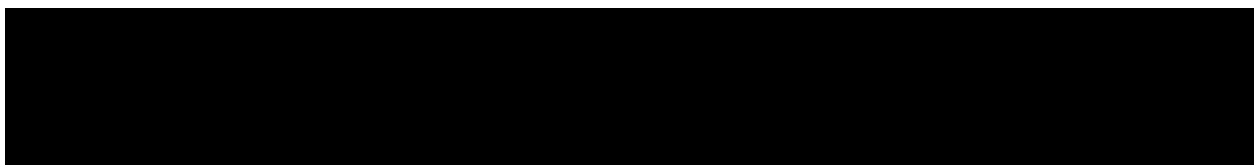




CLINICAL PROTOCOL

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

Compound:	PD-144723
Compound Name:	Pregabalin
US IND Number:	49393
European Clinical Trial Database (EudraCT) Number (if applicable):	2013-003420-37
Protocol Number:	A0081042
Phase:	3



Document History

Document	Version Date	Summary of Changes
Final Protocol	30 December 2013	Not applicable
Amendment 1 (Region specific – Asia, Europe, Middle East, South America)	15 December 2017	<p>This is a non-substantial protocol amendment.</p> <p>This protocol amendment clarifies the study protocol with regards to the change in the constant term in the transformation of seizure rate and the sample size decision rules. The changes outlined below are made to the Protocol Summary and Sections 2.2, 3, 7.2.1, 9.1, and 9.2.1. in all relevant parts of this document except where noted for historical accuracy.</p> <ol style="list-style-type: none"> 1. The transformation for the primary endpoint analysis is superseded in the protocol by the following: $\log_e(24\text{-hour seizure rate} + 1)$ where the revision is to the constant term, to address any circumstances of zero seizure rates, which is changed from “$+1/28$” to “$+1$”. The revised term provided better approximation of normal distribution of the seizure data based on blinded data distribution. The constant “$1/28$” added variability to the data and decreased its normality. Therefore, in agreement with the FDA, the constant has been revised from “$1/28$” $\log_e(24\text{-hour seizure rate} + 1/28)$ to “1” ($\log_e(24\text{-hour seizure rate} + 1)$). 2. The decision rules for the blinded sample size re-estimation were clarified as follows: <ol style="list-style-type: none"> a. If the recalculated sample size is less than or equal to the original sample size of 123 subjects total, then the sample size will not be adjusted. b. If the recalculated sample size is greater than the original sample size (123 subjects total) then the following information will be considered:

		<ul style="list-style-type: none">• If the re-estimated sample size is between 123 and 150, then the sample size will be adjusted to the re-estimated sample size.• If the re-estimated sample size exceeds 150 then it will be increased to a sample size of 150 (as agreed with the US FDA). <p>The blinded sample size re-estimation was conducted, and the sample size will be increased to approximately 150 subjects.</p> <p>The US FDA agreed with these two clarifications and that a protocol amendment would not be required. For other regions, these changes are made consistent with the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) guidance.</p>
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PROTOCOL SUMMARY

Indication:

Adjunctive therapy for children 1 month (44 weeks gestational age) through <4 years of age inclusive with partial onset seizures with or without secondary generalization.

Background and Rationale:

Epilepsy is a common disorder in childhood affecting 4 to 5 of every 1000 children. Although epilepsy is often well controlled with existing antiepileptic drug (AED) therapy, more than 25% of pediatric patients have seizures that are uncontrolled by currently available agents, or have adverse effects related to AEDs that complicate management of their seizures. In addition, children with epilepsy often suffer from impaired academic performance, with 55% functioning below their grade level and an additional 16% significantly behind in educational training.¹ Children with epilepsy also have a higher likelihood of developing behavioral difficulties, which may persist into adulthood.² Early age of onset and a higher number of total lifetime seizures are the strongest correlates of academic underachievement. Therefore, the availability of a new AED that has been shown to improve seizure control, and that is well tolerated, is needed.

Pregabalin is approved in more than 100 countries, with indications summarized below for the United States (US), European Union (EU), and Japan (JP). In the US, pregabalin is indicated for the adjunctive therapy for adult patients with partial onset seizures. In addition, pregabalin is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, and fibromyalgia and neuropathic pain associated with spinal cord injury. In the EU, pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization. In addition, pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults and for generalized anxiety disorder in adults. In Japan, pregabalin is indicated for the treatment of peripheral neuropathic pain and fibromyalgia. The approved dose range for the adjunctive treatment of partial onset seizures in adults is 150 to 600 mg/day, administered twice daily (BID) or 3 times daily (TID). The most common adverse effects reported with pregabalin in placebo controlled adjunctive trials in adults with partial onset seizures were dizziness (32%) and somnolence (22%). Since initial market approval of Lyrica® in 2004 through the first quarter of 2012, it is estimated that more than 15,900,000 patient years of exposure have accumulated worldwide.

This study is one of several studies that will be conducted to assess the safety and efficacy of pregabalin in pediatric subjects with epilepsy and to address post approval commitments to US and EU regulatory authorities.

Objectives:

Primary Efficacy Objective

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

Secondary Efficacy Objective

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

Study Design:

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

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

The study is composed of 4 phases:

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

- 7 day double-blind taper phase.

The total double-blind treatment phase is 21 days.

Every reasonable attempt should be made to obtain the minimum target Video-EEG recording of 48 hours, which may require up to 72-hours to obtain. Recognizing the inherent challenges in Video-EEG monitoring of pediatric subjects with epilepsy it is expected that the target minimum 48 hour Video-EEG recording may not be achievable in all cases. In the clinical investigator's opinion, should circumstances (eg, clinical care, child behavior, consent, etc.) mandate a Video-EEG monitoring period less than 48-hours for a given subject, please contact the study clinician to review the subject's clinical circumstances and document reasons for not achieving the target minimum duration.

Subjects who complete the treatment phases of this study through Visit 7 and enter the double-blind taper phase will be eligible for screening into Protocol A0081106, a 1-year open label safety study (Please refer to [1.5 Study A0081106: 1-Year Open Label Safety Study of Pregabalin](#) for more details). Subjects who participated in study A0081042 through Visit 7 will be considered to have completed the study.

In certain instances subjects who require withdrawal from this study may still be eligible for screening and entry into the long term safety study A0081106. Subjects who do not meet the inclusion criteria of at least 2 partial seizure during the 48 hour baseline Video-EEG may still be eligible for screening for A0081106. Subjects who have completed the dose escalation phase and received at least one dose during the fixed-dose phase may also be eligible for screening for Protocol A0081106. For example, subjects who withdrew due to poor tolerability or lack of efficacy may be considered. Such cases should be reviewed with the Pfizer study clinician to determine further eligibility.

Endpoints:

Primary Efficacy Endpoint

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

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

- When the log-transformation is used, the quantity 1 is added to the double-blind 24-hr EEG seizure rate for all subjects to account for any possible "0" seizure incidence. This will result in the following primary efficacy measure: \log_e (double blind 24-hr EEG seizure rate + 1). Results will be reported as "percent change in seizures" relative to placebo. For example, a difference between one of the pregabalin doses and placebo of -0.400 on the log transformed scale for the double blind 24-hr seizure rate, corresponding to a 33% reduction in the double-blind 24-hour EEG seizure rate of the pregabalin group from the placebo group (ie, $100\% * [\exp^{-0.400} - 1] = -33\%$).
- A minimum of 24 hours of evaluable Video-EEG will be required to utilize the EEG. In cases where there is less than 24 hours of evaluable Video-EEG, the seizure rate will be set to missing.
- The baseline 24 hour EEG seizure rate will be calculated in the same way.

Secondary Efficacy Endpoint

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

Safety Endpoints

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

Study Treatments:

Subjects who complete the baseline phase and meet the eligibility criteria will be randomized in a double-blind manner at Visit 3 to a fixed dose of either of the following. Study drug will be administered TID in equally divided doses:

- Placebo;
- Level 1: pregabalin 7.0 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age];
- Level 2: pregabalin 14.0 mg/kg/day [12 mg/kg/day for subjects 1 to 3 months of age].

Note that the dose levels will be adjusted by age to account for potential differences in renal drug clearance (see [Table 2](#)). For a given level of pregabalin dosing (eg, Level 1), the resultant total daily exposures are anticipated to be comparable throughout the age range of 1 month through <4 years.

Table 2 below summarizes dosing for the 3 double-blind treatments for the Escalation, Fixed-Dosing, and Taper Phases of the study. All active treatments will start at 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] and escalate to the final level as shown in **Table 2**, then taper back to 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] after the fixed dose phase.

Table 1. Double-Blind Dosing By Study Treatment, Study Phase

DOUBLE-BLIND PHASES						
	Dose Escalation Phase		Fixed-Dose Phase		Taper Phase*	
	Age >3 months	Age ≤3 months	Age >3 months	Age ≤3 months	Age >3 months	Age ≤3 months
Treatment ^a						
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Level 1:-	3.5 mg/kg/day x 5 days	3.0 mg/kg/day x 5 days	7.0 mg/kg/day x 9 days	6.0 mg/kg/day x 9 days	3.5 mg/kg/day x 7 days	3.0 mg/kg/day x 7 days
Level 2:	Step 1: 3.5 mg/kg/day x 2 days Step 2: 7.0 mg/kg/day x 3 days	Step 1: 3.0 mg/kg/day x 2 days Step 2: 6.0 mg/kg/day x 3 days	14 mg/kg/day X 9 days	12 mg/kg/day X 9 days	Step 1: 7.0 mg/kg/day x 4 days Step 2: 3.5 mg/kg/day x 3 days	Step 1: 6.0 mg/kg/day x 4 days Step 2: 3.0 mg/kg/day x 3 days

* Subjects who will not participate in Study A0081106 will discontinue study medication following the completion of the taper phase. For subjects who will enter Study A0081106, all subjects will initiate that study at a dose of 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] and may then escalate according to protocol requirements.

a Study drug will be administered TID in equally divided doses.

Statistical Methods:

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

Primary Efficacy Analysis

The primary analysis will be performed on the log_e (double-blind 24-hour EEG seizure rate + 1) using a linear model with treatment, age stratum, and geographical region (ie, US, Europe, Asia, Rest of the World as data allows) as fixed factor effects, and log_e (baseline 24-hour EEG seizure rate + 1) as a continuous covariate. This linear model will include both dose groups of pregabalin. The primary analysis will assess each dose of pregabalin versus placebo using ordinary estimation, in a step-wise fashion. Results will be summarized by treatment group as an approximation of a percent change from placebo in 24 hr seizure rate.

Secondary Efficacy Analysis

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

Sample Size Justification

A total of approximately 123 subjects was originally planned to be randomized in this study in a 2:2:1 ratio of placebo, Level 1 and Level 2. This randomization scheme was considered to allow a sufficient number of patients to be studied at each dose level for safety, while providing adequate power to detect a significant effect for dose Levels 1 and 2.

