizures.*

[redacted]

- *To demonstrate superior efficacy of pregabalin compared to placebo as determined by seizure-freedom of PGTC seizures over the last 28 days of the double-blind assessment phase and over the entire double-blind assessment phase. In those subjects with myoclonic, tonic/atonic, absence, or clonic seizures at baseline, seizure freedom over the last 28 days of the study and over the entire double-blind assessment phase will be summarized descriptively.*

- *To demonstrate superior efficacy of pregabalin compared to placebo as determined by the time to experience the same total number of PGTC seizures in the 12-week double-blind assessment phase that was observed during the baseline phase for each subject (referred to as 'Time to Nth Seizure').* This analysis will be reported separately from the main clinical study report.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

3.1. Interim Safety Analysis

In additional to the regular review of blinded safety data during the conduct of the study, as described in the "Safety Analysis" section, 2 unblinded Interim Safety Analyses (ISA) to be reviewed by an E-DMC will be conducted to further assess safety. The timing of the first ISA will be when the first one-third of the subjects enrolled (randomized) *has had an opportunity to complete the study. The second ISA will be performed when approximately two-thirds of the subjects enrolled* (randomized) *have had an opportunity to complete the study.*

The ISA will involve the descriptive review of deaths, SAEs, discontinuations due to AEs, and discontinuations due to the following 4 events:

1. *An episode of status epilepticus during the 12-week double-blind assessment phase.*
2. *A 28-day seizure rate for all PGTC seizures during the 12-week double-blind assessment phase that is greater than 2-times the maximum 28-day study seizure rate during the baseline phase (a 28-day period is defined as 4 consecutive study weeks).*
3. *An episode of a newly emergent generalized seizure type during the 12-week double-blind assessment phase.*
4. *An increase in the rate or intensity of PGTC or other generalized seizure activity during the 12-week double-blind assessment phase that, according to the investigator, is clinically significant.*

The ISA will not include any analysis for efficacy and therefore no type I error (alpha) spending penalty applies.

An External Data Monitoring Committee (E-DMC) will conduct this unblinded interim safety *analysis and provide recommendation to the sponsor.* 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.

3.2. Final Analysis and Unblinding

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 appropriate case report form.

The unblinding for the final analysis will follow standard Pfizer procedures.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

There will be 2 pair-wise comparisons of interest:

a) Dose Level 2: pregabalin 10 mg/kg/day (maximum 600 mg/day) - placebo, and

b) Dose Level 1: pregabalin 5 mg/kg/day (maximum 300 mg/day) - placebo.

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.

1) The first step will test the null hypothesis of equal treatment effect of Dose Level 2 vs. placebo at α=0.05 2-sided for the primary endpoint.

$$H_{01}: \mu_{PGB\ Dose\ Level\ 2} - \mu_{PBO} = \mathbf{0}$$

$$H_{a1}: \mu_{PGB\ Dose\ Level\ 2} - \mu_{PBO} \neq \mathbf{0}$$

2) The second step will test the null hypothesis of equal treatment effect of Dose Level 1 vs. placebo at α=0.05 2-sided for the primary endpoint.

$$H_{02}: \mu_{PGB\ Dose\ Level\ 1} - \mu_{PBO} = \mathbf{0}$$

$$H_{a2}: \mu_{PGB\ Dose\ Level\ 1} - \mu_{PBO} \neq \mathbf{0}$$

[redacted]

4.2. Statistical Decision Rules

If the null hypothesis (H_{01}) *of the first step is rejected, then proceed to the second step* (H_{02})*, otherwise, accept the null hypothesis of the first step* (H_{01})*, stop further testing, and claim no treatment effect.*

If the null hypothesis of the second step (H_{02}) *is rejected, then claim a treatment difference for both dose groups of pregabalin [Dose Level 2: 10 mg/kg/day (maximum 600 mg/day) and Dose Level 1: 5 mg/kg/day (maximum 300 mg/day)] from the placebo group for the primary endpoint only; otherwise accept the null hypothesis of the second step* (H_{02})*, stop further testing, and claim a treatment difference for only pregabalin Dose Level 2: 10 mg/kg/day (maximum 600 mg/day) from placebo for the primary endpoint only.*

5. ANALYSIS SETS

5.1. Full Analysis Set (Intent-to-Treat Population)

The efficacy analyses will be performed on the intent to treat (ITT) population which consists of randomized subjects who took at least 1 dose of investigational product during the double-blind assessment phase, have a baseline value and at least 1 post-baseline efficacy assessment (diary entry).

5.2. 'Per Protocol' Analysis Set (PP Population)

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 randomized subjects who took at least one dose of the investigational product.

5.4. Other Analysis Sets

Not applicable.

5.5. Treatment Misallocations

If a subject was randomized but took incorrect treatment, then they will be reported under their randomized treatment group for the efficacy analyses, but will be 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)

For all 28-day log seizure endpoints, the 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 28-day seizure rate translates into a 33% reduction in the 28-day seizure rate of the pregabalin group from the placebo group (ie, 100%*[exp-0.400-1]= -33%). The "percent reduction in seizures" will be calculated for changes versus placebo on the following statistics: the two-sided 95% confidence intervals, the least square means and their standard errors.

