Protocol A0081106

A 12-MONTH OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND TOLERABILITY OF PREGABALIN AS ADJUNCTIVE THERAPY IN PEDIATRIC SUBJECTS 1 MONTH TO 16 YEARS OF AGE WITH PARTIAL ONSET SEIZURES AND PEDIATRIC AND ADULT SUBJECTS 5 TO 65 YEARS OF AGE WITH PRIMARY GENERALIZED TONIC-CLONIC SEIZURES

Statistical Analysis Plan (SAP)

Version: 1.0 Final
Author: PPD (Study Statistician - PPD)
Date: August 15, 2011

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Author: PPD (Study Statistician - PPD)
Date: 05 OCTOBER 2015

Version: 3.0 Final
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Date: 03 September 2019

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version 2.0 Amendment 1:

Status of study when amendment made: Study is still ongoing.

Reason for amendment: Clarified safety endpoints. (Section 6.2).

Reason for amendment: Detailed for subjects participated in previous studies how ongoing AEs were handled from their previous study. (Section 6.2.1).

Reason for amendment: Explained handling of concomitant medication data, including for subjects participated in previous studies ongoing data from their previous study. (Section 6.2.3).

Reason for amendment: Seizure rates will be determined by visit rather than 28-day period as seizure data is collect from diaries at each visit. Detailed that seizure types will be computed based on previous study enrollment and added specifications in regards to handling of special cases of the seizure diary. (Section 6.2.3 and Appendix 1).

Reason for amendment: Suicidality is changed to suicidal ideation and behavior. (Section 6.2.4 and Appendix 2).

Reason for amendment: Age cohorts will be defined based on the Pediatric Written Request (PWR). Added how age and seizure cohorts will be determined. (Section 8).

Reason for amendment: Added safety analysis sections for Treatment and Disposition of Subjects (Section 8.3.1); Demographic Data and Clinical Examination data (Section 8.3.2); Discontinuations(s) (Section 8.3.3); Laboratory, Vital Signs (including height/weight), and ECG Data (Section 8.3.7); Physical and Neurological Examinations (Section 8.3.8); and Exposure and Compliance (Section 8.3.11).

Reason for amendment: AE presentations will also be done by primary seizure type cohort. (Section 8.3.5).

Reason for amendment: Specified how seizure frequency presentations should be handled, which is separated by previous study and age cohorts within the study. (Section 8.3.6).

Reason for amendment: All safety (excluding seizure frequency and cognitive function) will use age cohort only for their summary presentations (ie, no combined across age cohort summaries). AEs and Physical/Neurological examinations will be additionally presented combined across the age cohorts. (Section 8.3.5, Section 8.3.8).

Reason for amendment: Stated how to handle subjects who completed the CBCL but outside the range (listings only). Explained the handling of subjects who are unable to complete the CBCL due to translation issue for their language, they completed the C-SSRS (listings only). (Section 8.3.9).

Reason for amendment: Clarified that CogState information (cognitive function) is relevant for subject previously in A0081041 who participated in study A0081106 and A0081106 Direct Enrollers. Subgroup analysis will be done by age cohort (within this study type) and primary seizure type cohort. (Section 8.3.10).

Version 3.0 Amendment 2:

