CLINICAL PROTOCOL

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

Compound:	PD-144723
Compound Name (if applicable):	Pregabalin
US IND Number (if applicable):	49,393
European Clinical Trial Database (EudraCT) Number:	2011-001412-65
Protocol Number:	A0081106
Phase:	3

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 2	07 May 2014	• Updated to TID regimen for subjects <4 years old. • Added pediatric PK half-life that supports TID in subjects <4 years old. • Added information on the requirement to refer to a qualified mental health professional for subjects at-risk of suicide, and contact Pfizer study clinician. • On SOA, footnote "d", added information on the Tanner assessment for children. • On SOA, footnote "j" added to clarify dispensation procedure of study medication. Added also in Section 6.2. • Clarified in Section 4.1 the age limit for subjects completing A0081041 or A0081105. • Clarified the eligibility assessments for Direct enrolling subjects in Section 4.1 and 4.2. • Clarified the restriction associated with benzodiazepine use. • Clarified the restriction associated with non-AED. • Revised the list of prohibited anti-epileptic drugs. • Revised subject compliance or non-compliance definition. • Added new section Sponsor Qualified Medical Personnel. • Revised the list of procedures in Section 6.2. • Corrected the Creatinine concentration conversion formula in Section 7.3, and clarified PK assessment to be made. • Clarified CBCL administration and scoring in Section 7.6.1. • Clarified Mini-Kid and CSSRS administration in Sections 7.6.2 and 7.6.3. • Updated the Adverse Event reporting section. • Updated the Subject Information and Consent section. • Updated section Communication of Results by Pfizer.
Protocol Amendment 1	31 July 2012	• On SOA, footnote "c", added information on need for additional pregnancy tests based upon local regulations. • Added overall risk/benefit statement 1.2. • Clarified that direct enrolling subjects will come from

		selected sites within the United States only 1.2, 3. • Clarified that subjects completing in A0081041 or A0081105 a minimum of 4 weeks, but <12, must consult with Study Clinician prior to consideration for A0081106 3. • Inclusion Criteria 4 modified to add a reference to Appendix 1 for seizure types allowed. • CT/MRI requirement for direct enrollers extended to 60 months or if recent clinical change indicate necessity 4.1.1. • Added "allergy to pregabalin or excipients…" in exclusion criteria 4.16. • Added statement that investigator should interview subjects about sexual and contraceptive history 4.3.1. • Use of anti-epileptic drugs clarified 5.4.1, 5.4.2. • Clarified that creatinine clearance will be calculated only for direct enrolling subjects 7.3. • Specified blood volumes in the Section 7.3.2 of the protocol. • Clarified that subjects who are 4-5 years old and have Greek and Cebuano speaking parents will be excluded due to lack of CBCL translations. Greek and Cebuano subjects age 6 years and older can be included 7.6.1. • Modified MINI-KID assessment such that Suicidality module not necessary if CSSRS is given unless the subject has endorsed significant depressive symptoms on the MINI-KID 7.6.2. • Clarified rater selection and training process 7.6.2. • Clarified written risk assessment requirement 7.6.4. • Clarified that mentally or physically handicapped subjects do not have to complete CogState if they are unable 7.7.1. • Adverse event section updated due to protocol template updates 8.1-8.14. • Clarified description of posting of clinical trial results by Pfizer 15.1. • Added references for CBCL and MINI-KID.
Original protocol	06 July 2011	N/A

Protocol Summary

Indication:

Adjunctive therapy for children with partial onset seizures with or without secondary generalization and adjunctive therapy for children and adults with primary generalized tonic-clonic (PGTC) seizures.

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 generally well tolerated, is needed.