An additional back transformation will be calculated for percent reduction in seizures for each pregabalin treatment group relative to placebo for presentation as follows:

$$100\% \times \frac{[\exp(\text{LSMean(pregabalin)})-1]-[\exp(\text{LSMean(placebo)})-1]}{\exp(\text{LSMean(placebo)})-1}$$

6.1.1. Primary Endpoint

*The primary endpoint will be the log-transformed ($\log_e$) 28-day seizure rate for all PGTC seizures collected during the double-blind assessment phase (*not including the 1-week double-blind taper phase). *The 28-day seizure rate will be calculated as follows for the double-blind assessment phase:*

$$\textit{28-day seizure rate} = \frac{\textit{\# of seizures in the double-blind assessment phase of study}}{\textit{[\# of days in period - \# of missing diary days in period]}} \times 28$$

When the log-transformation is used, the quantity "1" is added to the 28-day seizure rate for all subjects to account for any possible "0" seizure incidence. This will result in the following primary efficacy endpoint: $\log_e$(28-day seizure rate + 1).

The 28-day seizure rate for all PGTC seizures collected during the baseline phase will be calculated similarly.

6.1.2. Secondary Efficacy Endpoint

Responder Rate, defined as subjects who have a ≥50% reduction in the 28-day seizure rate for all PGTC seizures during the double-blind assessment phase, as measured from baseline (data collected during the 8-week baseline phase) will be defined as a responder, otherwise they be considered as a non-responder.

The responder rate will be based on the percentage change from baseline in the 12-week double-blind treatment phase 28-day seizure rate, which is defined as follows:

% Change = [(28-day seizure rate$_t$ – 28-day seizure rate$_b$) / 28-day seizure rate$_b$] × 100%, where t is the 12-week double-blind treatment phase and b is for the 8-week baseline phase.

[redacted]

6.1.3. Exploratory Endpoints

6.1.3.1. Proportion of Seizure-Free Days

The proportion of seizure-free days for each seizure type: PGTC, myoclonic, tonic/atonic, absence, and clonic seizures will be computed. Proportion of PGTC seizure-free days is defined as number of seizure-free days in a period divided by "number of days in a period - number of missing Seizure diary days".

6.1.3.2. Number of Seizure-Free Days Gained

The number of seizure-free days gained for each seizure type: PGTC, myoclonic, tonic/atonic, absence, and clonic seizures will be calculated. The number of seizure-free days will be adjusted to a per 12 weeks value (ie, 84 days) for the baseline and 12-week double-blind assessment phases. Changes from baseline are to be computed and the analysis performed accordingly. The 12 week adjusted number of seizure-free days is defined as follows:

number of seizure-free days in a period * 84 / (number of days in a period – number of missing diary days in a period) .

Period refers to the length time in baseline, and in DB. The 12 week adjusted number of seizure-free days will be calculated for baseline and DB; change from baseline will also be calculated.

6.1.3.3. Proportion of Subjects with PGTC Seizure-Freedom

The proportion of subjects with PGTC seizure-freedom will be computed. The numerator for seizure-freedom is defined as the number of subjects that experience no PGTC seizures over the last 28 days of the double-blind assessment phase (must be a minimum of 4 weeks), patient must have received at least 42 days (2 weeks + 28 days) of study medication and have a minimum of 21 of the last 28 days as non-missing diary (ignore the first 2 weeks from dose escalation phase). The denominator is the number of subjects in the ITT population with 42 days (2 weeks + 28 days) of study medication.

The proportion of subjects with PGTC seizure-freedom over the entire double blind fixed dose assessment phase will also be computed. The numerator for seizure-freedom is defined as the number of subjects that experience no PGTC seizures over the fixed dose phase, patient must have received at least 84 days (2 weeks + 14 +28 +28 days) dosing and have a minimum of 11 of the 14 days and 21 of each of the two 28 day periods with non-missing seizure diary (ignore the first 2 weeks from dose escalation phase). The denominator is the number of subjects in the ITT population with 84 days of study medication.

6.1.3.4. Time to N^{th} Seizure

The time to experience the same total number of PGTC *seizures in the double-blind phase that were observed during the baseline phase for each subject, referred to as 'Time to N^{th}*

[redacted]

Seizure' will be assessed as an exploratory endpoint and will be described and conducted according to a separate exploratory statistical analysis plan (ESAP) for endpoint development, and reported separate from the main clinical study report.

6.2. Safety Endpoints

Safety endpoints include adverse event data (eg, occurrence, nature, intensity, and relationship to study drug), Hy's law, vital signs, weight, clinical laboratory assessments, ECG, neurological examination, physical examination, prior and concomitant medications, suicidal ideation and behavior assessments (as age appropriate).

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 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).

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.