Randomization of 123 subjects accounted for a potential 10% discontinuation rate, with a resulting sample size of the necessary 110 subjects (44 placebo, 44 Level 1, and 22 Level 2).

The sample size rationale was based on the observed difference in \log_e (double-blind 24-hour seizure rate + $\frac{1}{28}$) between pregabalin and placebo (Table 4). A difference in the least

squares means between pregabalin and placebo was estimated to be -0.668 and -0.448 for 600- and 300 mg doses respectively, with a pooled standard deviation (SD) of 0.73. This difference and pooled SD was obtained from a meta analysis of the -34, -11, -09 study data in adult subjects with partial onset seizures.

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

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

The constant utilized in the log transformation of the 24-hour seizure rate for the primary analysis was changed while the study was ongoing from “1/28” to “1” due to differences in the seizure rate distribution assumed during design of the study and the observed, blinded data distribution. Changing the constant to 1 provides a better approximation of a normal distribution of the seizure data. The constant “1/28” added variability to the data and decreased its normality.

The blinded sample size re-estimation procedure utilized for this study was revised per the Statistical Analysis Plan and did not allow for a reduction in the planned sample size of 123 subjects total or require an increase in sample size greater than 150 subjects. The following decision rules were utilized for the blinded sample size re-estimation:

- a. If the recalculated sample size is less than or equal to the original sample size of 123 subjects total, then the sample size will not be adjusted.

- b. If the recalculated sample size is greater than the original sample size (123 subjects total) then the following information will be considered:
- If the re-estimated sample size is between 123 and 150, then the sample size will be adjusted to the re-estimated sample size;
 - If the re-estimated sample size exceeds 150 then the sample size will be increased to 150.

The blinded sample size re-estimation was conducted, and the sample size will be increased to approximately 150 subjects.

Blinded Sample Size Re-estimation

A blinded sample size re-estimation procedure will be applied when approximately two thirds of the subjects that make up initial sample size have the opportunity to complete the study.

Safety Analysis

Safety will be assessed by summarizing and reviewing the nature, frequency, relationship to study drug, and severity of AEs, the results of physical and neurological examinations, weight, vital signs, ECG's and the results of clinical laboratory tests including hematology, blood chemistry, and urinalysis. Subject listings of all laboratory data will be provided using a standard computer program for laboratory data display. The listings will highlight values outside normal limits and those considered to be possible clinically important deviations. Medical history, physical exams, assessment of vital signs, and ECG will be displayed in standard listings and summary tables.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Study Periods	Screening	48 Hour Video-EEG Baseline Recording	Double Blind Dose Escalation Phase		Double-Blind Fixed Dose Treatment Phase		48 Hour Video-EEG Treatment Recording	Taper/Termination Phase	
								Completion of Double Blind Fixed Dose Phase and Begin Taper Phase ^b	End of Study or Early Termination
Clinic Visit Number	Visit 1	Visit 2	Visit 3	*PV	Visit 4	*PV	Visit 5 ^f	Visit 6	Visit 7
Study Day	-14 ± 3	-3 to -1	1 ± 1	4 ± 1	6 ± 1	9 ± 1	12 to 14 ± 1	15 ± 2	22 ± 3
Informed consent	X								
Record demographic information	X								
Record medical history	X								
Record seizure history	X								
Perform physical and neurological examination	X ^a		X ^c						X ^a
Review inclusion/exclusion criteria	X		X						
Record antiepileptic medication history	X								
Record all prior and/or concomitant medications and non-drug treatments and procedures	X	X	X	X	X	X	X	X	X
Dispense seizure event log		X ^f					X		
Collect and review seizure event log			X					X	
Initiate Video electroencephalogram (EEG)		X					X		
Download Video-EEG data and send to reader			X					X	
Perform head CT or MRI ^c	X								

Study Periods	Screening	48 Hour Video-EEG Baseline Recording	Double Blind Dose Escalation Phase		Double-Blind Fixed Dose Treatment Phase		48 Hour Video-EEG Treatment Recording	Taper/Termination Phase	
								Completion of Double Blind Fixed Dose Phase and Begin Taper Phase ^b	End of Study or Early Termination
Clinic Visit Number	Visit 1	Visit 2	Visit 3	*PV	Visit 4	*PV	Visit 5 ^l	Visit 6	Visit 7
Study Day	-14 ± 3	-3 to -1	1 ± 1	4 ± 1	6 ± 1	9 ± 1	12 to 14 ± 1	15 ± 2	22 ± 3
Perform 12-lead electrocardiogram (ECG)	X								X
Collect and record vital signs	X		X		X		X	X	X
Record height/length	X		X						
Record weight	X		X						
Collect blood and urine samples for clinical laboratory assessments ^m	X		X					X	X
Randomization ^d			X ^l						
CCl [REDACTED]					X ^f			X ^g	X ^h
Evaluate and record study medication compliance					X		X	X	X
Dosing compliance training/review and demonstration			X		X		X		
*Telephone visit to assess dosing compliance and AE's				X		X			
Dispense dosing diary			X		X		X	X	
Collect and review dosing diary					X		X	X	X
Dispense study medication			X ^k		X			X	
Assess and record adverse events		X	X	X	X	X	X	X	X

- Full physical and neurological exams at this visit.
- Subjects who require early discontinuation should begin the taper period at the time the decision is made to discontinue. All Visit 6 and 7 procedures should be performed as possible.
- If not performed previously. In the event that a CT or MRI scan is needed, it should be performed as soon as possible after Visit 1 if it cannot be performed the day of this visit and must be completed and reviewed prior to randomization.
- Subjects who meet all inclusion and none of the exclusion criteria will be randomized on Day 1 of Visit 3 and study drug will be dispensed at this visit.

- e. Neuro and physical exams at this visit will be brief.
- f. CCI [REDACTED] (CCI [REDACTED]).
- g. CCI [REDACTED]
- h. CCI [REDACTED]
- i. Dispense seizure event log to track seizure events during Video-EEG and train parent(s)/guardian(s)/caregiver(s) on its use and completion.
- j. Verify the criteria for total number of qualifying seizures has been met by review of the Video-EEG by the investigator prior to randomization.
- k. Administer first dose of study medication in clinic.
- l. Subjects who complete or terminate Video-EEG recording before Day 15 will continue fixed dosing until beginning the taper phase at Visit V6 on Day 15.
- m. If it is not possible to collect a urine sample, despite appropriate efforts, the urine sample can be omitted for that visit. The reason for lack of sample must be recorded and documented in source documentation.

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1. INTRODUCTION

Epilepsy is a common disorder in childhood affecting 4 to 5 of every 1000 children. Although epilepsy is often well controlled with existing antiepileptic drug (AED) therapy, more than 25% of pediatric patients have seizures that are uncontrolled by currently available agents, or have adverse effects related to AEDs that complicate their seizure control. In addition, children with epilepsy often suffer from impaired academic performance, with 55% functioning below their grade level and an additional 16% significantly behind in educational training.¹ Children with epilepsy also have a higher likelihood of developing behavioral difficulties, which may persist into adulthood.² Early age of onset and a higher number of total lifetime seizures are the strongest correlates of academic underachievement. Therefore, the availability of a new AED that has been shown to improve seizure control and that is generally well tolerated is needed.

1.1. Indication

Adjunctive therapy for pediatric subjects 1 month (44 weeks gestational age) through <4 years of age with partial onset seizures with or without secondary generalization.

1.2. Background and Rationale

Pregabalin [CI-1008, (S)-3-(amino methyl)-5-methylhexanoic acid] binds with high affinity to the $\alpha_2\delta$ site (an auxiliary subunit of voltage gated calcium channels) in central nervous system tissues. Results with genetically modified mice and with compounds structurally related to pregabalin indicate that binding to the $\alpha_2\delta$ subunit may be involved in pregabalin's anti-seizure effects in animal models. In vitro, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

Gabapentin (Neurontin[®]) and pregabalin (Lyrica[®]) are the only 2 $\alpha_2\delta$ agents that are approved for use as medications for the treatment of partial onset seizures. Both are believed to exert their pharmacologic action by binding to the $\alpha_2\delta$ site of voltage gated calcium channels. Gabapentin is approved as adjunctive therapy in the treatment of partial seizures in adults and children (US children aged 3 years of age and older; EU-children aged 6 years of age and older). Gabapentin is well tolerated in both adult and pediatric patients. The most common treatment-emergent adverse events reported in a controlled trial of gabapentin for the adjunctive treatment of epilepsy in subjects 3 to 12 years of age were viral infection, fever, nausea and/or vomiting, and somnolence.

Pregabalin is approved in more than 100 countries, with indications summarized below for the United States (US), European Union (EU), and Japan (JP). In the US, pregabalin is indicated for the adjunctive therapy for adult patients with partial onset seizures. In addition, pregabalin is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia, and fibromyalgia and neuropathic pain associated with spinal cord injury. In the EU, pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization. In addition, pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults and for generalized anxiety disorder in adults. In Japan, pregabalin is indicated for the treatment of peripheral neuropathic pain and fibromyalgia. The approved dose range for the adjunctive

treatment of partial onset seizures in adults is 150 to 600 mg/day, administered twice daily (BID) or 3 times daily (TID). The most common adverse effects reported with pregabalin in placebo controlled adjunctive trials in adults with partial onset seizures were dizziness (32%) and somnolence (22%). Since initial market approval of Lyrica® in 2004 through the first quarter of 2012, it is estimated that more than 15,900,000 patient years of exposure have accumulated worldwide.

Pregabalin pharmacokinetic (PK) data from adult clinical pharmacology studies and one clinical pharmacology study in pediatric subjects with epilepsy (Study A0081074) show that pregabalin pharmacokinetics are linear and predictable. Multiple dose pharmacokinetics are predictable from single dose data. Pregabalin is rapidly absorbed when administered in the fasted state. The rate of pregabalin absorption is decreased when given with food. However, administration of pregabalin with food has no clinically relevant effect on the total amount of pregabalin absorbed. Therefore, pregabalin can be taken with or without food. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean plasma pregabalin half-life of 6.3 hours in adults. Pregabalin clearance is proportional to creatinine clearance, and the major influence on its clearance is reduced or impaired renal function. Since pregabalin is predominantly excreted unchanged in the urine (<2% of a dose recovered in urine as metabolites), undergoes negligible metabolism, and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions. In adult subjects, no pharmacokinetic interactions were seen between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and other commonly used antiepileptic drugs.