Pregabalin (Lyrica®) is an alpha$_2$-delta ($\alpha_2\delta$) agent approved for use the treatment of partial onset seizures in adults. It is believed to exert its pharmacologic action by binding to the $\alpha_2\delta$ site of voltage-gated calcium channels. The spectrum of activity of pregabalin in rodent models of epilepsy shows that it is potent to reduce or prevent both partial seizures from hippocampal stimulation and also primary generalized tonic-clonic (PGTC) seizures from either sound stimulation to genetically audiogenic mice or cranial electroshock in mice or rats.[12] The efficacy of pregabalin in patients with PGTC seizures has not been assessed to date in a placebo-controlled study.

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 and EU, pregabalin is indicated for the adjunctive treatment of adult patients with partial onset seizures. In addition, pregabalin is indicated for the treatment of central and peripheral neuropathic pain (EU), and for the management of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy and for fibromyalgia (US) and for the treatment of peripheral neuropathic pain (JP). In the EU, pregabalin is also approved for the treatment of Generalized Anxiety Disorder in adults. The approved dose range for the adjunctive treatment of partial onset seizures in adults is 150 to 600 mg/day, administered 2 times 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 and somnolence. Since initial market approval of Lyrica® in 2004, it is estimated that more than 11,700,000 patient-years of exposure have accumulated worldwide. More detailed information, including efficacy results in adults and the possible risks associated with

administration of pregabalin, are summarized in the Investigator's Brochure which serves as the Single Reference Safety Document for this study.

Study A0081106 will assess the long term (12 month) safety and tolerability of pregabalin in pediatric subjects as adjunctive treatment for partial onset seizures and as adjunctive treatment in pediatric and adult subjects with primary generalized tonic-clonic seizures. 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 address post approval commitments to US and EU regulatory authorities.

Objectives:

- To evaluate the long-term safety and tolerability of pregabalin in pediatric subjects 1 month through 16 years of age with partial onset seizures and pediatric and adult subjects 5-65 years of age with PGTC seizures.

Study Design:

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

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

Endpoints:

The following safety and tolerability data will be collected at each clinic visit according to the schedule of activities:

- Adverse event (AE) data (occurrence, nature, intensity, and relationship to study drug).

- Physical and neurological examinations.

- Vital signs.
- Growth and development parameters (height and weight) including Tanner stage.
- Clinical laboratory data (hematology, chemistry, urinalysis).
- Electrocardiograms (ECGs).
- 28-day seizure rate (number of seizures per 28 day period).
- Assessments of suicidal ideation and behavior.
- Cognitive testing.

Study Treatments:

A0081106 study medication will be provided as pregabalin liquid oral solution or oral capsules. Subjects <4 years of age at Visit 1 or who are enrolling from A0081042 will receive study medication 3 times daily (TID) in equally divided doses. Subjects who are ≥4 years of age at Visit 1 will receive study medication twice daily (BID) in equally divided doses.

- All eligible pediatric subjects 1 month to 16 years and 11 months of age will take pregabalin in Study A0081106 at a dosage according to their body weight:
    - Pediatric subjects weighing ≥30 kg will begin pregabalin dosing at 2.5 mg/kg/day (maximum 150 mg/day). Subjects will remain at the starting dose for 8 days until Visit 2. Thereafter, dosing will be flexible based on individual seizure response and tolerability. Pediatric subjects may have their dose adjusted up or down at clinic visits in increments of no more than 2.5 mg/kg/day (maximum 150 mg/day) to daily dose levels of 5.0 (maximum 300 mg/day), 7.5 (maximum 450 mg/day), or 10.0 mg/kg/day (maximum 600 mg/day).
    - Pediatric subjects with body weight <30 kg will begin pregabalin dosing at 3.5 mg/kg/day until Visit 2. Thereafter, dosing will be flexible based on individual seizure response and tolerability. Pediatric subjects may have their dose adjusted up or down at clinic visits in increments of no more than 3.5 mg/kg/day to daily dose levels of 7.0, 10.5, or 14.0 mg/kg/day. This 40% higher dose per kg in pediatric subjects with body weight <30 kg is needed to achieve exposures similar to those of adults or pediatric subjects weighing ≥30 kg.
- All eligible adult subjects 17 to 65 years of age will begin dosing of pregabalin in Study A0081106 at the level of 150 mg/day. Subjects will remain at this dose for 8 days until Visit 2. Thereafter, dosing will be flexible based on individual seizure response and tolerability. Adult subjects may have their dose adjusted up or down at

clinic visits in increments of no more than 150 mg/day to dose levels of 300, 450, or 600 mg/day.