6.2.3. Suicidal Ideation and Behavior Assessments During the Clinical Trial

C-SSRS responses will be mapped to the Columbia Classification Algorithm of Suicide Assessment (C-CASA). (see Appendix 2)

The following 3 endpoints are for suicidality data analysis and evaluation:

- Suicidal Behavior;
- Suicidal Ideation;
- Suicidal Behavior or Ideation.

Suicidal behavior: A subject is said to have suicidal behavior if the subject has experienced any of the following events (C-CASA event codes 1-3):

- Completed suicide;
- Suicide attempt; or
- Preparatory acts toward imminent suicidal behavior.

[redacted]

Suicidal ideation: Any observed suicidal ideation maps to a single C-CASA category. The C-SSRS, for example, includes five ideation questions (that map to C-CASA category 4) with increasing severity.

Subjects with new onset suicidal ideation and behavior: A subject will be considered to have a new onset of suicidal ideation and behavior if the subject reported no ideation and no behavior at the baseline assessment (note that self-injurious behavior, no suicidal intent [C-CASA code 7] is not considered to be suicidal ideation or behavior) and reported any behavior or ideation post-baseline. Data observed at screening is not considered in the definition of new onset.

Subjects with worsening suicidal ideation and behavior relative to baseline: A subject will be considered to have a worsening of suicidal ideation and behavior if the subject moved to a lower numbered C-CASA category (observed in categories 1-4) than was reported at baseline. Movement within C-CASA categories 5-9 would not be considered worsening. In addition, worsening will be considered within the suicide ideation C-CASA category 4 if there is an increase in severity identified in the C-SSRS which captures additional granularity on suicide ideation. A subject who reports only ideation at baseline and who reports any behavior post-baseline is considered to have worsened. Data observed at screening is not considered in the definition of worsening.

6.3. Other Endpoints

6.3.1. PK/PD Endpoints

PK/PD endpoints and analyses will be described in a separate document created by Clinical Pharmacology.

6.4. Covariates

Log-transformed 28-day seizure rate [$\log_e$(28-days seizure rate$_b$ + 1)] at baseline will be utilized as a covariate in the linear model used in the primary analysis, and for secondary analyses utilizing a similar model.

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 below).

Two covariates about age are defined as follows.

Age strata will be defined as Stratum 1: 5-7 years of age; Stratum 2: 8-11 years of age; Stratum 3: 12-16 years of age; or Stratum 4; 17-65 years of age. This covariate is applied to primary analysis.

[redacted]

Age group will be defined as: group 1, 5-16 years of age (at randomization); group 2: 17-65 years of age (at randomization). This covariate is applied to the analysis of primary efficacy endpoint as a sensitivity analysis. This age group definition will also be used to investigate treatment-by-age interaction for the primary efficacy endpoint.

Age will be defined as subjects' age at randomization. If a subject turns 66 at randomization after screening, he/she will be counted in the 17-65 age group.

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

- *United States (US)*: Subjects who participate in the U.S. or Puerto Rico centers will be pooled together;
- *European Union*: All subjects who participate in European Union (eg, Austria, Belgium, Denmark, France, Germany, Greece, Italy, Netherlands, Portugal, Spain, Sweden, United Kingdom, Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Lithuania, Poland, Romania, and Slovakia,) centers will be pooled together. The member countries of European Union are explained in more detail at https://europa.eu/european-union/about-eu/countries_en;
- *Asia-Pacific*: All subjects participating in Asia-Pacific (China, India, Korea, Malaysia, Philippines, Singapore) centers will be pooled together;
- *Others*: All subjects not participating in above three regions (eg, Russian Federation, Ukraine, Belarus, Bosnia and Herzegovina, Serbia, Montenegro, Turkey) centers will be pooled together.

Any region not enrolling any subjects will not be included in the analysis.

7. HANDLING OF MISSING VALUES

Missing data will be handled based on the nature of the endpoint and the proposed statistical methods for analyzing the data.

For all endpoints that include seizure rate, days with missing seizure diary data will be subtracted from the seizure rate calculations. If seizure rate for any phase cannot be calculated for a subject due to missing information, the endpoint that involves seizure rate during that phase will be also missing for that subject.

For scales used in this study, scores will be imputed according to the imputation rules and algorithms for missing component scores that are provided in the data standard documents. Partial dates for AEs and concomitant medications will be imputed according to Pfizer standard algorithms.

[redacted]

The assessment of missing data for the primary endpoint will require the construction of the following windows and drop-out categories:

- *Windowing for each subject will be constructed for the 1st month, 2nd month, and 3rd month the subject was in the study. Thus a 28-day seizure rate will be determined for each windowed month for which seizure data exist, otherwise the seizure data will be considered missing with a corresponding reason for it being missing.* Specific details are provided in Appendix 3.