The pharmacokinetics (PK), safety, and tolerability of pregabalin were evaluated in pediatric subjects 1 month to 16 years of age with partial onset seizures in the double-blind, placebo-controlled Phase 1 Study A0081074. Dose levels 2.5, 5.0, 10.0, and 15.0 mg/kg/day (given in equally divided doses twice daily) were administered for 8 days. Single and multiple dose PK were evaluated. Pregabalin peak concentration (C_{max}) and total exposure (area under the curve AUC) increased linearly with increasing dose (2.5, 5.0, 10.0 and 15.0 mg/kg/day) for each age group (1 month to 23 months, 2 to 6 years, 7 to 11 years, and 12 to 16 years). Pregabalin terminal $t_{1/2}$ averaged about 3 to 4 hours in pediatric subjects from 1 month to 6 years of age, and 4 to 6 hours in those 7 years of age and older. Pregabalin oral clearance normalized per body weight was 43% higher in the children with body weight less than 30 kg than in children whose body weight was 30 kg and higher. Apparent oral clearance of pregabalin was directly related to creatinine clearance. When dosed on a mg/kg/day basis, pregabalin daily exposure was approximately 30% lower in these subjects weighing less than 30 kg. The data from Study A0081074 has been used to define the dose range and frequency to be investigated in this study (Study A0081042) and additional Phase 3 efficacy and safety studies in the pediatric epilepsy population.

Pregabalin has been shown to be effective in the treatment of epilepsy in adults and is currently approved for the adjunctive treatment of POS in adults over a dose range of 150 to 600 mg/day (when taken 2 or 3 times a day). Thus, pregabalin's mechanism of action, being different from other anti-epileptic drugs, has the potential to expand treatment choices for children with epilepsy. This study is considered to have a positive risk benefit ratio for enrolling patients based on extensive previous experience with pregabalin in adults with POS and with the comprehensive safety screening and monitoring plans included in the present study design.

This study is one of several studies that will be conducted to assess the safety and efficacy of pregabalin in pediatric subjects with epilepsy and to address post approval commitments to US Food Drug Administration (FDA) and EU European Medicines Agency (EMA) regulatory authorities.

Complete information for pregabalin may be found in the Single Reference Safety Document which for this study is the Investigator Brochure.

1.3. Dose Rationale

The recommended dosing regimen in both the US and EU for adjunctive therapy with Lyrica® in adults with partial onset seizures ranges from 150 to 600 mg/day given BID or TID. This dosing regimen approximates that for the range of 2.5 mg to 10.0 mg/kg/day assuming a 60 kg adult individual. The two dose levels for this study will, therefore, provide exposures comparable to those achieved in adults with 300 mg/day or 600 mg/day dosing. Pregabalin will be administered TID in equally divided doses.

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

Throughout the protocol, Level 1 will be used to indicate pregabalin 7.0 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age] dosing and Level 2 will be used to indicate pregabalin 14.0 mg/kg/day dosing [3 mg/kg/day for subjects 1 to 3 months of age].

Since pregabalin clearance normalized for body weight is approximately 40% higher in pediatric subjects weighing less than 30 kg relative to adults and pediatric subjects weighing >30 kg, a daily dose 40% higher relative to that for adults is needed to achieve exposure similar to that of adults. In addition, since pregabalin terminal $t_{1/2}$ is expected to be approximately 3 to 4 hours in pediatric subjects from 1 month to <4 years of age, shorter than the $t_{1/2}$ in older pediatric and adult subjects, a TID dosing regimen will be utilized for this study. In addition, in consideration of potential differences in renal drug clearance in subjects 1 month to 3 months of age relative to subjects >3 months of age, a downward dose adjustment is needed to achieve similar exposures. Throughout the protocol, 7 mg/kg/day will be used to indicate Level 1 dosing and 14.0 mg/kg/day will be used to indicate Level 2 dosing. The adjusted dose for pediatric subjects 1 to 3 months of age will be shown in brackets/parentheses in select sections, but for brevity will not be shown in all sections.

The rate of pregabalin taper in this pediatric study in patients with epilepsy is consistent with the taper rate used in the adult epilepsy trials and reflected in approved labeling. Study medication will, therefore, be gradually discontinued over 1 week to minimize the potential of increased seizure frequency.

1.4. Justification for Placebo Arm

The placebo arm is critical to include in Study A0081042 to achieve the scientific objectives of the study in evaluating the safety and efficacy of pregabalin and to then provide important medical information in labeling for the potential use of pregabalin in pediatric epilepsy patients. Given the variability and episodic nature that can influence the number, type, and frequency of seizures in epilepsy patients, use of a placebo control is an inherent and critical component of the study design to test the hypothesis of seizure reductions in the 2 pregabalin-treated groups necessarily compared with placebo treated subjects. Use of placebo is also critical to characterize the safety and tolerability of pregabalin in pediatric subjects. In addition, Study A0081042 is designed to meet regulatory requirements for demonstrating safety and efficacy in pediatric epilepsy subjects with data compared typically to a placebo control for that purpose. However, it should be noted that adjunctive therapy is used in this study and therefore all placebo and actively treated subjects will be required to continue their current AED therapy concomitant to study medication.

1.5. Study A0081106: 1-Year Open Label Safety Study of Pregabalin

Subjects who complete the treatment phases of this study through Visit 7 and enter the double-blind taper phase will be eligible for screening into 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. Subjects will be considered to have completed Study A0081042 at Visit 7.

In certain instances subjects who require withdrawal from this study may still be eligible for screening and entry into the long term safety study A0081106. Subjects who do not meet the inclusion criteria of at least 1 partial seizure during the 48 hour baseline Video-EEG may still be eligible for screening for A0081106. Subjects who have completed the dose escalation phase and received at least one dose during the fixed-dose phase, but withdraw due to poor tolerability or lack of efficacy, may also be eligible for screening for Protocol A0081106. Such cases should be reviewed with the Pfizer study clinician to determine further eligibility.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Efficacy Objective:

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

Secondary Efficacy Objective:

- To evaluate the efficacy of pregabalin compared to placebo on the frequency of partial onset seizures as determined by responder rate in pediatric subjects 1 month through <4 years of age.
- To assess the safety and tolerability of pregabalin in pediatric subjects 1 month (44 weeks gestational age) through <4 years of age with partial onset seizures.

2.2. Endpoints

Primary Efficacy Endpoint:

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

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

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

Secondary Efficacy Endpoint:

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

Safety Endpoints:

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

3. STUDY DESIGN

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

Approximately 150 subjects will be enrolled in this study as determined from the blinded sample size re-estimation (refer to [Section 9.1](#)).

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

The study is composed of 4 phases:

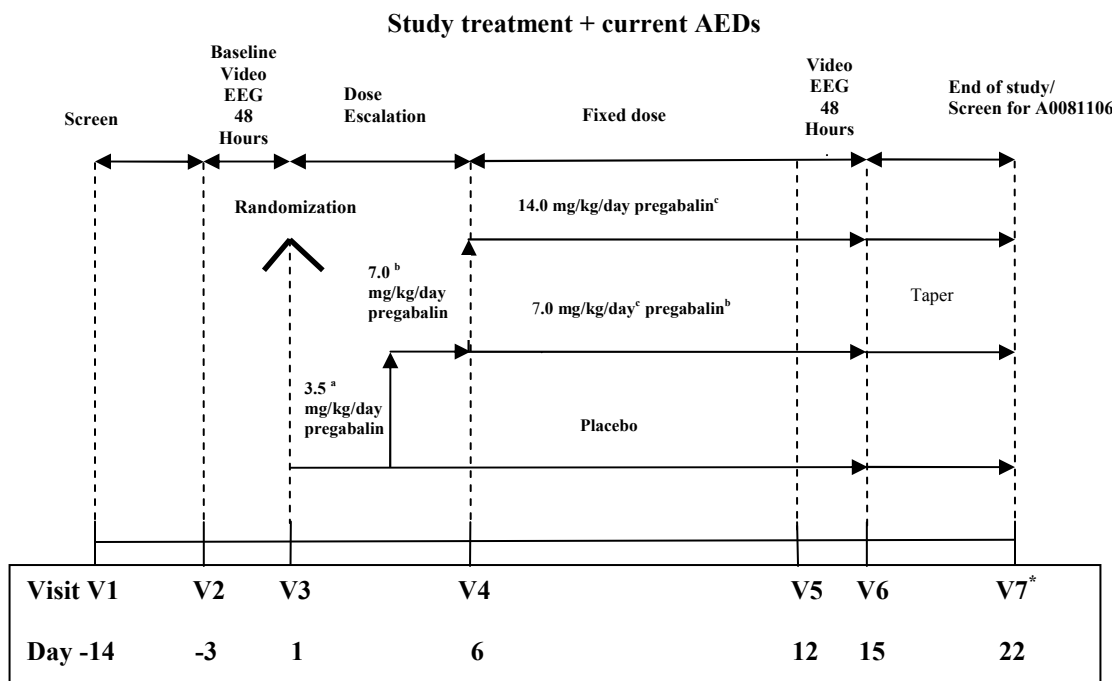
- Video-Electroencephalographic (EEG) baseline phase with a target minimum of 48 hours. To ensure that the target minimum of 48 hours of Video-EEG is obtained, the total duration of the Video-EEG baseline phase will be up to 72 hours.
- 5 day double-blind dose escalation phase.
- 9 day double-blind fixed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

The total double-blind treatment phase is 21 days.

Every reasonable attempt should be made to obtain the minimum target Video-EEG recording of 48 hours, which may require up to 72-hours of recording. Recognizing the inherent challenges in Video-EEG monitoring of pediatric subjects with epilepsy it is expected that the target minimum 48 hour Video-EEG recording may even then not be achievable in all cases. In the clinical investigator's opinion, should circumstances (eg, clinical care, child behavior, consent, etc.) mandate a Video-EEG monitoring period less than 48-hours for a given subject, please contact the study clinician to review the subject's clinical circumstances and document reasons for not achieving the target minimum duration.

Subjects who complete the treatment phases of this study through Visit 7 and enter the double-blind taper phase will be eligible for screening into Protocol A0081106, a 1-year open label safety study (Please refer to [Section 1.5](#) Study A0081106: 1-Year Open-Label Safety Study of Pregabalin for more details). Subjects who participated in study A0081042 through Visit 7 will be considered to have completed the study.

Study Design Diagram:



* Eligible subjects may be assessed for screening into study A0081106 and complete end of study activities for A0081042 at Visit 7 (V7)

a [3 mg/kg/day for subjects 1 to 3 months of age];

b [6 mg/kg/day for subjects 1 to 3 months of age];

c [12 mg/kg/day for subjects 1 to 3 months of age]

3.1. Screening and Baseline Phase

Prior to screening, informed consent will be obtained from the parents/guardians. Subjects must have had at least 3 partial onset seizures in the month prior to screening. Subjects must be receiving a stable dose of 1-3 AEDs for 7 days before screening. Subjects meeting the inclusion/exclusion criteria on the first Screening Visit (Visit 1) are enrolled in the study.

After verification of the diagnosis, at Visit 2, the subject is fitted with a continuous EEG recording device for a 48 hour Video-EEG baseline partial onset seizure frequency evaluation. During the 48 hr baseline phase subjects will be maintained on their current AED regimen. The investigator will evaluate the baseline Video-EEG for the purpose of determining if the subject meets the inclusion criteria. Subjects who experience at least 2 partial-onset seizures, with or without secondary generalization, during the 48 hour Video-EEG observation period will be randomized to treatment at Visit 3. A central reader will evaluate the Video-EEG data to determine the number of baseline seizures for the analysis of efficacy. Subjects that are randomized, but are subsequently determined by the central reader to have less than 2 partial-onset seizures will be allowed to continue in the study. Subjects who are determined by the central reader to have potentially exclusionary seizures types will be discussed with the study clinician and investigator to determine if the subject must be withdrawn from the study.