General Reason: To fulfill study A0081106 protocol requirements and to streamline some of the analyses that were previously required by PWR and PREA. Since PWR and PREA obligations have met previously, this version of the SAP addresses study A0081106 protocol requirements only, whereas previous versions of the SAP had also addressed PWR and PREA specified analyses. Results for study A0081106 subjects will be reported 1) overall and 2) by primary diagnosis of POS or PGTC seizures and 3) by 2 age cohorts (1 month to 16 years of age, 17 years of age and older) for majority of the endpoints. For cases where the endpoint summarization does not lend itself to the 3 sets of analysis above, more details will be provided at the endpoint level in the specific section.
Section 6.2.1 was modified to clarify reporting of AEs for subjects in previous studies who participated in study A0081106.
Section 6.2.2 was modified to clarify reporting of prior medications and nondrug treatment/procedures for subjects in previous studies who participated in study A0081106.
Section 6.2.3 Seizure Frequency was modified to clarify the reporting of the following: • Reporting of PGTC and POS 28-day seizure rate and time point to reflect study A0081106 timepoints. • Other types of seizure that were not part of 28-day PGTC or POS seizure rate (unclassified epileptic seizure, status epilepticus, myoclonic, tonic/atonic, & clonic) and time point to reflect study A0081106 timepoints.
Section 8. Statistical methodology was modified to define the 3 sets of analysis and analyses cohorts and to clarify which cohorts were used for the different endpoints. Additionally, language was added to clarify that all analyses will be conducted for each of the 3 treatment groups and combined. Definition of treatments and cohorts used for the analysis described in Section 8.1-Section 8.3.11 were subsequently removed from these sections.
Section 8.3.6 Seizure Frequency was modified to clarify the following: • POS and PGTC seizure cannot be reported as combined due the different nature of seizure. • To distinguish between other seizure types which are not part of 28-day seizure

rate for PGTC or POS • To clarify the method of analysis for other types of seizure that are not part of 28-day PGTC or POS seizure rate. • To clarify reporting of baseline 28-day seizure rate for PGTC seizure and to provide the reason for not presenting baseline 28-day seizure rate for POS seizure.
Section 8.3.9- Suicidal Ideation and Behavior: Added or removed wording for clarification. Section 8.3.10 Cognition was modified as follows: • Added the age cohort for analysis of CogState data as 4 -11 years 12-16 years. • CogState will perform the analysis of the CogState Detection and CogState Pediatric Identification.
Section 8.3.11 – Exposure was modified to add compliance definition for TID dosing.

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APPENDICES

2. INTRODUCTION

This is a 12-month open-label, flexible-dose study in pediatric subjects 1 month through 16 years of age with partial-onset seizures (POS), who have participated in Study A0081041 (4-16 years of age) or Study A0081042 (1 month-3 years of age) and pediatric and adult subjects 5-65 years of age with Primary Generalized Tonic-Clonic (PGTC) seizures who have participated in Study A0081105. Subjects who have completed the studies cited above will be eligible for screening for this study. For subjects who have participated in, but did not complete Studies A0081041, A0081042, or A0081105, eligibility for Study A0081106 will be considered on a case by case basis. A minimum of 4 weeks in the double-blind treatment phase of either Study A0081041 or Study A0081105 will be required for consideration of enrollment into Study A0081106.

Selected sites that are not participating in studies A0081041 or A0081042 may screen and enroll pediatric subjects (1 month to 16 years of age) with partial onset seizures directly into Study A0081106 provided they meet the study inclusion/exclusion criteria. When subject enrollment for Studies A0081041 and A0081042 is complete, sites that were enrolling subjects in Studies A0081041 or A0081042 may screen and enroll pediatric subjects (1 month to 16 years of age) with partial onset seizures directly into Study A0081106 until enrollment into Study A0081106 is closed by Pfizer.