- *Drop-out patterns will be constructed based on the reason the seizure data is missing for the corresponding windowed month. Hence, the following drop-out patterns will be defined for three specific categories of related to lack of efficacy or adverse event or other reason:*

  - *Completed study as planned.*

  - *Drop-out due to lack of efficacy:*

    - *Drop-out at month 1 due to lack of efficacy;*

    - *Drop-out at month 2 due lack of efficacy;*

    - *Drop-out at month 3 due to lack of efficacy.*

  - *Drop-out due to an adverse event:*

    - *Drop-out at month 1 due to an adverse event;*

    - *Drop-out at month 2 due to an adverse event;*

    - *Drop-out at month 3 due to an adverse event.*

  - *Drop-out due to other reason:*

    - *Drop-out at month 1 due to other reason;*

    - *Drop-out at month 2 due to other reason;*

    - *Drop-out at month 3 due to other reason.*

  Other reason includes any drop-outs excluding efficacy and adverse event.

These drop-out patterns will be summarized by treatment group to assess any imbalance using frequency counts. If there is a significant amount of missing data, then multiple imputation techniques will also be applied to the primary analysis model. However, if the amount of missing data is not significant (ie, less than 5% across all treatment groups),

[redacted]

then the assessment of missing data will not include multiple imputation techniques applied to the primary analysis model.

Further details regarding the statistical strategy of assessing missing data will be provided in AppendicesAppendix 4, Appendix 5, and Appendix 6.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

The ITT 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. Analysis of Primary Efficacy Endpoint

The primary efficacy analysis of the primary endpoint, $\log_e$(28-days seizure rate_t + 1) as defined in Section 6.1 of this document, *will utilize a linear model with the following fixed effect terms:*

- A $\log_e$ transformed baseline seizure rate *$\log_e$(28-days seizure rate_b + 1) for all PGTC seizures, as a continuous covariate;*
- *Age strata (Stratum 1: 5-7 years of age; Stratum 2: 8-11 years of age; Stratum 3: 12-16 years of age; Stratum 4; 17-65 years of age);*
- *Geographic region* (See Section 6.4) by pooling of investigator centers;
- *Treatment group [placebo, Dose Level 1: pregabalin 5 mg/kg/day (maximum 300 mg/day), Dose Level 2: pregabalin 10 mg/kg/day (maximum 600 mg/day)].*

There will be two pair-wise comparisons of interest:

1) Dose Level 2: pregabalin 10 mg/kg/day (maximum 600 mg/day) - placebo, and
2) Dose Level 1: pregabalin 5 mg/kg/day (maximum 300 mg/day) - placebo.

The difference in the least squares means and their standard errors for these two pair-wise comparisons will be used for constructing test statistics and two sided 95% confidence intervals.

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:

1. *The first step will test the null hypothesis of equal treatment effect of Dose Level 2 vs. placebo at α=0.05 2-sided for the primary endpoint.*

   If the null hypothesis of the first step is rejected, then proceed to the second step, otherwise accept the null hypothesis of the first step, stop further testing, and claim no treatment effect.

[redacted]

2. *The second step will test the null hypothesis of equal treatment effect of Dose Level 1 vs. placebo at α=0.05 2-sided for the primary endpoint.*

If the null hypothesis of the second step is rejected, then claim a treatment difference for both dose groups of pregabalin [Dose Level 2: 10 mg/kg/day (maximum 600 mg/day) and Dose Level 1: 5 mg/kg/day (maximum 300 mg/day)] from the placebo group for the primary endpoint only; otherwise accept the null hypothesis of the second step, stop further testing, and claim a treatment difference for only pregabalin Dose Level 2: 10 mg/kg/day (maximum 600 mg/day) from placebo for the primary endpoint only.

The difference in the least squares means and their standard errors for these 2 pair-wise comparisons will be used for constructing test statistics and 2-sided 95% confidence intervals. Results will be reported as "percent reduction in seizures from baseline" relative to placebo. For example, a difference between 1 of the pregabalin doses and placebo of -0.358 on the log-transformed scale for the 28-day seizure rate, translates into a 30.1% reduction in the 28-day seizure rate of the pregabalin group from the placebo group (ie, 100%[exp$^{-0.358}$-1] = -30.1%).*

An additional back transformation will be calculated for percent reduction in seizures for each pregabalin treatment group relative to placebo for presentation as follows:

$$100\% \times \frac{[\exp(\text{LSMean(pregabalin)})-1]-[\exp(\text{LSMean(placebo)})-1]}{\exp(\text{LSMean(placebo)})-1}$$

The 28-day seizure rate of log scale in the double-blind treatment phase will be summarized by each month and the entire 12-weeks double-blind period for each treatment group, age group [pediatrics overall (<17 years) and adults (17-65 years)], and geographic region.

Contingency plan for the primary ANCOVA analysis model

If after unblinding, the primary ANCOVA analysis model as described above performs well without any issues, the primary analysis model will stay as described above. However, in case of ANCOVA analysis issues, for example, with convergence or missing cells in a particular treatment within a region or within an age strata, the cause of the analysis model issues will be mitigated, for example, as follows:

- If a small region, say US region, causes the model issue alone, the small region (say US region) will be pooled with European Union; Other ANCOVA model terms will stay as is;

- If age strata causes the model issue alone, the age group (5-16 years of age and 17-65 years of age) as described in Section 6.4 will be used instead of the age strata; Other ANCOVA model terms will stay as is;

- If both a small region and age strata cause the model issue, then ANCOVA analysis will be performed with the small region (say US region) pooled with European Union and age group (instead of age strata), Other ANCOVA model terms will stay as is.