Subjects who fail screening and cannot enter the study, may, under certain circumstances, be re-screened for study inclusion at a later date. For example, re-screening may occur if a subject fails due to exclusionary lab values, use of disallowed concomitant medications or intercurrent illness should this change at a later date. Any subjects being considered for re-screening should be discussed by the Investigator with the Pfizer Study Clinician or Medical Monitor.

3.2. Dose Escalation Phase (5 Days) and Fixed Dose Phase (9 Days) and Taper Phase (7 Days)

Subjects who complete the baseline phase and meet the eligibility criteria will be randomized in a double-blind manner at Visit 3 to one of the following study treatments in a 2:2:1 ratio (placebo: Level 1: Level 2). Level 1 and Level 2 pregabalin doses will be based on weight recorded at Visit 3. Study drug will be administered TID in equally divided doses.

Study Treatments:

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

Subjects randomized to receive either Level 1 or Level 2 pregabalin will have a 5 day escalation phase, a 9 day fixed dose phase, and a 7 day taper phase. The taper phase should begin following the completion of the Double-Blind Fixed Dose Treatment Phase at Visit 6. Note: subjects who require early discontinuation should begin the taper period after the

decision is made to discontinue. Subject's daily dosing will be recorded by their parent(s)/guardian(s)/caregiver(s) as appropriate, in a daily dosing diary. Table 2 below summarizes dosing for the 3 double-blind treatments for the Escalation, Fixed-Dosing, and Taper Phases of the study. All active treatments will start at 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] and escalate to the final level as shown in Table 2, then taper back to 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] after the fixed dose phase.

Table 2. Double-Blind Dosing By Study Treatment, Study Phase

DOUBLE-BLIND PHASES						
Treatment ^a	Dose Escalation Phase		Fixed-Dose Phase		Taper Phase [*]	
	Age >3 months	Age ≤3 months	Age >3 months	Age ≤3 months	Age >3 months	Age ≤3 months
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Level 1:-	3.5 mg/kg/day x 5 days	3.0 mg/kg/day x 5 days	7.0 mg/kg/day x 9 days	6.0 mg/kg/day x 9 days	3.5 mg/kg/day x 7 days	3.0 mg/kg/day x 7 days
Level 2:	Step 1: 3.5 mg/kg/day x 2 days Step 2: 7.0 mg/kg/day x 3 days	Step 1: 3.0 mg/kg/day x 2 days Step 2: 6.0 mg/kg/day x 3 days	14 mg/kg/day X 9 days	12 mg/kg/day X 9 days	Step 1: 7.0 mg/kg/day x 4 days Step 2: 3.5 mg/kg/day x 3 days	Step 1: 6.0 mg/kg/day x 4 days Step 2: 3.0 mg/kg/day x 3 days

* Subjects who will not participate in Study A0081106 will discontinue study medication following the completion of the taper phase. For subjects who will enter Study A0081106, all subjects will initiate that study at a dose of 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] and may then escalate according to protocol requirements.

a Study drug will be administered TID in equally divided doses.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the parent(s)/guardian(s) have been informed of all pertinent aspects of the study. When there are 2 parents, or 2 guardians, consent should be obtained from both of the child's parents/guardians if present at the meeting where the informed consent document is signed.
2. Subjects and Parent(s)/guardian(s)/caregiver(s) who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Male and female subjects, 1 month (44 weeks gestational age) through <4 years of age inclusive on the date of the Screening Visit with a diagnosis of epilepsy with seizures classified as simple partial, complex partial or partial becoming secondarily generalized, according to the International League Against Epilepsy (ILAE 2010³ see [Appendix 1](#)) Diagnosis must be established by:
 - Subject's seizure history (eg, description of seizures excluding confounding disorders such as pseudoseizures etc), family history and neurological exam.
 - Subjects must have previously had a contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain and EEG testing. Results must be consistent with the diagnosis of focal onset epilepsy and must demonstrate that no abnormality is likely to be progressive.
 - In the event that a CT or MRI scan is needed, it should be performed as soon as possible after Visit 1 if it cannot be performed the day of this visit and must be completed and reviewed prior to randomization.
4. Currently receiving a stable dose of 1 to 3 antiepileptic drugs (stable within 7 days prior to screening). Benzodiazepine medication used on a regular basis at a stable dosage will be considered 1 of the concurrent antiepileptic treatments, Vagus Nerve Stimulator when present will also be considered 1 of the concurrent antiepileptic treatments.
5. A 12-lead ECG at screening without clinically significant abnormal findings as determined by the investigator. Potentially clinically significant abnormal findings will be reviewed by a pediatric cardiologist at the central ECG laboratory.
6. Subjects must have had at least 3 observed seizures in the month prior to screening.
7. Subjects must have at least 2 partial onset seizures as determined by the investigator or designee during the 48 hour baseline Video-EEG phase.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Primary generalized seizures (including in the setting of co-existing partial onset seizures) which may include, for example:
 - Clonic, tonic, and clonic-tonic seizures (note that partial onset seizures that become secondarily generalized are not exclusionary);
 - Absence seizures;
 - Infantile spasms;
 - Myoclonic, myoclonic atonic, myoclonic tonic seizures.
2. Lennox-Gastaut syndrome, Benign Epilepsy with Centrotemporal Spikes (BECTS) and Dravet syndrome.
3. A current diagnosis of febrile seizures or seizures related to an ongoing acute medical illness.
4. Exacerbation of partial onset seizures due to fever occurring within 60 days of screening.
5. Status epilepticus within 1 year prior to screening.
6. Seizures related to acute medical illness.
7. Any change in AED regimen (type of medication or dose) within 7 days of the Screening Visit or during the Baseline Phase.
8. Progressive structural central nervous system (CNS) lesion or a progressive encephalopathy.
9. Progressive errors of metabolism.
10. Known or suspected chronic hematologic, hepatic or renal disease (AST and ALT above 3 times the upper limit of normal (ULN); or bilirubin, BUN, or creatinine above 2 times the ULN within the previous 6 months prior to screening). Subjects who experienced neonatal hyperbilirubinemia may be included after consulting with the study clinician.
11. Estimated creatinine clearance (ClCR) $<80 \text{ mL/min/1.73 m}^2$ (see [Section 7.4.1](#)).
12. Subjects whose parents/caregivers are investigational site staff members directly involved in the conduct of the trial or otherwise supervised by the Investigator.

13. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days before the current study begins and/or during study participation.
14. Other severe acute or chronic medical, psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of the study results or in the judgment of the investigator, would make the subject inappropriate for entry into this study. Patients with complex medical histories, including genetic or chromosomal syndromes, should be discussed with the study clinician prior to screening.
15. The concomitant use of gabapentin, felbamate, and vigabatrin is prohibited.
16. Previous treatment of epilepsy with pregabalin.
17. Weight >30.0 kg.

4.3. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list. To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subject's parents/caregivers are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subjects parents/caregivers directly and if a subjects parents/caregiver calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Subjects who complete the 48 hr Baseline Phase and meet the eligibility criteria will be randomized in a double-blind manner at Visit 3. Subjects will be randomized to placebo or one of 2 fixed doses divided TID, either Level 1: pregabalin 7.0 mg/kg/day [6 mg/kg/day for subjects 1 to 3 months of age], or Level 2: pregabalin 14.0 mg/kg/day divided TID [12 mg/kg/day for subjects 1 to 3 months of age], in a 2:2:1 ratio (Section [Dose Escalation Phase \(5 Days\) and Fixed Dose Phase \(9 Days\) and Taper Phase \(7 Days\)](#)). Randomization will be stratified by site and subject age (Stratum 1: <1 year of age; Stratum 2: 1-2 years of

age; Stratum 3: >2 years of age). Every reasonable effort will be made to enroll a minimum of 10 subjects in each of the 3 age strata.

Table 2 below summarizes dosing for the 3 double-blind treatments for the Escalation, Fixed-Dosing, and Taper Phases of the study.

Table 3. Double-Blind Dosing By Study Treatment, Study Phase

DOUBLE-BLIND PHASES						
	Dose Escalation Phase		Fixed-Dose Phase		Taper Phase*	
	Age >3 months	Age ≤3 months	Age >3 months	Age ≤3 months	Age >3 months	Age ≤3 months
Treatment ^a						
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Level 1:-	3.5 mg/kg/day x 5 days	3.0 mg/kg/day x 5 days	7.0 mg/kg/day x 9 days	6.0 mg/kg/day x 9 days	3.5 mg/kg/day x 7 days	3.0 mg/kg/day x 7 days
Level 2:	Step 1: 3.5 mg/kg/day x 2 days Step 2: 7.0 mg/kg/day x 3 days	Step 1: 3.0 mg/kg/day x 2 days Step 2: 6.0 mg/kg/day x 3 days	14 mg/kg/day X 9 days	12 mg/kg/day X 9 days	Step 1: 7.0 mg/kg/day x 4 days Step 2: 3.5 mg/kg/day x 3 days	Step 1: 6.0 mg/kg/day x 4 days Step 2: 3.0 mg/kg/day x 3 days

* Subjects who will not participate in Study A0081106 will discontinue study medication following the completion of the taper phase. For subjects who will enter Study A0081106, all subjects will initiate that study at a dose of 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] and may then escalate according to protocol requirements.

a Study drug will be administered TID in equally divided doses.

5.2. Breaking the Blind

This will be a double-blind study, ie, the subject/parent(s)/caregiver(s) and investigator will not know what study medication the subject will receive. The study drug and placebo will be identical in appearance in order to achieve the study blinding.

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

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Study medication will be supplied by Pfizer as 20 mg/mL solution and matching placebo solution (see Appendix 2 for more detail). All study medication is to be packaged in bottles that are child resistant.

Pregabalin oral solution and the matching placebo contain a sweetening agent (sucralose) and a flavor (artificial strawberry).

5.3.2. Preparation and Dispensing

The Investigator will receive shipments of clinical drug supplies, must verify and acknowledge their receipt, and retain related documentation.

The Sponsor will provide study medication that will be dispensed through the telrandomization system (Interactive Voice Response System or IVRS) according to a randomization code provided by the Clinical Statistics Department. The supplies will be identified by the IVRS using a container number. The IVRS will monitor the study medication inventory and re-supply as necessary.

The double-blind medication will be dispensed at Visit 3 and Visit 4. The 1-week taper medication will be dispensed at Visit 6 or, for those subjects who discontinue before completing 2 weeks of treatment, at an unscheduled early termination visit.

5.3.3. Administration

Pregabalin or matching placebo will be administered orally TID. The dose (volume of solution) to be drawn from the bottle will be based on the weight of the subject at Visit 3 as well as the randomized treatment arm.