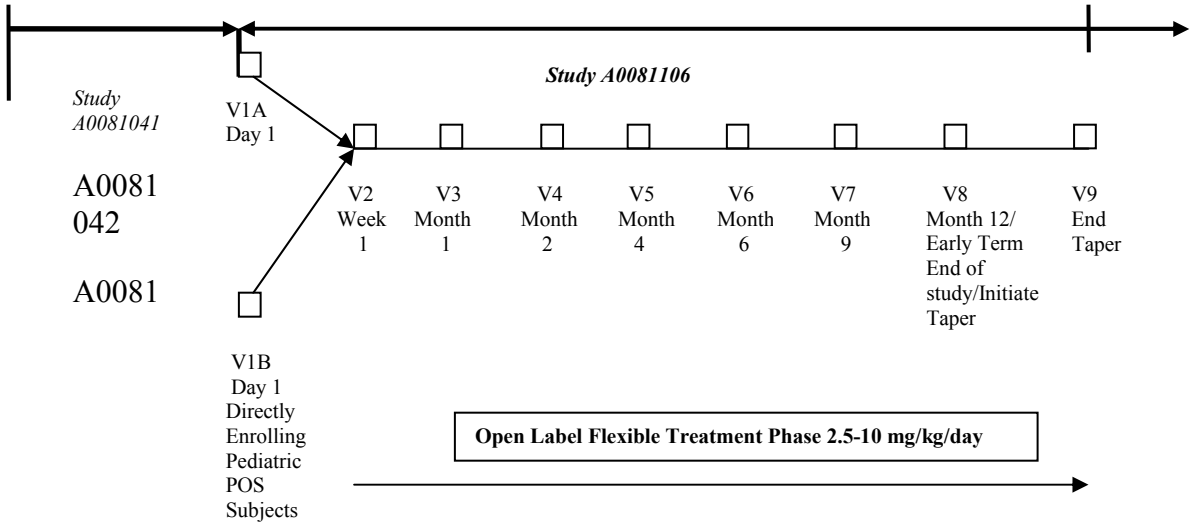
2.1. Study Design

The day of the last visit (completion of taper phase) of Studies A0081041, A0081042, and A0081105 is designated as Day 1 (Visit 1A) of this study. Baseline values for analysis of change in safety endpoints will be the assessments made prior to initiating double-blind dosing at Visit 1 of Studies A0081041, A0081042, or A0081105. For subjects directly entering Study A0081106 without participation in one of the studies above, baseline values for analysis of change in safety endpoints will be the assessments made at the first visit (Screening Visit 1B) of this study.

Subjects will return for the designated assessments of safety, tolerability, and drug accountability at Week 1 (Visit 2), Month 1 (Visit 3), Month 2 (Visit 4), Month 4 (Visit 5), Month 6 (Visit 6), Month 9 (Visit 7), Month 12/Early Termination (Visit 8), and Follow-up (Visit 9). Investigator site staff will contact the subject and/or parent/caregiver by telephone at least monthly between visits, to address questions, assess safety and adverse events, and ensure compliance with study directives.

At Visit 2 and subsequent visits thereafter, the investigator or designee will review seizure diary data and tolerability with the subject and may adjust the dose at his/her discretion.

Study Design Diagram:



2.2. Statistical Power and Sample Size

This study will enroll a sufficient number of subjects to ensure that 100 pediatric subjects (1 month to 16 years of age) complete one year of adjunctive treatment. Pediatric subjects with partial onset seizures (who have participated in Studies A0081041, A0081042, or directly enrolled into this study) or with PGTC seizures (who have participated in Study A0081105) are included.

2.3. Study Objectives

To evaluate the long-term safety and tolerability of pregabalin in pediatric subjects 1 month through 16 years of age with partial onset seizures and pediatric and adult subjects 17-65 years of age with PGTC seizures.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

Not applicable. This is an open-label trial.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Not applicable. No formal statistical analysis will be performed.

4.2. Statistical Decision Rules

Not applicable. No formal statistical analysis will be performed.

5. ANALYSIS SETS

5.1. Full Analysis Set (Safety Population)

The primary analysis set will be the Safety population which will include subjects who took at least one dose of the study medication in this study.

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 subjects who took at least one dose of the study medication in this study.

5.4. Other Analysis Sets

Not applicable.

5.5. Treatment Misallocations

Not applicable.

5.6. Protocol Deviations

The list of protocol deviations will be compiled and evaluated for major deviation prior to database closure and the listing will be provided.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

All seizure information will be addressed in safety.

6.2. Safety Endpoints

Safety and tolerability will be evaluated at each study visit. Data on the following endpoints will be collected:

- Adverse event (AE) data (occurrence, nature, intensity, and relationship to study drug).
- Physical and neurological examinations.
- Vital signs.
- *Growth and development parameters (height and weight) including Tanner stage* (Tanner stage not applicable for subject from study A0081042) for pediatric subjects.
- Clinical laboratory data (hematology, chemistry, urinalysis).