The pregabalin liquid oral solution formulation (20 mg/ml) will be used for all subjects weighing less than 30 kg. Pediatric and adult subjects weighing more than 30 kg may use either the liquid oral solution or solid capsule formulation. Study medication formulation for administration will be as outlined below, with investigators (and subjects) determining the choice of solution or capsule for subjects ≥30 kg. The choice will be based upon subject's preference. If capsules are preferred, the subject must demonstrate the ability to swallow the capsule without difficulty at the study visit using a placebo capsule for the demonstration. Pregabalin capsules and pregabalin liquid oral solution are bioequivalent.

Weight	Formulation
<30 kg	Liquid
Pediatric subjects ≥30 kg	Liquid or capsule
Adult subjects	Capsules or liquid

Statistical Methods:

Data will be summarized into 3 groups as defined by a combination of the subject's randomized treatment group in studies A0081041, A0081042, or A0081105 (subjects previously on pregabalin will be combined across treatment groups) and the treatment received during this study. All subjects in this study will receive pregabalin. The 3 treatment summary groups will be described as:

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

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

3. Direct Pregabalin: pregabalin only in this study.

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

Summaries will include data for all subjects who took at least one dose of study medication in this study (Safety population). The safety data (including adverse events, clinical laboratory assessments, ECGs, vital signs, height/weight/Tanner stage, suicidality assessments, cognitive assessments, and physical/neurological examinations) will be summarized by treatment group and overall through standard data tabulations, descriptive statistics, and/or graphical presentations. Twenty-eight day seizure rate will be calculated from the seizure diaries and will be reviewed as a means of determining seizure control. Seizure frequency for each seizure type will be summarized using descriptive statistics every

4 weeks thereafter until the end of the study by treatment group and overall. No statistical inferences will be performed.

Subgroup analysis will be done on the safety data and seizure rates for each age cohort and primary seizure type.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES (Section 6) and ASSESSMENTS (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