Medication errors may result in this study from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the case report form (CRF) and on the serious adverse event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to [ADVERSE EVENT REPORTING](#) section for further details).

5.3.4. Compliance

Subjects will be administered the study medication according to the instructions provided, and should adhere to the dosing schedule as closely as possible, with study medication administered TID. Parent(s)/guardian(s)/caregiver(s) will complete a dosing diary and will bring the diary and the medication bottle(s) back to the clinic at each visit. Medication bottles will be weighed by the site staff when dispensed. The bottles will again be weighed when returned at each visit, in order to determine the approximate volume of study medication used. The caregiver will be queried about any volume discrepancies. All dispensed study medication bottles should be locally kept available for checks by the study monitor.

Compliance will be defined as the percentage of required doses that were ingested. Subjects who are consistently not compliant with the dosing regimen should be evaluated by the Investigator and discussed with the Pfizer Clinician for possible discontinuation from the study.

The following guidelines are provided in the event a pediatric subject does not retain the oral dose administered. If the subject regurgitates or spits out the study drug within 15 minutes after administration, the study drug should be re-administered at the same dose/volume. If the subject regurgitates after more than 15 minutes have elapsed post administration, no additional study drug should be administered until the next scheduled dose. Regurgitation and any additional dosing should be noted in the Dosing Diaries and captured in the dosing log CRFs. Subjects with repeated regurgitation/redosing should be discussed with the Pfizer clinician.

Administration of the liquid oral dose through a nasogastric (NG) feeding tube will be permitted and should be documented accordingly. If a subject has an NG tube that was inserted prior to entry into the study, it should be documented in the subjects' "Medical History". If a subject has an NG tube inserted during the course of the study, it should be documented in the subjects' "Concomitant Treatments" as a non-drug treatment. Specifying whether the NG tube was inserted or removed during the study is to be documented.

5.4. Drug Storage and Drug Accountability

It is the site's responsibility to handle and store the clinical study supplies under secure and locked conditions. Note that pregabalin is a controlled substance in the US, and therefore must be stored according to US/Federal Drug Enforcement Agency (DEA) regulations in the US. The US sites will provide a copy of the DEA license, and proper state/local license if applicable, to the Sponsor. For those countries where pregabalin is not a controlled substance, the sites are to comply with their local regulations.

Study medication should be stored at 15-25°C. Access to the stored study medication should be limited to the Investigator, Subinvestigators, the Study Coordinator, and the Pharmacist (when applicable). The Investigator, or an approved representative, eg, Pharmacist, will ensure that all study medications are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Investigators and site

staff are reminded to check temperatures daily (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of investigational products. Any temperature excursions should be reported to the sponsor. If the study medication is determined to have been stored or delivered outside the outlined temperature range, the study team should be informed to evaluate the circumstances and provide appropriate guidance.

Storage conditions stated in the Single Reference Safety Document (SRSD) (ie, Investigator Brochure (IB)) will be superseded by the label storage.

The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Study medication will be dispensed under the supervision of investigator site personnel.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the study medication(s). All medication bottles dispensed to study subjects must be returned to the Investigator. A Pfizer approved drug accountability form must be used. The form must identify the study medication, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

Unused study drug and unused or used study drug materials must be kept in a secure location for final accountability and reconciliation. At the end of the clinical trial all drug supplies unallocated or unused should be returned to a Pfizer vendor for destruction by completing the Destruction of Investigational Product Form. The Investigator must provide an explanation for any destroyed or missing study drug and/or study drug materials. Pfizer may authorize destruction at the trial site, and the Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

5.5. Concomitant Medication(s)

Subjects are required to maintain their current AED therapy of 1-3 AE treatments at stable dosages throughout the baseline, double-blind and taper phases of the study. Subjects who require AED dose or regimen change during this period must exit the study.

Prior and concomitant medication information will be collected for all subjects for the period of 30 days prior to screening and during the study. Once enrolled, any medication a subject takes other than the study medication specified by the protocol is considered a concomitant medication. This includes all antiepileptic medications. All concomitant medication must be recorded in the subject's medical record and on the appropriate Case Report Form (CRF) page. Information collected must include medication, start date and stop date. Additionally,

for stable (nonPRN) antiepileptic medications, information collected must include medication, dosage, start date, and stop date.

5.5.1. Permitted Medications

The Investigator must be aware of all medications the subject is receiving prior to participation in the study. The following listing of medications/classes of medications is meant to provide guidance regarding permitted medications but should not be considered a comprehensive list. A member of the Pfizer study team should be consulted for assistance in determining whether or not specific medications not contained on this list should be permitted or prohibited.

Non-prescription medications, including herbal and home remedies, are also considered concomitant medications and should be recorded, along with other medications on the Concomitant Medication Log of the Case Report Form (CRF).

Examples of medications or classes of medications for which Episodic Use is permitted:

- Acetaminophen/paracetamol;
- Aspirin (chronic use also permitted);
- Bronchodilators (chronic use also permitted);
- Inhaled steroids (chronic use also permitted);
- Nonsteroidal anti-inflammatory drugs (NSAIDs).

Examples of medications or classes of medications for which Chronic Use is permitted:

- Antiepileptic drugs;
- Aspirin;
- Bronchodilators;
- Inhaled steroids;
- Multivitamins.

5.5.2. Prohibited Medications

Concurrent treatment with other investigational agents or devices is not allowed during the study. The washout period of all centrally- acting compounds (CNS-active) that have to be discontinued per protocol has to be at least 2 weeks prior to screening Visit 1.

The use of gabapentin, Felbamate, or Vigabatrin is prohibited during the study.

Administration of CNS – active compounds, regardless of indication, is prohibited during the trial, with the following **exceptions**:

- Prescribed medications consistent with inclusion/exclusion criteria;
- During study participation subjects must remain on stable AED regimens (same dosage as at screening and throughout the baseline observation period) of 1 to 3 anti-epileptic treatments (eg, drugs or vagus nerve stimulator (VNS)) concomitantly throughout the trial.

6. STUDY PROCEDURES

The trial schedule of events and the specific procedures performed at each visit are shown in the [Schedule of Activities](#). A subject may be seen at any time for reasons of safety.

6.1. Visit 1 Screening (Day -14 ±3)

Prior to study entry the following screening procedures will be performed at Visit 1:

- Obtain written informed consent from one or both parents (if available), or the child's legal guardian(s);
- Review eligibility per inclusion/exclusion criteria;
- Record demographic data (eg, date of birth, sex race, etc);
- Record primary diagnosis; classify seizure types. Record complete medical history including seizure related history and antiepileptic medication history;
- Perform full physical exam which includes vital signs, including blood pressure (BP) and pulse;
- Record height/length and weight;
- Perform full neurological examination;
- Record all prior/concomitant medications and non-drug treatments and procedures, including any ongoing AED's, currently and within 30 days of Visit 1;
- Perform computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain if it has not been performed previously;

Note: in the event that a CT or MRI scan is needed, it should be performed as soon as possible after Visit 1 if it cannot be performed the day of this visit and must be completed and reviewed prior to randomization.

- Perform 12-lead electrocardiogram (ECG).

- Collect blood and urine specimens for clinical laboratory assessments. If it is not feasible to obtain a urine sample, then no urine sample will be required.

Note: In the event that the subject has an abnormal laboratory value and the subject meets all other entry criteria, the laboratory test may be repeated within 7 days of the receipt of the screening visit results at the discretion of the investigator. If repeat test is within normal limits the subject may be considered eligible after consultation with the medical monitor or study clinician.

6.1.1. Visit 2 Baseline Video-EEG (Day -3 to -1)

The following activities will be performed at Visit 2, which is scheduled to assess partial onset seizure frequency by Video-EEG monitoring as an inpatient.

- Placement of EEG electrodes and recording device and instruction of parent(s)/guardian(s)/caregiver(s) of its usage.
- Dispense seizure event log to track observed seizure events during Video-EEG and train parent(s)/guardian(s)/caregiver(s) on its use and completion.
- Record all concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Assess and record adverse events.

6.2. Double-Blind Dose Escalation Phase

6.2.1. Visit 3 (Day 1 \pm 1) Randomization and Entry into Double-blind Dose Escalation Phase

Randomization: Subjects who satisfy all of the eligibility criteria at this study visit may be randomized and will receive the initial dose of study medication at the clinic during this visit.

The following activities will be performed at Visit 3:

- Verify conformance with entry criteria by reviewing inclusion/exclusion criteria.
- Verify the criteria for total number of qualifying seizures has been met by review of the Video-EEG by the investigator/or designee.
- Record all concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Record weight and height/length.
- Assess and record adverse events.
- Perform brief physical examination which includes recording vital signs including blood pressure and pulse.

- Perform brief neurological examination.
- Collect blood and urine specimens for clinical laboratory assessments. If it is not feasible to obtain a urine sample, then no urine sample will be required.
- Assign randomization number and dispense blinded study medication via tele-randomization system.
- Train parent(s)/guardian(s)/caregiver(s) on study medication dosing and administration and demonstrate use of oral syringe/bottles. Have parent(s)/guardian(s)/caregiver(s) practice dosing in office to verify comprehension of dosing instructions.
- Administer first dose of study medication in clinic.
- Dispense daily dosing diary.
- Download Video-EEG recording data.
- Transmit Video-EEG data to central reader for assessment.
- Collect seizure event log and send to central reader.

6.2.2. Telephone Visit (Day 4 \pm 1)

The Investigator (or designee) will contact the parent(s)/guardian(s)/caregiver(s) by telephone on Day 4 to ensure study medication compliance and provide guidance for accurate dosing as required.

- Review compliance with dosing regimen.
- Review completion of daily dosing diary.
- Review concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Assess and record adverse events.

6.3. Double-Blind Fixed-Dose Treatment Phase

6.3.1. Visit 4 (Day 6 \pm 1)

CCI [REDACTED]. If possible, this visit should be scheduled around the usual time of dosing. Parent(s)/guardian(s)/caregiver(s) should be instructed to hold the dosing of study medication prior to the visit. If the visit is scheduled to occur more than 12 hours since the last dose, the subject should take the scheduled dose of study medication as usual.

The following activities will be performed at Visit 4:

- CCI [REDACTED];
- For subjects who held their dose of study medication (see Section CCI [REDACTED]).
 - CCI [REDACTED].
 - CCI [REDACTED].
 - CCI [REDACTED]. Have parent(s)/guardian(s)/caregiver(s) administer this dose to verify continued comprehension of dosing instructions. This dose should be taken using previously dispensed study medication and not the medication dispensed at Visit 4. Record if a meal was consumed within 2 hours prior to and 1 hour following this dose of study medication.
 - CCI [REDACTED].
- For subjects who did not hold their dose of study medication (see Section CCI [REDACTED]).
 - Subject should take his/her dose of study medication as usual. This dose should be taken using previously dispensed study medication and not the medication dispensed at Visit 4.
 - CCI [REDACTED]
 - CCI [REDACTED]
- Record all concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Collect and record vital signs, including sitting or supine BP and pulse.
- Evaluate and record study medication compliance.
- Collect and review dosing diary.