- Electrocardiograms (ECGs).
- 28-day seizure rate (number of seizures per 28-day period).
- Assessment of suicidal ideation and behavior.
- *Cognitive testing* (Only A0081041 subjects who participated in study A0081106 and A0081106 Direct Enrollers).

In addition, identification of subjects meeting the definition of Hy's law will be evaluated.

6.2.1. Adverse Events

All AEs will be coded using the MedDRA coding dictionary. All AEs (serious and non-serious) reported from onset of the first day of A0081106 study treatment through and including 999 calendar days after the last administration of the study drug will be considered treatment emergent AEs (TEAEs). For subjects who participated in the previous studies, AEs that were ongoing from their previous study were recorded in A0081106 and were considered treatment-emergent only if the severity worsened.

6.2.2. Prior and Concomitant Treatments and Medications

Concomitant medications, defined as medications that are ongoing or started on or after the first day of A0081106 study treatment up to the last dose of study treatment, and prior medications, defined as medications that stopped prior to the first day 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. Seizure Frequency

The seizure frequency for PGTC and POS seizure will be based on the 28-day seizure rate at each visit and overall (all treatment days during the treatment phase, excluding the taper phase), calculated as follows:

$$\text{28 day seizure rate} = \frac{\text{\# of seizures since last visit}}{\text{[\# of days since last visit - \# of missing diary days since last visit]}} \text{ X 28}$$

- Number of days since last visit is defined as: Date of last diary data entry since last visit – Date of first diary data entry since last visit +1.

Calculations will be made, using A0081106 visit schedule, for Week 1 (Visit 2), Month 1 (Visit 3), Month 2 (Visit 4), Month 4 (Visit 5), Month 6 (Visit 6), Month 9 (Visit 7), Month 12 (Visit 8) and Overall.

The 28-day seizure rate for all POS will be computed for subjects from Studies A0081042, A0081041, and direct enrollers, for each visit in study A0081106 and overall. Since these subjects were all <17 years of age at the time of entry to the previous studies, there will be only one age cohort.

The 28-day seizure rate for PGTC seizures will be computed for subjects from Study A0081105 for each visit in Study A0081106 and overall. The 28-day PGTC seizure rate will also be summarized by age cohort (5 to 16 years and >=17 years).

Number and percent of subjects who experienced at least one unclassified epileptic seizure, status epilepticus, myoclonic, absence seizure, tonic/atonic & clonic seizure will be computed for all subjects for each visit in study A0081106 by primary seizure type cohorts (PGTC, POS). These seizure types are not part of the PGTC or POS 28-day seizure rate.

The following specifications in regard to the handling of special cases for the seizure diary are also considered:

1. Any unplanned diary records will be mapped to planned visits by comparing the diary date against the dosing visits and assigned to the first visit that occurs after the unplanned diaries date.

2. If the subject has multiple diary records on the same date, then the below algorithm will be used to select the record for analysis:

   a. Select 'DONE' records over 'NOT DONE'.

   b. If one of the repeated records has 'NO Seizures' and the other is with some positive number as result, then select record with positive number of seizures.

   c. If both/multiple repeated records have positive number of seizure, then include all seizures from both pages.

3. The data is collected in two ways due to CRF amendment. Per earlier version of CRF, the diary data is collected daily. Per the revised CRF, diary start and end dates are collected and the data are entered only when a seizure has occurred. If the data are collected on the revised CRF, then dates collected on CRF are used. Otherwise the minimum/maximum dates per visit from daily collection dates are used.

6.2.4. Suicidal Ideation and Behavior (SIB) Assessments During the Clinical Trial

The correct age appropriate scale to assess suicidal ideation and behavior risk was used based on the guidance in the protocol, specifically the use of the Child Behavior Checklist (CBCL) for subjects <6 years of age) and the Columbia-Suicide Severity Rating Scale (C-SSRS) for subjects 6 - 65 years of age.