Study Period	**Screening/ Baseline**		**12 Month Treatment Phase**												**End of Treatment & Taper Phase**	
Clinic Visit Number	**Visit 1A**	**Visit 1B**	**Visit 2**	**Visit 3**	**Visit 4**	**TC***	**Visit 5**	**TC***	**Visit 6**	**TC***	**TC***	**Visit 7**	**TC***	**TC***	**Visit 8**	**Visit 9**
Study Month	**Prior Study Subjects**	**Direct Enroll**		**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12/EOS/ Early Term[g] Begin Taper**	**End Taper/ Follow up**
Study Day	**Day 1A[a]**	**Day 1B[a]**	**8 (±1)**	**30 (±4)**	**60 (±4)**	**90 (±4)**	**120 (±4)**	**150 (±4)**	**180 (±4)**	**210 (±4)**	**240 (±4)**	**270 (±4)**	**300 (±4)**	**330 (±4)**	**365 (±7)**	**7 days post completion[i] (±3)**
Informed Consent/Assent	X	X														
Record Demographic Information	X	X														
Record Medical History	X[b]	X														
Record Seizure History	X[b]	X														
Perform Physical and Neurological Examination	X[b]	X[d]							X						X[d]	
Review Inclusion/Exclusion Criteria	X	X														
Record Antiepileptic Medication History	X[b]	X														
Record All Prior Medications	X[b]	X														
Record all concurrent medications and non-drug treatment/procedures (include any ongoing AEDs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Period	**Screening/ Baseline**		**12 Month Treatment Phase**												**End of Treatment & Taper Phase**	
Clinic Visit Number	**Visit 1A**	**Visit 1B**	**Visit 2**	**Visit 3**	**Visit 4**	**TC***	**Visit 5**	**TC***	**Visit 6**	**TC***	**TC***	**Visit 7**	**TC***	**TC***	**Visit 8**	**Visit 9**
Study Month	**Prior Study Subjects**	**Direct Enroll**		**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12/EOS/ Early Term[g] Begin Taper**	**End Taper/ Follow up**
Study Day	**Day 1A[a]**	**Day 1B[a]**	**8 (±1)**	**30 (±4)**	**60 (±4)**	**90 (±4)**	**120 (±4)**	**150 (±4)**	**180 (±4)**	**210 (±4)**	**240 (±4)**	**270 (±4)**	**300 (±4)**	**330 (±4)**	**365 (±7)**	**7 days post completion[i] (±3)**
Perform 12-Lead Electrocardiogram (ECG)	X[b]	X													X	
Collect and Record Vital Signs	X[b]	X			X				X			X			X	
Record Height & weight	X[b]	X							X						X	
Collect Urine Sample for Pregnancy Test[c]	X[b]	X							X			X			X	X
Collect Blood and Urine Samples for Clinical Laboratory Assessments	X[b]	X							X						X	
Suicidality Assessments: Child Behavior Checklist (CBCL)/MINI-KID, C-SSRS **"Lifetime"**[f]	X[b]	X														
Suicidality Assessments Child Behavior Checklist (CBCL)/CSSRS **"Since Last Visit"**	X[b]		X	X	X		X		X			X			X	X
Complete CogState Battery[h]	X[b]	X													X	
IVRS assignment	X	X														
Dispense Daily Seizure and Dosing Diary	X	X	X	X	X		X		X			X			X	
Collect and Review Seizure/Dosing Diary			X	X	X		X		X			X			X	X

Study Period	Screening/ Baseline		12 Month Treatment Phase												End of Treatment & Taper Phase	
Clinic Visit Number	Visit 1A	Visit 1B	Visit 2	Visit 3	Visit 4	TC*	Visit 5	TC*	Visit 6	TC*	TC*	Visit 7	TC*	TC*	Visit 8	Visit 9
Study Month	Prior Study Subjects	Direct Enroll		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12/EOS/ Early Term[g] Begin Taper	End Taper/ Follow up
Study Day	Day 1A[a]	Day 1B[a]	8 (±1)	30 (±4)	60 (±4)	90 (±4)	120 (±4)	150 (±4)	180 (±4)	210 (±4)	240 (±4)	270 (±4)	300 (±4)	330 (±4)	365 (±7)	7 days post completion[i] (±3)
Dosing Compliance Training/Review and Demonstration		X	X			X		X		X	X		X	X		
Evaluate Study Medication Compliance	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
* Telephone contact to assess dosing and diary compliance, concomitant medications and AE's						X		X		X	X		X	X		
Dispense Study Medication	X	X[j]	X[k]	X[k]	X[k]		X[k]		X[k]			X[k]			X[e]	
Assess and Record Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. **Visit 1A = Screening Visit for subjects from A0081041, A0081042, or A0081105:** This visit should be completed for subjects who previously participated in double-blind Studies A0081041, A0081042 or A0081105. These subjects will enroll into Study A0081106 on the last day of the double-blind study with no interruption in their pregabalin treatment.