- Assess and record adverse events.
- Dispense study medication.
- Dispense daily dosing diary.
- Verify accurate dose administration via oral syringe/bottles. Have parent(s)/guardian(s)/caregiver(s) demonstrate dosing in office to verify continued comprehension of dosing instructions.

6.3.2. Telephone Visit (Day 9 ±1)

The Investigator (or designee) will contact the parent(s)/guardian(s)/caregiver(s) by telephone on the third day of the fixed dose period to ensure study medication compliance and provide guidance for accurate dosing as required.

- Review compliance with dosing regimen.
- Review completion of dosing diary.
- Review concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Assess and record adverse events.

6.3.3. Visit 5 Video-EEG (Day 12 to 14 ±1)

The following activities will be performed at Visit 5, which is scheduled to assess partial onset seizure frequency by inpatient Video-EEG monitoring.

- Placement of EEG electrodes and recording device and instruction of parent(s)/guardian(s)/caregiver(s) of its usage.
- Dispense seizure event log to track observed seizure events during Video-EEG and train parent(s)/guardian(s)/caregiver(s) on its use and completion.
- Record all concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Evaluate and record study medication compliance.
- Collect and record vital signs.
- Assess and record adverse events.
- Collect and review dosing diary.
- Dispense daily dosing diary.

- Dosing compliance training/review and demonstration.

6.3.4. Visit 6 Begin Taper Phase (Day 15 ±2)

The Double-blind Fixed Dose Treatment phase is completed. Following completion of the 9-day fixed dose treatment and double-blind Video-EEG assessment subjects will begin the 1 week Taper Phase. Subjects who require early termination prior to Visit 6 should also begin the taper and follow the procedures for Visits 6 and 7 below.

- Collect blood and urine samples for clinical laboratory assessments. If it is not feasible to obtain a urine sample, then no urine sample will be required.
- CCI [REDACTED]
- CCI [REDACTED]
- Record all concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Evaluate and record study medication compliance.
- Download on treatment Video-EEG recording data.
- Transmit Video-EEG data to central reader for assessment.
- Collect seizure event log and send to central reader.
- Assess and record adverse events.
- Collect and record vital signs, including BP and pulse.
- Collect and review dosing diary.
- Dispense study medication for taper.
- Dispense subject daily dosing diary.

6.4. Completion of Taper (End of Study/Early Termination)

The taper phase is completed at Visit 7. Subjects will complete Study A0081042 at this visit. Subjects may be screened for Study A0081106.

6.4.1. Visit 7 (Day 22 ±3)

- Record all concomitant medications and non-drug treatments and procedures, including any ongoing AED's.
- Perform 12-lead ECG.
- Perform full physical examination which includes recording vital signs including BP and pulse.
- Perform full neurological examination.
- Collect blood and urine specimens for clinical laboratory assessments. If it is not feasible to obtain a urine sample, then no urine sample will be required.
- Evaluate and record study medication compliance.
- Collect and review dosing diary.
- Assess and record adverse events.

If the subject terminates the study early, then samples for clinical laboratory analysis and CCI will be collected at this visit. If greater than 48 hr have elapsed since the last dose of study medication, then do not collect CCI :

- CCI

6.5. Subject Withdrawal

Subjects may be withdrawn from the study at any time at their parent(s)/guardian(s) request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject/parent(s)/guardian(s) to comply with the protocol required schedule of study visits or procedures at a given site.

Events to consider that may result in withdrawal could include but are not limited to:

- Adverse events;
- Intercurrent illness;
- Loss to follow-up;
- Lack of efficacy;
- Exacerbation of seizures relative to screening/baseline;

- Non-compliance with study medication, protocol requirements, or study related procedures;
- Serious eligibility or violations of the protocol (eg, the subject does not have the target disease);
- Study termination by Sponsor or regulatory authorities;
- Parent's/guardian decision to withdraw/withdrawal of consent;
- Investigator discretion in case of occurrence of any medical condition, requirement for prohibited concomitant medication or treatment, or circumstances that would expose the subject to substantial risk and/or would not allow the subject to adhere to protocol requirements.

Protocol specified withdrawal procedures are the same as those to be performed at Visits 6 and 7 (Section [STUDY PROCEDURES](#)).

In certain instances subjects who require withdrawal from this study may still be eligible for screening for entry into long term safety Study A0081106. Such cases should be reviewed with the Pfizer study clinician to determine further eligibility. Subjects who are withdrawn due to reasons of loss to follow up, protocol non-compliance, protocol violations or who have withdrawn consent will not be eligible for Study A0081106 under any circumstances.

Under certain circumstances, when subjects leave the study early (early termination ET), dosing with the taper medication may be inadvisable. The decision not to taper the subject is upon agreement from the Sponsor's Study Clinician or Designee. If the taper will not be utilized then all assessments required at Visit 6 and 7 should be conducted as possible.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject's parent/caregiver subject and information received during contact attempts must be documented in the subject's medical record). In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the parent(s)/guardian(s) return all unused investigational product, request that the subject/parent(s)/guardian(s) return for a final visit, if applicable, and follow-up with the parent(s)/guardian(s) regarding any unresolved adverse events.

If the subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study sponsor will be informed of these incidents in a timely fashion.

7.1. Efficacy Assessments

Efficacy assessment will be evaluated based on seizure frequency in the last 48 hours of the 2 week double-blind treatment phase determined from the central read of the Video-EEG. The seizure event log will be utilized by the central reader to assist in evaluation of difficult to interpret Video-EEG findings. Assessment of efficacy is based on the reduction in the frequency of partial onset seizures during the same 48 hours of the 2 week double-blind treatment phase.

7.2. Acquisition of Seizure Counts: Video-Electroencephalogram (EEG)

Baseline and treatment phase Video-EEG will include a target minimum of 48 hours of continuous Video-EEG monitoring after placement of electrodes. Every reasonable attempt should be made to obtain the minimum target Video-EEG recording of 48 hours, which may require up to 72-hours of recording. Recognizing the inherent challenges in Video-EEG monitoring of pediatric subjects with epilepsy it is expected that the target minimum 48 hour Video-EEG recording may not be achievable in all cases. In the clinical investigator's opinion, should circumstances (eg, clinical care, child behavior, consent, etc.) mandate a Video-EEG monitoring period less than 48-hours for a given subject, please contact the study clinician to review the subject's clinical circumstances and document reasons for not achieving the target minimum Video-EEG duration. Results of the baseline monitoring must be available and reviewed by the central reader as soon as possible. EEG tracings will be done with a placement of 20 recording electrodes including FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz and reference and ground electrodes. The initial recording impedance should be below 5 KOhms.

7.2.1. Primary Efficacy Parameter

The primary efficacy parameter is the log transformed double blind 24-hour EEG seizure rate during Visit 6 (48-hour Video-EEG Assessment Phase) of the Double-Blind Treatment Phase.

This 24-hour seizure rate will be calculated for each subject using the following algorithm:

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

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

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

The baseline 24-hr Video-EEG seizure rate will be calculated similarly.

7.2.2. Secondary Efficacy Parameter

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

7.3. Safety Assessments

All subjects who have taken 1 dose of study medication (Safety population) will be included in the evaluation for safety, using adverse event data (eg, occurrence, nature, intensity, and relationship to study drug and dosing level), clinical laboratory data, and the results of physical examinations, vital signs, neurological examinations and ECGs.

7.4. Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory measurements will be analyzed by a central laboratory.

7.4.1. Estimated Creatinine Clearance (mL/min/1.73m²)

Creatinine clearance will be calculated by the central laboratory at Screening (Visit 1) only. For laboratories using the Jaffe chromogen reaction to quantify serum creatinine levels, the following equations should be used to calculate creatinine clearance. Other equations may be considered when serum creatinine levels are measured by other methods.

For Subjects ≥ 1 year of age and < 4 years of age:

$$Cl_{CR} = 0.55 \times \text{length (cm)} / \text{serum creatinine (mg/dL)}$$

For Subjects 1 month of age and < 1 year of age:

$$Cl_{CR} = 0.45 \times \text{length (cm)} / \text{serum creatinine (mg/dL)}$$

If the unit of the serum creatinine value is in micromoles/L, the serum creatinine concentration must first be converted to mg/dL using the following equation.

Converting serum creatinine concentration from $\mu\text{moles/L}$ to mg/dL :

$$\text{Serum Creatinine (mg/dL)} = \frac{\text{Serum Creatinine } (\mu\text{M/L})}{88.4}$$

7.4.2. Hematology

Blood samples will be collected at Screening (Visit 1), Visit 3, and at the completion of the Double-Blind Fixed Dose Phase (Visit 6) or at the Early Termination Visit, if necessary, to assess hematology parameters, including: red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), platelets, and white blood cell count (WBC) (with differential), neutrophils, lymphocytes, monocytes and eosinophils.

7.4.3. Clinical Chemistry

Blood samples will be collected at Screening (Visit 1), Visit 3, and at the completion of the Double-blind Fixed Dose Phase (Visit 7) or at the Early Termination Visit, if necessary, to assess clinical chemistries, including: total bilirubin, direct and indirect bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), creatine phosphokinase (CPK) blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, total cholesterol, triglycerides, sodium, potassium, chloride and calcium. In addition, Endocrine panel (free T4 and TSH, IGF-1, and IGFBP-3) and Hepatitis serology (Anti-HAV IgM; S-HB Ag; S-HCV) will be assessed at Visit 1 only.

Approximate blood volumes to be obtained, per visit, are as follows, for children $>5\text{kg}$ in weight*:

V1 Screening:	10.5 mL
V3:	4.5 mL
V4:	<2 mL (for CCI)
V6:	4.5 mL plus <1 mL (for CCI)
V7 EOS or ET:	4.5 mL plus optional <1 mL (for CCI)
Unscheduled visit:	12.3 mL maximum (all testing optional)
CCI:	<1 mL

* Blood sampling may be reduced for potential subjects who do not have the weight/blood volume capacity to undergo the protocol-specified blood collection requirements [for example <5 kg], as per local regulations and institutional guidelines. Prior to implementation of any reduction in blood sampling, the investigator is required to contact the Pfizer Study Clinician (via e-mail or phone) to discuss the applicability of a proposed reduced blood sampling plan. At a minimum, samples for chemistry and hematology will be collected at indicated visits.

7.4.4. Urinalysis

Urine samples will be collected at Screening (Visit 1), Visit 3, and completion of the Double-blind Fixed Dose Phase (Visit 6) or at the Early Termination Visit, if necessary, to assess the following: pH, specific gravity, colorimetric urine protein, glucose and ketones. Microscopic analysis will be performed only if the results of the urinalysis are abnormal and will include: red blood cells (RBCs), white blood cells (WBCs), casts, crystals, and bacteria. If it is not possible to collect a urine sample, despite appropriate efforts, the urine sample can

be omitted for that visit. The reason for lack of sample must be recorded and documented in source documentation.