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

The following 3 endpoints are key endpoints for suicidal ideation and behavior data analysis and evaluation:

1. Suicidal Behavior.

2. Suicidal Ideation.

3. 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, according to the 2010 FDA draft guidance to industry):

1. Completed suicide.

2. Suicide attempt; or

3. Preparatory acts toward imminent suicidal behavior.

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.

There are currently no validated scales to assess suicidal ideation and behavior in children below age 6, and suicidal ideation and behavior is an extremely rare occurrence in this age group. Children in this age group and young school-aged children are more likely to demonstrate aberrant behaviors that place them at-risk for self-injurious behaviors. The CBCL will be used in this trial for children <6 years of age at Screening and follow-up visits to assess for behavioral and emotional issues, including those that may be related to suicidal ideation and behavior. For this trial, scores on the Withdrawn, Internalizing Problems subscales and the Total Problem scales will be examined. Higher scores on the CBCL indicate higher levels of problematic behaviors or dysfunction. The CBCL scoring algorithm allows for a subject's scores to be standardized using scores from a normal population. These standardized scores are referred to as T-scores on the CBCL report. For this study, a cut-off of ≥68 on the T-scores for the Withdrawn, Internalizing Problems subscales and the Total Problem scales will be used. The CBCL in this study is used for subjects age 4 to <6 years of age.

6.2.5. Cognitive Testing During the Clinical Trial

The *CogState Battery will be completed for pediatric partial onset seizure subjects 4-16 years of age only* (subjects from A0081041 and A0081106 Direct Enrollers).

Measures of psychomotor function and attention before and after treatment with study medication will be used to determine the extent to which the compound is associated with any adverse cognitive outcome. Two tests will be used to measure psychomotor function and attention; these are the CogState Detection (psychomotor function) and CogState Pediatric Identification (Go-No Go: attention) tasks.

CogState Detection and CogState Pediatric Identification will assess task speed and accuracy, with faster task speeds and higher accuracy an indicator of a higher-level of cognition.

6.3. Other Endpoints

6.3.1. PK/PD Endpoints

Not applicable.

6.4. Covariates

- Not applicable.

6.4.1. Exploratory Endpoint

Not applicable.

7. HANDLING OF MISSING VALUES

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

For all endpoints that include seizure rate, number of days with missing seizure diary data will be subtracted from the denominator of the 28-day seizure rate calculations. If seizure rate for a given subject and for any phase cannot be calculated due to missing information, the endpoint that involves seizure rate during that phase will be also missing.

For scales used in this study (eg, CBCL, C-SSRS), 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.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

All subject in this study will receive pregabalin, and all doses of pregabalin will be combined. *Data will be summarized into 3 groups defined by a combination of the subject's randomized treatment group in one of the previously participated studies (subjects previously on pregabalin will be combined across treatment groups) and the treatment received during this study. The 3 summary treatment groups will be described as:*

1. Pregabalin-Pregabalin: any dose of pregabalin from the previous study and pregabalin in this study.

2. Placebo-Pregabalin: placebo in the previous study and pregabalin in this study.

3. Direct Pregabalin: pregabalin only in this study and did not participate in any previous study.

Additionally, all pregabalin data in this study will be combined "Overall". Other than baseline, where relevant, information will be presented only for this study. Baseline values will be the last observation made prior to initiating double-blind dosing in Studies A0081041, A0081042, and A0081105. Subjects entering Study A0081106 directly will have baseline observations made at screening (Visit 1B).

There will be 3 sets of analyses performed for most of safety endpoints where it is relevant. 1) Overall; 2) age cohorts); 3) primary seizure type. The three sets are described below.

1. Overall (all subjects in A0081106). This analysis is not applicable for seizure related endpoints due to nature of primary seizure type (PGTC, POS) and for some other safety endpoints where the assessment is not required for all subjects due to age differences.