Other analyses of continuous dependent variables with ANCOVA model will follow the same procedure as the primary efficacy endpoint analysis. Responder rates and any other binary variables that use the same planned model as primary efficacy endpoint analysis will similarly be adjusted as needed.

Sensitivity Analysis

As a sensitivity analysis of the primary endpoint, multiple imputation methods will be used to evaluate the impact of missing data (See Appendix 4).

Subjects who discontinue the study for insufficient clinical response, adverse event, or death will be imputed based on the observed placebo distribution, regardless of randomized treatment assignment. Imputation will be based on baseline $\log_e$(28-days seizure rate_b +1), geographical region, baseline weight (continuous), and age strata.

Subjects who discontinue the study for other reasons, or who complete the study but have a missing double blind seizure rate, will be imputed based on observed subjects in the same randomized treatment group. Imputation will be based on treatment group, baseline $\log_e$(28-days seizure rate_b +1), geographical region, baseline weight (continuous), and age strata.

A sensitivity analysis will be performed using the same linear model as the primary efficacy analysis except for the age covariate, which will be applied for the 2 age groups (5-16 years of age; 17-65 years of age).

An additional sensitivity analysis will be performed using the same linear model as the primary efficacy analysis with two age groups covariate as well as pooled region of US and European Union.

A ranked ANCOVA will be performed for the change from baseline to double blind phase *of log-transformed ($\log_e$) 28-day seizure rate for all PGTC seizures, including age strata, treatment group, and region.*

A Wilcoxon-Mann Whitney test will also be performed and reported for the change from baseline to double blind phase *of log-transformed ($\log_e$) 28-day seizure rate for all PGTC seizures.*

[redacted]

Supplemental Analysis

A supplemental analysis will be performed to investigate generalizability of the treatment difference with respect to the 2 *age categories (ie, a possible treatment-by-age interaction that is statistically and clinically relevant).* The estimated seizure rate, standard error and the corresponding 95% confidence interval in addition to the treatment difference between each pregabalin treatment group and placebo will be calculated for both pediatric (5-16 years of age) and adult population (17-65 years of age). This supplemental analysis will also be a re-evaluation of the primary analysis model with an interaction term for treatment-by-age. This model will not replace the primary model.

As a supplemental analysis, a generalized linear model assuming a Poisson and negative binomial distributions and canonical log link function will be applied to the raw seizure counts.[1, 2] *The model will have an off-set parameter for the amount of time (i.e.,* log_e*(days)) the subject was in the double blind treatment phase.* A scale parameter of Pearson will be specified to fit the Poisson distribution.

The analyses with Poisson and negative binomial models will be performed with baseline seizure count as covariate.

The raw 28-day seizure rate will be summarized overall, and separately by age group of pediatrics overall (<17 years) and adults (17-65 years).

8.2. Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoint will be the responder rate, defined as the proportion of subjects who had at least a 50% reduction in the 28-day seizure rate for all PGTC seizures during the double-blind assessment phase, as measured from baseline (data collected during the 8-week baseline phase) on the ITT population. *This secondary endpoint will be analyzed using a logistic regression model with the following fixed covariate terms: treatment, age stratum, and geographical region. No adjustments for multiplicity will be taken, and nominal p-values from 2-sided tests* and the correspondence odds ratio with 95% confidence interval *will be reported.*

NOTE: The "PARAM=GLM" option in CLASS statement of SAS will be applied for logistic regression.

The responders and non-responders will be summarized descriptively by treatment using counts and percentages, and additionally by treatment group, age strata. Descriptive statistics for responder will also be provide for pediatrics overall (<17 years) and adults (17-65 years) *and geographical region.*

8.3. Analysis of Exploratory Endpoints

The proportion of seizure-free days for each seizure type: PGTC, myoclonic, tonic/atonic, absence, and clonic seizures will utilize ANCOVA *model.*

The number of seizure-free days gained for each seizure type: PGTC, myoclonic, tonic/atonic, absence, and clonic seizures will be analyzed utilizing a linear model similar to the primary analysis.

The proportion of subjects with PGTC seizure-freedom will utilize a logistic regression model similar to the responder rate analysis.

No adjustments for multiplicity will be taken and nominal p-values from 2-sided tests will be reported.

The exploratory endpoints will additionally be presented descriptively overall, and separately by age group of pediatrics overall (<17 years) and adults (17-65 years).

8.4. Safety Analyses

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 a baseline.

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

All safety analyses will be presented overall, and separately by age group of pediatrics overall (<17 years) and adults (17-65 years).

8.4.1. 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 from the first day of study treatment through and including 28 calendar days after the last administration of the study drug will be considered treatment emergent AEs (TEAEs). An overall summary of treatment-emergent AEs will be provided. TEAEs will also be summarized by system organ class, preferred term, severity, and relationship to study drug. TEAEs will be presented overall, and separately by age group of pediatrics overall (<17 years) and adults (17-65 years).