7.5. Vital Signs, Height/Length and Weight

Blood pressure and pulse in the sitting or supine position are to be recorded at each visit as specified in the [STUDY PROCEDURES](#) section. Height/length will also be recorded at the Visit 1 and Visit 3, Weight will be recorded at Visits 1 and 3. Weight recorded at Visit 3 will be used to calculate the dosing assignment for all subsequent visits.

7.6. Physical and Neurological Examination

A physical examination will be performed and must be completed by a Medical Doctor (MD), Doctor of Osteopathy (DO), Nurse Practitioner (NP) or Physician Assistant (PA) or appropriate equivalent based upon normative country specific practices.

Full physical and neurological exams will be performed at Visit 1 and Visit 7 (ie, at the completion of the study or early termination). A brief physical exam and neurological exam documenting significant changes from the baseline exam will be performed at Visit 3.

Physical examinations will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological.

Any clinically significant changes from the entry examination will be recorded as adverse events and the specific finding(s) documented with an Investigator Comment.

Neurological exam will assess: level of consciousness, mental status, cranial nerve assessment, muscle strength and tone, reflexes, pin prick and vibratory sensation (the latter using a 128-Hz tuning fork), coordination and gait.

7.7. Electrocardiogram (ECG)

A 12-lead ECG will be performed at screening (Visit 1) and at the completion of the study (Visit 7). A central ECG reader will be used for this study. The following parameters will be assessed: PR interval, RR interval, QRS complex/duration, QT interval, QTc, and heart rate.

7.8. Imaging

MRI or CT scan with contrast will be performed at screening if not performed previously. Results must be available and reviewed as soon as possible and before the subject is randomized.

Note: in the event that a CT or MRI scan is needed, it must be performed as soon as possible after Visit 1 if it cannot be performed on the day of that visit.

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8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

- AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;

- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;

- Is life-threatening (immediate risk of death);
- Requires in subject hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect;

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject, or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on [Serious Adverse Event Reporting Requirements](#))

8.5.2. Potential Cases of Drug-Induced Liver Injury

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

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

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

- For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥ 2 times the baseline values and $\geq 3 \times \text{ULN}$, or $\geq 8 \times \text{ULN}$ (whichever is smaller).
- **Concurrent with**
 - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥ 3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;

- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

As required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious adverse event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Withdrawal Due to Adverse Events (See also section on [Subject Withdrawal](#))

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.10. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject's/parent/legal guardian. In addition, each study subject's/parent/legal guardian will be questioned about adverse events.

8.11. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.11.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.11.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.11.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Sample Size Justification:

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

The sample size rationale was based on the observed difference in \log_e (double-blind 24-hour seizure rate + $\frac{1}{28}$) between pregabalin and placebo (Table 4). A difference in the least squares means between pregabalin and placebo was estimated to be -0.668 and -0.448 for 600- and 300 mg doses respectively, with a pooled standard deviation (SD) of 0.73. This difference and pooled SD was obtained from a meta analysis of the -34, -11, -09 study data in adult subjects with partial onset seizures.

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

Details of the sample size re-estimation procedure were included in the Statistical Analysis Plan.

Table 4. Power Calculations and Sample Size Assumptions for the Primary Endpoint
(log_e (24-hour seizure rate + $\frac{1}{28}$; original constant)

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

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

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

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

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

Randomization will be stratified by subject age (Stratum 1: <1 year of age; Stratum 2: 1-2 years of age; Stratum 3: >2 years of age). Every reasonable effort will be made to enroll a minimum of 10 subjects in each of the 3 age strata.

The constant utilized in the log transformation of the 24-hour seizure rate for the primary analysis was changed while the study was ongoing, from “1/28” to “1” due to differences in the seizure rate distribution assumed during design of the study and the observed, blinded data distribution. Changing the constant to 1 provides a better approximation of a normal distribution of the seizure data. The constant “1/28” added variability to the data and decreased its normality. The planned difference for the blinded sample size re-estimation between pregabalin 7 mg/kg/day and placebo was -0.355 based on an update of the meta analysis referenced in Table 4, using the constant “1” in place of “1/28”.

Blinded Sample Size Re-estimation:

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

The blinded sample size re-estimation procedure for this study originally did not allow for a reduction in the planned sample size of 123 subjects, nor did it pre-specify any cap to the suggested increase in sample. The procedure was conducted by a statistician not associated with the study during its conduct or during the final analysis. There was no penalty applied to the final analysis p-values or confidence intervals for assessing treatment difference from placebo due to this blinded sample size re-estimation procedure. Details of the sample size re-estimation procedure are included in the Statistical Analysis Plan.

The blinded sample size re-estimation procedure utilized for this study was revised per Statistical Analysis Plan and did not allow for a reduction in the planned sample size of 123 subjects total or require an increase in sample size greater than 150 subjects. The following decision rules were utilized for the blinded sample size re-estimation:

- a. If the recalculated sample size is less than or equal to the original sample size of 123 subjects total, then the sample size will not be adjusted.
- b. If the recalculated sample size is greater than the original sample size (123 subjects total) then the following information will be considered:
 - If the re-estimated sample size is between 123 and 150, then the sample size will be adjusted to the re-estimated sample size.
 - If the re-estimated sample size exceeds 150 then the sample size will be increased to 150.

The blinded sample size re-estimation was conducted, and the sample size will be increased to approximately 150 subjects.

9.2. Efficacy Analysis

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

9.2.1. Analysis of Primary Endpoint

The primary analysis will be performed on the primary endpoint, \log_e (double blind 24-hour EEG seizure rate + 1), using a linear model with treatment, age stratum, and geographical region (ie, US, Europe, Asia, Rest of the World) as fixed factor effects, and \log_e (baseline 24-hour EEG seizure rate + 1) as a continuous covariate. This linear model will include both dose groups of pregabalin. Each dose of pregabalin and placebo will be compared using a sequential step-wise testing procedure outlined in [Section 9.2.3](#). Least square means will be calculated using the observed marginal distribution.

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

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

9.2.2. Analysis of Secondary Endpoints

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

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

- treatment group, as a fixed effect;
- age stratum, as a fixed effect;
- geographical region (ie, US, Europe, Asia, Rest of the World as data allows) by pooling of investigator centers, as a fixed effect.

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

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

9.2.3. Multiple Testing Procedures

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

- Step 1: Test the difference between the Level 2 group and placebo.

- $H_{01}: \mu_{\text{Level 2}} - \mu_{\text{Placebo}} = 0$

- $H_{a1}: \mu_{\text{Level 2}} - \mu_{\text{Placebo}} \neq 0$

If H_{01} is rejected ($p \leq 0.05$) then move to step 2, otherwise claim no difference and stop.

- Step 2: Test the difference between the Level 1 group and placebo.

- $H_{02}: \mu_{\text{Level 1}} - \mu_{\text{Placebo}} = 0$

- $H_{a2}: \mu_{\text{Level 1}} - \mu_{\text{Placebo}} \neq 0$

If H_{02} is rejected ($p \leq 0.05$) then claim a difference for all the comparisons, otherwise claim differences between 14 mg/kg/day and placebo only.

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

9.3. Sensitivity Analysis to Assess the Impact of Missing Data

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

Due to the use of Video-EEG assessments to collect seizure data (at baseline and the end of the double blind period), subjects who discontinue from the study may have no post-baseline efficacy data. If there is missing post-baseline 24-hour seizure rate for more than 5% of any treatment group, then multiple imputation techniques will be applied to the primary analysis model. The multiple imputation will consider age stratum and gender and will impute data using the method of propensity scores.

As a supplemental analysis, a generalized linear model assuming a Poisson distribution and canonical log link function will be applied to the raw seizure counts.^{5,6} The model will have an off-set parameter for the amount of time (ie, $\log_e(\text{days})$) the subject was in the double blind treatment phase. Over-dispersion will be investigated, and if it appears to exist for this model, then the scale parameter will be set to the deviance in the Poisson model, and a negative binomial will be also be explored in addition to analyzing the data with a quasi-likelihood function. This analysis will assume missing completely at random, and will assess seizure frequency in relation to the amount of time each subject was at risk relative to their time on treatment. In addition, this analysis will not be subject to any potential extrapolation of applying the 24 hour seizure rate.

Further details regarding sensitivity analyses will be provided in the statistical analysis plan.

9.4. Safety Analysis

Safety will be assessed by summarizing and reviewing the nature, frequency, relationship to study drug, and severity of AEs, the results of physical and neurological examinations, weight, vital signs, ECG's and the results of clinical laboratory tests including hematology, blood chemistry, and urinalysis. Subject listings of all laboratory data will be provided using a standard computer program for laboratory data display. The listings will highlight values outside normal limits and those considered to be possible clinically important deviations. Medical history, physical exams, assessment of vital signs, and ECG will be displayed in standard listings and summary tables.

9.5. Interim Analysis

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

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

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

9.6. Data Monitoring Committee

This study will use an External Data Monitoring Committee (EDMC). The DMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonization guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject.

In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document(s) must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC, and available for inspection.

The investigator must ensure that each study subject's legal representative is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Other Participating Countries

End of Trial in all other participating countries is defined as Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of Pregabalin at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer registers study protocols and posts Basic Results on ClinicalTrials.gov for Pfizer-sponsored interventional studies in human subjects that evaluate the safety and/or efficacy of a Pfizer product; and for Pfizer-sponsored NI studies, regardless of design or data source, where the primary endpoint is to study whether a Pfizer product is associated with an increased incidence of a specific safety outcome.

The results are posted in a tabular format called Basic Results.

For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA-approved products, Pfizer posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV);
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);
- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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Appendix 1. International League Against Epilepsy 2010 and Revised 1981 Classification

2010 ILAE criteria:

"Descriptors of focal seizures. For pragmatic reasons and to facilitate continuity with the 1981 classification of seizures, descriptors of focal seizures may be used, individually or in combination with other features depending on the purpose. We have listed examples chosen to facilitate continuity with the 1981 seizure document and which have been drawn from the glossary of ictal semiology (Blume et al 2001⁴) (Table 2).

Table 2. Descriptors of focal seizures according to degree of impairment during seizure^a
Without impairment of consciousness or awareness With observable motor or autonomic components. This roughly corresponds to the concept of "simple partial seizure." "Focal motor" and "autonomic" are terms that may adequately convey this concept depending on the seizure manifestations). Involving subjective sensory or psychic phenomena only. This corresponds to the concept of an aura, a term endorsed in the 2001 Glossary. With impairment of consciousness or awareness. This roughly corresponds to the concept of complex partial seizure. "Dyscognitive" is a term that has been proposed for this concept (Blume et al., 2001). Evolving to a bilateral, convulsive ^b seizure (involving tonic, clonic, or tonic and clonic components). This expression replaces the term "secondarily generalized seizure."
^a For more descriptors that have been clearly defined and recommended for use, please see Blume et al., 2001. ^b The term "convulsive" was considered a lay term in the Glossary; however, we note that it is used throughout medicine in various forms and translates well across many languages. Its use is, therefore, endorsed.