   Visit 1B = Direct-Enroll Screening Visit: This visit should be completed for subjects who did NOT participate in Studies A0081041, A0081042, or A0081105. These subjects will enroll directly into Study A0081106 to initiate treatment with open label pregabalin and must complete all of the screening assessment noted under Visit 1B.

b. If procedures were performed during participation in Studies A0081041, A0081042, or A0081105 the actual procedure will not need to be repeated for the Study A0081106 Screening Visit 1A (data from the subject's previous study will be utilized).
   - For at-risk subjects, a mental health risk assessment must be performed by a qualified mental health professional.

c. Female subjects who are menarchal must have negative urine pregnancy test. Pregnancy tests may be completed more frequently as per IRB's/IEC's or as required based upon local regulations.

d. Include Tanner stage assessment at screening for direct enrolling pediatric/adolescent, and at last visit Month 12 for all pediatric/adolescent subjects only. This assessment is not applicable to subjects who participated in study A0081042.

e. This is a taper medication dispensation only for subjects who will cease treatment with pregabalin. If the subject will continue to receive pregabalin treatment post-study, initiation of taper is at the discretion of the investigator. Subjects who require early discontinuation and require taper, should begin the taper at the time the decision is made to discontinue. These subjects should return approximately 1 week later for follow-up Visit 9.

f. Assessment of suicidal ideation and behavior:

I. MINI-KID only for children and adolescents 6 -<17 years of age at Visit 1B or if they did not have a MINI-KID performed during prior participation to studies referred in Visit 1A.

II. C-SSRS "Lifetime" version performed at Visit 1 for all subjects aged 6-65 years who did not have a C-SSRS performed previously. C-SSRS "Since Last Visit" version for all subjects ages 6-65 years for each visit beginning at Visit 2 through Visit 9 or Early Termination.

III. Child Behavior Checklist (CBCL) performed for children 4-<6 years of age beginning at Visit 1 and at every subsequent visit until Visit 9 or Early Termination.

g. Month 12, Visit 8 is the End of Treatment/End of Study visit for subjects who will not initiate taper of pregabalin per the discretion of the investigator. Visit 8 will be the final study visit for these subjects. For subjects who will taper their pregabalin treatment, Visit 8 is considered End of Treatment/End of Study Visit but they will initiate taper at this visit and return for a follow-up Visit 9 to end taper. For early terminations, all Visit 8 procedures should be performed and if taper is initiated, subjects should return for follow-up Visit 9.

h. Cogstate Battery will be completed only for pediatric partial onset seizure subjects (Protocol A0081041) 4-16 years of age.

i. The follow-up visit is only required for subjects who received taper medication.

j. All screening procedures must be completed prior to administration of first study medication. All eligibility criteria should be confirmed prior to, or on, Visit 2.

k. Adjust the dose if needed based on seizure response and tolerability.

* TC = Telephone Contact to assess dosing and diary compliance, concomitant medications, and AE's.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

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 with partial onset seizures with or without secondary generalization and adjunctive therapy for pediatric and adult subjects with primary generalized tonic-clonic (PGTC) seizures.

1.2. Background and Rationale

Pregabalin [CI-1008, (S)-3-(aminomethyl)-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 antiseizure 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 (α_2-δ) 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. Gabapentin clearance, normalized for body weight, is higher in children younger than 5 years of age than in older children and adults.

Pregabalin is approved in more than 100 countries, with indications summarized below for the United States (US), European Union (EU), and Japan. In the US and EU, pregabalin is indicated for the adjunctive treatment of adult patients with partial onset seizures. In addition, pregabalin is indicated for the treatment of central and peripheral neuropathic pain (EU), and for the management of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy and for the treatment of fibromyalgia (US) and for the treatment of peripheral neuropathic pain (JP). In the EU, pregabalin is also approved for the

treatment of Generalized Anxiety Disorder (GAD) in adults. The efficacy of pregabalin in subjects with PGTC seizures has not been assessed to date in a placebo-controlled study. The approved dose range for the adjunctive treatment of partial onset seizures in adults is 150 to 600 mg/day, administered 2 times (BID) or 3 times (TID) a day. The most common adverse effects reported with pregabalin in placebo-controlled adjunctive trials of pregabalin in adults with partial onset seizures were dizziness and somnolence. Since initial market approval of Lyrica® in 2004, it is estimated that more than 11,700,000 patient-years of exposure will have accumulated worldwide. More detailed information, including efficacy results in adults and the possible risks associated with administration of pregabalin, are summarized in the Investigator's Brochure which will serve as the Single Reference Safety Document for this study.