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 standards.

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

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

[redacted]

The Tier 2 and 3 AEs will be presented overall, and separately by age group of pediatrics overall (<17 years) and adults (17-65 years).

8.4.2. Suicidal Ideation and Behavior

C-CASA/C-SSRS

The denominator used in the percentages will be the number of subjects assessed for suicidal ideation and behavior. For worsening, the denominator would include the subset of subjects who had any level of suicidal ideation and behavior reported at baseline. For new onset, the denominator would include the subset of subjects with no suicidal ideation and behavior reported at baseline.

A subject listing of C-CASA categories as well as the underlying C-SSRS scale data will be presented.

In addition, a summary table with the number and percent of subjects within each C-CASA category by treatment group at screening, baseline, and at any time post-baseline without regard to baseline will be reported.

C-CASA will be presented overall, and separately by age group of pediatrics overall (<17 years) and adults (17-65 years).

[redacted]

8.5. Summary of Efficacy Analyses

Endpoint (Key Summary Metrics)	Analysis Set	Statistical Method	Model/ Covariates/ Strata	Missing Data	Interpretation
Log_e 28-day PGTC seizure rate (N, LS Mean Diff/SE)	ITT	ANCOVA	Treatment, region, age strata, baseline seizure rate	Days missing from Seizure Diary will be subtracted from rate calculations	Primary Analysis Note: age strata is protocol defined age strata. Baseline is the log of 28-day PGTC rate at baseline
Key summary statistics will be presented for the Log_e 28-day PGTC seizure rate and for the back transformed "percent reduction in seizures" relative to placebo.					
Log_e 28-day PGTC seizure rate (N, LS Mean Diff/SE) (treatment-by-age p-value)	ITT	ANCOVA	Treatment, region, age group, treatment-by-age group interaction, baseline seizure rate	Days missing from Seizure Diary will be subtracted from rate calculations	Supplemental Analysis Note: age groups are Age< 17 yrs and Age>= 17 yrs. Baseline is the log of 28-day PGTC rate at baseline.
Key summary statistics will be presented for the Log_e 28-day PGTC seizure rate and for the back transformed "percent reduction in seizures" relative to placebo.					
Responder rate (%)	ITT	Logistic regression	Treatment, region, age strata	Days missing from Seizure Diary will be subtracted from rate calculations	Secondary Analysis
Proportion Seizure-free days (%)	ITT	ANCOVA	Treatment, region, age strata, baseline	Days missing from Seizure Diary will be subtracted from rate calculations	Exploratory Analysis Each seizure type: PGTC, myoclonic, tonic/atonic, absence, and clonic seizures. Baseline for this endpoint is the proportion of seizure free days at baseline.
Number of seizure-free days gained (N, Mean, SE)	ITT	ANCOVA	Treatment, region, age strata, baseline	Days missing from Seizure Diary will be subtracted from rate calculations	Exploratory Analysis Each seizure type: PGTC, myoclonic, tonic/atonic, absence, and clonic seizures. Baseline for this endpoint is the number of adjusted seizure free days at baseline.

[redacted]

Proportion PGTC Seizure-freedom (%)	ITT	Logistic regression	Treatment, region, age strata	Days missing from Seizure Diary will be subtracted from rate calculations	Exploratory Analysis
Log_e 28-day PGTC seizure rate (N, LS Mean Diff/SE)	ITT	ANCOVA	Treatment, region, age strata, baseline	Multiple imputation will be applied.	Sensitivity Analysis. Baseline is the log of 28-day PGTC rate at baseline.
Log_e 28-day PGTC seizure rate (N, LS Mean Diff/SE)	ITT	ANCOVA	Treatment, region, **2 age groups**, baseline	Days missing from Seizure Diary will be subtracted from rate calculations	Sensitivity Analysis Note: age group are Age< 17 yrs and Age>= 17 yrs. Baseline is the log of 28-day PGTC rate at baseline
Log_e 28-day PGTC seizure rate (N, LS Mean Diff/SE)	ITT	ANCOVA	Treatment, pooled region, **2 age groups**, baseline	Days missing from Seizure Diary will be subtracted from rate calculations	Sensitivity Analysis Note: age group are Age< 17 yrs and Age>= 17 yrs. US and European Union will be pooled in the region class. Baseline is the log of 28-day PGTC rate at baseline
Change from baseline to double blind phase of Log_e 28-day PGTC seizure rate	ITT	Rank ANCOVA	Treatment, region, age strata, region and ranked log-BL		Sensitivity Analysis (Log-Scale). Baseline is the ranked log of 28-day PGTC rate at baseline.
Change from baseline to double blind phase of Log_e 28-day PGTC seizure rate (DB Phase)	ITT	Wilcoxon-Mann Whitney Test			Sensitivity Analysis (Log-Scale)
Raw Seizure Count	ITT	GENMOD, Poisson and negative binomial distribution with log link	Treatment, and baseline		scale parameter = Pearson for the Poisson model. Baseline for this endpoint is seizure count at baseline.