2. Age cohorts: This c*ohort analysis will consist of an age cohort defined as:* 1 month to 16 years of age or age >=17. For subjects from previous studies entering study A0081106, the age at randomization from their previous study will be used to determine the age cohort. For direct enrollers, age at screening/baseline of the present study will be used.

    - For some of vital signs and ECGs data where mean and standard deviation of the measurement are reported, the age cohorts will be (1 month to <2 years, 2 years to <4 years, 4 years to <10 years, 10 years to 16 years and >=17 years) and the "overall" summary and by seizure cohort summary will not be performed due to differences in normal range in younger age group.

3. *Primary seizure type cohorts are POS or PGTC seizures).* The partial onset seizure cohort consists of subjects from studies A0081041, A0081042, and A0081106 Direct Enrollers. The PGTC seizure cohort includes subjects from Study A0081105.

8.1. Analysis of Primary Efficacy Endpoint

Not applicable.

8.2. Analysis of Secondary Efficacy Endpoints

Not applicable.

8.3. Safety Analyses

Summaries will include data for all subjects who took at least one dose of study medication in this study (Safety population).

The safety data (including adverse events, clinical laboratory assessments, ECGs, vital signs, height/weight, and physical/neurological examinations) will be summarized through standard data tabulations, descriptive statistics, and/or graphical presentations.

The 3-tier safety analysis approach will not be utilized as this is not a comparative study.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show subject disposition and number of subjects analyzed for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s)

Data will be reported in accordance with the sponsor reporting standards.

8.3.2. Demographic Data and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight and height. Each will be summarized by sex at birth.

8.3.3. Discontinuation

8.3.4. Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be summarized.

8.3.5. Adverse Events

AEs will be reported in accordance with the sponsor reporting standards, including frequency and severity.

8.3.6. Seizure Frequency

Twenty-eight-day seizure rate will be calculated from the seizure diaries and will be reviewed as a means of determining seizure control. Seizure frequency for each seizure type will be summarized using descriptive statistics by visit *until the end of the trial by treatment group and overall. No statistical inferences will be performed.* PGTC and POS seizure types will be summarized separately.

PGTC Seizure Frequency: will be summarized for subjects from study A0081105 with primary diagnosis of PGTC, and age range from 5 to 65 years. Baseline 28-day seizure rates for PGTC subjects will be the diary data collected prior to initiating double-blind dosing study A0081105. Other than baseline, time points are relative to study A0081106 open-label treatment phase. The 28-day PGTC seizure rate during treatment phase will be reported descriptively for each visit in study A0081106 and overall and will be also reported by age cohorts (5 to 16 years, >=17 years). For other types of seizure which are not part of the 28-day PGTC rate (ie, myoclonic, absence seizure, tonic/atonic, clonic, unclassified, status epileptic) percent of subjects who experienced at least one myoclonic, absence seizure, tonic/atonic, clonic, unclassified, status epileptic will be summarized.

POS Seizure Frequency: will be summarized for subjects from study A0081041, A0081042 and from direct enrollers with primary diagnosis of POS, and age range from 1 month to 16 years. Baseline is not represented for POS subjects as only a subset of these subjects (those from Study A0081041) had seizure diary observations prior to the initiation of study treatment. Baseline seizure data were collected using V-EEG for subjects previously in Study A0081042, which are not comparable to seizure data collected in Study A0081106 using diaries. Direct enrollers into Study A0081106 did not have observation of seizures prior to initiation of study treatment.

The 28-day POS seizure rate during treatment phase will be reported descriptively for each visit in study A0081106 and overall. For other types of seizure which are not part of the 28-day POS rate (ie, unclassified, status epileptic) percent of subjects who experienced at least one unclassified, status epileptic will be summarized.

8.3.7. Laboratory, Vital Signs, Height, Weight, and ECG Data

Laboratory, vital signs, height, weight and ECG data will be reported in accordance with the sponsor reporting standards for cohorts described in Section 8 by treatment group and overall.