Revised 1981 criteria:

I. PARTIAL (FOCAL, LOCAL) SEIZURES

Partial seizures are those in which, in general, the first clinical and electroencephalographic changes indicate initial activation of a system of neurons limited to part of one cerebral hemisphere. A partial seizure is classified primarily on the basis of whether or not consciousness is impaired during the attack. When consciousness is not impaired, the seizure is classified as a simple partial seizure. When consciousness is impaired, the seizure is classified as a complex partial seizure. Impairment of consciousness may be the first clinical sign, or simple partial seizures may evolve into complex partial seizures. In patients with impaired consciousness, aberrations of behavior (automatisms) may occur. A partial seizure may not terminate, but instead progress to a generalized motor seizure. Impaired consciousness is defined as the inability to respond normally to exogenous stimuli by virtue of altered awareness and/or responsiveness (vide infra: Definition of Terms).

There is considerable evidence that simple partial seizures usually have unilateral hemispheric involvement and only rarely have bilateral hemispheric involvement; complex partial seizures, however, frequently have bilateral hemispheric involvement.

Partial seizures can be classified into one of the following three fundamental groups:

- A. Simple partial seizures
- B. Complex partial seizures
 1. With impairment of consciousness at onset
 2. Simple partial onset followed by impairment of consciousness
- C. Partial seizures evolving to generalized tonic-clonic convulsions (GTC)
 1. Simple evolving to GTC
 2. Complex evolving to GTC (including those with simple partial onset)

Clinical seizure type	EEG seizure type	EEG interictal expression
A. <i>Simple partial seizures</i> (consciousness not impaired)	Local contralateral discharge starting over the corresponding area of cortical representation (not always recorded on the scalp)	Local contralateral discharge
1. With motor signs <ol style="list-style-type: none"> (a) focal motor without march (b) Focal motor with march (Jacksonian) (c) Versive (d) Postural (e) Phonatory (vocalization or arrest of speech) 		
2. With somatosensory or special-sensory symptoms (simple hallucinations, e.g., tingling, light flashes, buzzing) <ol style="list-style-type: none"> (a) Somatosensory (b) Visual (c) Auditory (d) Olfactory (e) Gustatory (f) Vertiginous 		
3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, pilo-erection and pupillary dilatation)		
4. With psychic symptoms (disturbance of higher cerebral function). These symptoms rarely occur without impairment of consciousness and are much more commonly experienced as complex partial seizures <ol style="list-style-type: none"> (a) Dysphasic (b) Dysmnestic (e.g., déjà-vu) (c) Cognitive (e.g., dreamy states, distortions of time sense) (d) Affective (fear, anger, etc.) 		

Clinical seizure type	EEG seizure type	EEG interictal expression
<ul style="list-style-type: none"> (e) Illusions (e.g., macropsia) (f) Structured hallucinations (e.g., music, scenes) 		
<p>B. <i>Complex partial seizures</i> (with impairment of consciousness; may sometimes begin with simple symptomatology)</p> <ul style="list-style-type: none"> 1. Simple partial onset followed by impairment of consciousness <ul style="list-style-type: none"> (a) With simple partial features (A.1.–A.4.) followed by impaired consciousness (b) With automatisms 2. With impairment of consciousness at onset <ul style="list-style-type: none"> (a) With impairment of consciousness only (b) With automatisms 	Unilateral or, frequently bilateral discharge, diffuse or focal in temporal or frontotemporal regions	Unilateral or bilateral generally asynchronous focus; usually in the temporal or frontal regions
<p>C. <i>Partial seizures evolving to secondarily generalized seizures</i> (This may be generalized tonic-clonic, tonic, or clonic)</p> <ul style="list-style-type: none"> 1. Simple partial seizures (A) evolving to generalized seizures 2. Complex partial seizures (B) evolving to generalized seizures 3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures 	Above discharges become secondarily and rapidly generalized	

II. GENERALIZED SEIZURES (CONVULSIVE OR NONCONVULSIVE)

Generalized seizures are those in which the first clinical changes indicate initial involvement of both hemispheres. Consciousness may be impaired and this impairment may be the initial manifestation. Motor manifestations are bilateral. The ictal electroencephalographic patterns initially are bilateral, and presumably reflect neuronal discharge which is widespread in both hemispheres.

Clinical seizure type	EEG seizure type	EEG interictal expression
A. 1. <i>Absence seizures</i>	Usually regular and symmetrical 3 Hz but may be 2–4 Hz spike-and-slow-wave complexes and may have multiple spike-and-slow-wave complexes. Abnormalities are bilateral	Background activity usually normal although paroxysmal activity (such as spikes or spike-and-slow-wave complexes) may occur. This activity is usually regular and symmetrical
(a) Impairment of consciousness only		
(b) With mild clonic components		
(c) With atonic components		
(d) With tonic components		
(e) With automatisms		
(f) With autonomic components		
(b through f may be used alone or in combination)		
2. <i>Atypical absence</i>	EEG more heterogeneous; may include irregular spike-and-slow-wave complexes, fast activity or other paroxysmal activity. Abnormalities are bilateral but often irregular and asymmetrical	Background usually abnormal; paroxysmal activity (such as spikes or spike-and-slow-wave complexes) frequently irregular and asymmetrical
May have:		
(a) Changes in tone that are more pronounced than in A.1		
(b) Onset and/or cessation that is not abrupt		
E. <i>Tonic-clonic seizures</i>	Rhythm at 10 or more c/sec decreasing in frequency and increasing in amplitude during tonic phase, interrupted by slow waves during clonic phase	Polyspike and waves or spike and wave, or, sometimes, sharp and slow wave discharges
F. <i>Atonic seizures</i> (Astatic) (combinations of the above may occur, e.g., B and F, B and D)	Polyspikes and wave or flattening or low-voltage fast activity	Polyspikes and slow wave

III. UNCLASSIFIED EPILEPTIC SEIZURES

Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, e.g., rhythmic eye movements, chewing, and swimming movements.

Appendix 2. Clinical Dosing Instructions for Liquid Oral Solution:

Liquid Oral Solution

Pregabalin 20 mg/mL and matching placebo oral solutions are provided as clear, colorless, flavored solutions in bottles. To accommodate the broad dose range that may be encountered during clinical studies, pregabalin 20 mg/mL and matching placebo oral solutions can be administered using a variety of oral dosing syringes. An example of the syringes are provided in this document for reference.

Subjects/parents/guardians will receive training on dose preparation, administration, storage, and disposal prior to release for outpatient dosing. Parent/caregivers will need to demonstrate proper use of dosing supplies to site personnel at Visits 3, 4 and 5 and sites will be required to document training and demonstration.

DOSING:

Dosing is accommodated by the use of either a 0.5, 1.0, 3.0, or 10.0 mL oral dosing syringe depending on the required dose. The 1 mL oral dosing syringe can accommodate 0.1-1 mL doses in 0.1 mL increments. The 3 mL oral dosing syringe can accommodate doses from 1.25-3.0 mL in 0.25 mL increments. The 10 mL oral dosing syringe can accommodate doses from 3.5-10 mL in 0.5 mL increments.

Illustrations of the oral dosing syringes are provided in [Figure 1](#).

Figure 1. Liquid Oral Dosing Syringes (1, 3, and 10 mL left to right)



LIQUID ORAL DOSING AND ADMINISTRATION PROCEDURE:

1. Insert the appropriate oral dosing syringe into the bottle.
2. Pull back on the plunger of the oral dosing syringe to the appropriate measurement mark on the oral dosing syringe barrel.
3. Measure the dose by aligning the fin on the plunger to the appropriate marking on the barrel (Figure 2).
4. Place the oral dosing syringe down onto a clean surface and securely close the bottle.
5. Deliver the dose by placing the tip of the oral dosing syringe into the mouth of the subject with the subjects head tilted slightly back and pushing the plunger to expel the liquid. Be careful to not expel the dose directly into the back of the throat, to avoid choking. Alternatively dose can be transferred into a cup for administration.

6. Remove the plunger from the oral dosing syringe and rinse the barrel and plunger under warm water. Allow the plunger and barrel to air dry or use a fresh paper towel or clean cloth to dry. When dry, push the plunger back into the barrel prior to the next dose.

Figure 2. Liquid Oral Dosing Example



LIQUID DOSING SUPPLIES:

Subjects should be supplied with a suitable oral dosing syringe for self-administration. Examples of oral dosing syringes are provided in [Figure 1](#).

STABILITY AND STORAGE:

A single dose that has been prepared in an oral dosing syringe should be administered within 1 hr. Bottles containing the dosing solution should be stored at room temperature.

Appendix 3. List of Abbreviations

A	
AE	Adverse Event
AED	Antiepileptic Drug
α_2 - δ	Alpha-2-Delta
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the curve
B	
B12	Vitamin B12
BID	Twice Daily
BP	Blood Pressure
C	
CI	Confidence Interval
CLcr	Creatinine Clearance
C _{max}	Maximum Concentration
CNS	Central Nervous System
CP	Complex Partial
CR	Controlled Release
CRF	Case Report Form
CT	CAT Scan (Computerized Tomography Scan)
CTA	Clinical Trial Application or Clinical Study Application
D	
DMC	Data Monitoring Committee
DPN	Diabetic Peripheral Neuropathy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version IV
E	
ECG	Electrocardiogram
EEG	Electroencephalogram
ET	Early Termination
EMA	European Medicines Agency
F	
FDA	Food and Drug Administration
FSFV	First Subject First Visit
G	
GCP	Good Clinical Practice
GI	Gastrointestinal

H	
HEENT	Examination of Head, Ears, Eyes, Nose, and Throat
I	
ISA	Interim Safety Analysis
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Initial New Drug
IRB	Institutional Review Board
L	
LFT	Liver Function Test
LSLV	Last Subject Last Visit
M	
MHP	Mental Health Professional
mL	Milliliter
mITT	Modified Intention to Treat
MRI	Magnetic Resonance Imaging
N	
N/A	Not applicable
NONMEM	Nonlinear Mixed Effects Modeling
	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
P	
PBO	Placebo
PD	Pharmacodynamic
PHN	Postherpetic Neuropathy
PI	Principal Investigator
PK	Pharmacokinetic/Pharmacokinetics
PP	Per Protocol
R	
RBC	Red Blood Cell
RDC	Research Diagnostic Criteria
S	
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Status Epilepticus

SGTC	Secondarily Generalized Tonic-Clonic Seizures (a type of Partial Epilepsy Seizure)
SP	Simple Partial
SRSD	Single Reference Safety Document
SSID	Single Subject Identification Number
T	
TID	Three Times A Day
U	
US	United States
V	
V	Visit
VNS	Vagus Nerve Stimulation
W	
WBC	White Blood Cell

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