[redacted]

- All efficacy endpoints will be presented descriptively overall, and separately as by age group of pediatrics overall (<17 years) and adults (17-65 years).

9. REFERENCES

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

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

3. Friede, T. and Keiser, M. (2011). "Blinded sample size recalculation for clinical trials with normal data and baseline adjusted anlaysis" *Pharmaceutical Statistics,* **10:** 8-13.

[redacted]

APPENDICES

Appendix 1. Data Derivation Details

This table describes how seizure related endpoints have been defined.	
Endpoint	**Derivation**
8-week baseline phase (b) 28-day seizure rate	28-day seizure $rate_b$= [(# of $seizures_b$) ÷ (#of $days_b$ - # of missing $diary_b$)] × 28, where #of $days_b$ is defined as (first dose date-1) – screening date +1.
12-week double-blind treatment phase (t) 28-day seizure rate	28-day seizure $rate_t$ = [(# of $seizures_t$) ÷ (#of $days_t$- # of missing $diary_t$)] × 28, where #of $days_t$ is defined as date of last dose in phase – date of first dose in phase +1.
Primary endpoint: Log_e of 28-day seizure rate during 12-week double-blind treatment phase	Log_e (28-day seizure $rate_t$ +1)
"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 28-day seizure rate translates into a 33% reduction in the 28-day 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: $100\% \times \frac{[\exp(\text{LSMean(pregabalin)})-1]-[\exp(\text{LSMean(placebo)})-1]}{\exp(\text{LSMean(placebo)})-1}$
Percent change from baseline in 12-week 28-day seizure rate	% Change = [28-day seizure $rate_t$ -28-day seizure $rate_b$)/ 28-day seizure $rate_b$] × 100%
Responders	≥50% reduction in the 28-day seizure rate from baseline during the 12-week double-blind treatment phase, then response = 1 (responder) otherwise response = 0 (non-responder). The response status will be set as missing if the baseline seizure rate is missing. If baseline seizure rate is non-missing but there are no double-blind phase seizure rates, then the response status will be set as non-response
Proportion Seizure-free days	The numerator for seizure-free days is defined as the number of days the subject experience no seizures over the double-blind assessment phase.

[redacted]

Number of seizure-free days gained	The number of seizure-free days will be adjusted to a per 12 weeks value (ie, 84 days) for the baseline and 12-week double-blind assessment phases. Changes from baseline are to be computed and the analysis performed accordingly. Number of 12 week adjusted seizure free days is defined as follows: Number of seizure free days in a period x 84 / number of days in a period.
Proportion PGTC Seizure-freedom	The numerator for seizure-freedom is defined as the number of subjects that experience no PGTC seizures over the last 28 days of the double-blind assessment phase (Patient must have received at least 42 days (2 weeks + 28 days) of study medication and have a minimum of 21 of the last 28 days as non-missing diary). The denominator is the ITT population with 42 days (2 weeks + 28 days) of study medication.

[redacted]

Appendix 2. C-SSRS Mapped to C-CASA - Suicidal Ideation and Behavior Events and Codes

C-CASA Event Code	C-CASA Event	C-SSRS Response
1	Completed suicide	As captured in the safety database
2	Suicide attempt	"Yes" on "Actual Attempt"
3	Preparatory acts towards imminent suicidal behavior	"Yes" on any of the following: • "Aborted attempt", or • "Interrupted attempt", or • "Preparatory Acts or Behavior"
4	Suicidal ideation	"Yes" on any of the following: • "Wish to be dead", or • "Non-Specific Active Suicidal Thoughts", or • "Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act", or • "Active Suicidal Ideation with Some Intent to Act, without Specific Plan", or • "Active Suicidal Ideation with Specific Plan and Intent"
7	Self-injurious behavior, no suicidal intent	"Yes" on "Has subject engaged in Non-suicidal Self-Injurious Behavior?"

[redacted]

Appendix 3. Windowing for Study Months 1, 2 and 3

A 28-day seizure rate will be determined for each windowed month for which seizure data exist. Assignment of seizure data to visits during the Double-Blind Treatment Phase will use visit windows based on the day of the assessment relative to the date of the start of the double blind treatment phase. The following visit windows will be defined for statistical outputs:

Visit Windows

Month	Time Interval (Days)
Month 1	1 to 28
Month 2	29 to 56
Month 3	57 to 90

Derive study day as the (assessment date-date of start of double blind treatment phase) + 1. A subject must have at least 24 diary days to be counted in any monthly visit window data. Any data collected after Day 90 will be excluded from the monthly visit window calculations.

[redacted]

Appendix 4. Analysis Strategy Using Multiple Imputations

If the amount of missing data is not significant in the primary endpoint (ie, less than 5% within each treatment groups), then the multiple imputation analysis will not be performed.

Concept of multiple imputation strategy

Multiple imputation procedure is used under the assumption of missing at random (MAR) data and under the assumption of a monotone missing data pattern. In general, let Y be the response data (monthly seizure rate) where that part of **Y** which is missing is denoted by $\mathbf{Y}_{mis}$, and that part of **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.