8.3.8. Physical and Neurological Examinations

Physical and neurological examination data will be presented for cohorts described in Section 8 by treatment group and overall.

8.3.9. 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 (6 to 65 years of age).

The number and percent of subjects within each C-CASA category by treatment group and overall at baseline screening (lifetime) and at any time post-baseline without regard to baseline will be reported.

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

CBCL

For the CBCL (4 to <6 years of age), the denominator used in the percentages will be the number of subjects assessed. Only subjects who fall within the age range for CBCL will be summarized. For subjects who falls outside of this age range and have CBCL data collected, CBCL data will only be displayed in the listing.

Additionally, some subjects <6 years are unable to have the CBCL administered due to translation issues (eg, Greek and Cebuano speaking subjects) and are administered the C-SSRS, which can be answered by the parents/caregivers. These children who have the C-SSRS administered will be displayed in listings only, ie, not summarized within the C-SSRS table.

A subject listing of CBCL scale data will be presented. Also, a summary table with the number and percent of subjects with a cut-off ≥68 on the T-scores for the Withdrawn, Internalizing Problems subscales and the Total Problem scales by treatment group at baseline screening (lifetime), and at any time post-baseline without regard to baseline will be reported.

C-CASA and CBCL will be presented combined for all subjects and subgroup summaries for each age cohort (for C-CASA only; see Section 8) and primary seizure type.

8.3.10. Cognitive Function

CogState Detection task speed and accuracy, and CogState Pediatric Identification speed and accuracy will be summarized using descriptive statistics for subjects who participated in previous study 1041 and Study A0081106 direct enrollers, overall and by age group (4 to 11 years, 12 to 16 years).

CogState will perform the analysis of the CogState Detection and CogState Pediatric Identification. CogState SAP will be a separate document and developed by CogState.

8.3.11. Exposure and Compliance

Exposure will be calculated as (date of last dose – date of first dose + 1) across the open-label treatment phase and categorized using Pfizer Data Standards.

Compliance will be based on frequency (BID or TID) of dosing recorded on the dosing record and calculated as:

Compliance = (Actual Dosing/Expected dosing) X 100%.

Study medication compliance algorithm:

1. Open-label treatment phase: date of last dose – date of first dose + 1 (excluding taper phase).

2. Actual Dosing over the open-label treatment phase (excluding taper phase): Using the dosing record to determine the doses reported taken: count number of capsules/doses taken per day (capsule or liquid, as relevant) during the open-label treatment phase and add any recorded extra doses or subtract any recorded missed doses.

3. Expected BID dosing over the open-label treatment phase (excluding taper phase): open-label treatment phase duration *2; adjusting for AM/PM dosing on first and last days of dosing period.

    - Example of BID dosing: If a subject took only PM dose on the first day of dosing and AM on the final day of dosing, subtract two from expected dosing.

    - Expected TID dosing over the open-label treatment phase (excluding taper phase): open-label treatment phase duration *3 (excluding first and last day of dosing in addition to the taper phase).

Compliance will be calculated and summarized by liquid dosing, capsule dosing and overall across the whole open-label treatment phase (excluding taper phase), and by visit.

8.4. Summary of Efficacy Analyses

Not applicable.

Appendix 1. Data Derivation Details

This table describes how seizure related endpoints have been defined.	
Endpoint	**Derivation**
PGTC 28-day seizure rate at baseline: Baseline 28-day seizure rates will be observation made prior to initiating double-blind dosing in studies A0081105 during the 8 weeks baseline period) There will not be baseline seizure rate for POS subject for reason described in Section 8.	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.
28-day seizure rate during treatment phase (excluding taper phase) POS, PGTC	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 diary data entry for that visit – date of first diary data entry for that visit +1.
Seizure frequency for other type of seizure (ie, myoclonic, absence seizure, tonic/atonic, clonic, unclassified, status epileptic) which are not part of 28-day seizure rate.	n (%) of subject experienced at least each other type of seizure will be calculated for POS population and PGTC population separately

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?"