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, we will let *m* take on the value 100.

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 imputation. Use of this assumption allows the analyst to generate imputations ($\mathbf{Y}_{\{1\}}, \mathbf{Y}_{\{2\}}, \ldots \mathbf{Y}_{\{m\}}$) 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:

$$\mathbf{Y}_j = \beta_0 + \beta_1 * \mathbf{Y}_1 + \beta_2 * \mathbf{Y}_2 + \ldots + \beta_{(j-1)}\, \mathbf{Y}_{(j-1)}.$$

The fitted model has parameter estimates ($b_0, b_1, b_2, \ldots, b_{(j-1)}$) and the associated covariance matrix $s^2_j V_j$, where V_j is the usual $X^T X$ matrix from the intercept and variables $\mathbf{Y}_1, \mathbf{Y}_2, \ldots, \mathbf{Y}_{(j-1)}$.

For each imputation, new parameters (β^*_0, β^*_1, β^*_2, …, $\beta^*_{(j-1)}$; 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:

$$\beta^*_0 + \beta^*_1 * y_1 + \beta^*_2 * y_2 + \ldots + \beta^*_{(j-1)} * y_{(j-1)} + z_i * \sigma^{*2}$$

where y_1, y_2, …, $y_{(j-1)}$ are covariates values for the first (j-1) variables 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.

SAS sample programs for multiple imputation strategy for this study

A pattern mixture model of multiple imputation is applied, and sample SAS programs are described as below. 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 (See covariates Section 6.4).
- TRT: Treatment group (Placebo, Pregabalin Level 1, Pregabalin Level 2).
- LN_BSZRT: A $\log_e$ transformed baseline seizure rate $\log_e$(28-days seizure rate_b +1).
- LN_SZRATE: A $\log_e$ transformed double-blind seizure rate $\log_e$(28-days 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, 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;
  else 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 = 100;
  class region age_strata;
  var region age_strata ln_bszrt ln_szrate weight;
  monotone regression(ln_szrate = ln_bszrt region age_strata weight);
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 = 101 ;
class region age_strata trt ;
  var region age _strata trt ln_bszrt ln_szrate weight;
  monotone regression(ln_szrate = trt ln_bszrt region age_strata weight) ;
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 Level 1, and Pregabalin Level 2 ;
proc glm data=main;
 by _imputation_ ;
 class region age_strata trt ;
 model ln_szrate = trt region age_strata ln_bszrt;
```


[redacted]

```
  lsmeans trt / diff=control('Placebo') tdiff pdiff cl ;
  estimate ‘Pregabalin Level 1 vs Placebo’ trt -1 1 0 ;
  estimate ‘Pregabalin Level 2 vs Placebo’ trt -1 0 1 ;
  ods output lsmeans=lsm diffs=lsdiff estimates=estdiffs ;
run ;
quit ;

*integrated summary of results of imputed datasets;
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 ;
  by parameter ;
  modeleffects estimate ;
  stderr stderr ;
run ;
```


[redacted]

Appendix 5. 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 time (T) in the Model

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

Exposure time T is derived in months as study day/28, where study day is derived as the (assessment date-date of start of double blind treatment phase) + 1. Eg, if the subject dropped out at day 26, the exposure time would be 26/28=0.93 months.

The scale parameter will be set to Pearson in the Poisson model.

[redacted]

Appendix 6. Blinded Sample Size Re-Estimation

The proposed sample size re-estimation formula (Friede and Keiser, 2011)[3] is the following:

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

where,

n^* is the revised total sample size of two treatment groups for this estimation;

γ is the ratio of the estimated sample size of two treatment groups;

$z_{1-\alpha/2}$ is a percentile from a standard normal cdf with α/2=0.025;

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

σ^2 is the blinded estimate of pooled variance for outcome variable at the interim review;

ρ is the blinded estimate for the correlation between an outcome and a covariate variable;

Δ is the clinically meaningful difference between *Dose Level 1: pregabalin 5 mg/kg/day (maximum 300 mg/day)* and placebo (i.e., 0.358) as specified in the protocol.

For this study, the ratio of estimated sample size of two treatment group (γ) is assumed as one due to 1:1 randomization with respect to placebo versus dose level 1. In addition, the estimates for correlation (ρ) and pooled variance (σ^2) is estimated based on the residual variance of ANCOVA. Therefore, the simplified equation for this study is:

$$n^* = \frac{4 \cdot (z_{1-\alpha/2} + z_{1-\beta})^2 \cdot \tilde{s}^2}{\Delta^2}$$

where,

$\tilde{s}^2$ is the blinded estimate of the residual variance based on ANCOVA at the interim review.

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 110 subjects have had the opportunity to complete the study. Since baseline 28 day 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

[redacted]

estimate of the variance under the null hypothesis will be biased upwards, this bias is negligible when the overall sample is reasonably large. Results from a thorough simulation study indicated that the re-estimated sample size using the uncorrected pooled variance required only 2 -to-3 more subjects per group relative to using a corrected pooled variance estimate. 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}=195).

[redacted]