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, with oral bioavailability of ≥90% and peak plasma pregabalin concentrations occurring 0.7 to 1.5 hours following both single- and multiple- dose administration. Pregabalin can be dosed either 2 or 3 times a day. Pregabalin is essentially not metabolized and administration with food has no clinically relevant effect on the total amount of pregabalin absorbed. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug, with a mean plasma pregabalin half-life of 6.3 hr in adults. Pregabalin terminal t½ 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. Pregabalin clearance is proportional to creatinine clearance, and the major influence on its clearance is reduced or impaired renal function.

Pregabalin, at concentrations approximately 10 times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. *In vitro* drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Population pharmacokinetic analyses of adult data have shown no interactions between pregabalin and either carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, or valproic acid. Similar analyses show that tiagabine has no effect on the pharmacokinetics of pregabalin.

Study A0081074 was a placebo-controlled, parallel-group, multiple-dose, dose escalation study to characterize the safety, tolerability, and the single- and multiple-dose pharmacokinetics of pregabalin at several dose levels in pediatric subjects with partial onset seizures. The adverse event profile observed in pediatric subjects aged 2-16 years of age in Study A0081074 is similar in nature to that seen in adult subjects with somnolence and dizziness being the most commonly reported adverse events. Somnolence was observed at pregabalin doses of 2.5, 5.0, and 15.0 mg/kg/day. Dizziness was the next most common adverse event and was seen only at the pregabalin dose of 10.0 and 15.0 mg/kg/day. The data from Study A0081074 has been used to define the dose range to be investigated in this

study (Study A0081106) and additional Phase 3 efficacy and safety studies in the pediatric epilepsy population.

Pregabalin has not yet been studied in large numbers of pediatric patients. This study will enroll those subjects who have participated in Studies A0081041, A0081042, and A0081105 and in whom pregabalin shows acceptable safety and tolerability in those studies. In addition to subjects who have participated in Studies A0081041, A0081042 and A0081105, pediatric subjects (1 month to 16 years of age) with partial onset seizures will also be considered for direct enrollment into Study A0081106 from selected sites (within the United States only) that are not participating in Studies A0081041, A0081042, or A0081105.

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 and EU regulatory authorities.

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

The name, title, addresses, and telephone number(s) of the sponsor's medical expert for the study is documented in the study contact list.

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. The recommended dose range in adults is approximated by the 2.5 mg/kg/day to 10 mg/kg/day pregabalin dose range for pediatric subjects <60 kg in this study. This range of doses is anticipated to provide efficacy for the subjects enrolled and will characterize safety and tolerability of this dose range for pediatric subjects.

Doses in the range of 2.5 to 15 mg/kg/day were studied in pediatric subjects between 1 month and 16 years of age in Study A0081074 and serial blood samples were collected to assess the pharmacokinetics of pregabalin in the pediatric population. Data from Study A0081074 were compared with the adult data in a population pharmacokinetic analysis which showed that the relationship between creatinine clearance (CLcr) and pregabalin clearance (CL/F) was similar between both populations. Therefore, knowing a subject's CLcr value, the pregabalin oral clearance and thus pregabalin exposure can be estimated with a high degree of accuracy.

The noncompartmental and population pharmacokinetic analyses utilizing data from pediatric subjects from Study A0081074 indicated that for subjects with body weight ≥30 kg exposure equivalent to that observed in adults would be achieved when the pediatric subjects were dosed on a mg/kg/day basis. Due to higher clearance/kg in pediatric subjects with body weight <30 kg, a daily dose/kg 40% higher is needed to achieve exposure similar to that of adults or pediatric subjects weighing ≥30 kg. Thus, pediatric subjects with body weight ≥30 kg will initiate dosing at the daily dose of 2.5 mg/kg/day for a minimum of 1 week. Thereafter, dosing will be flexible, based on individual seizure response and tolerability. Doses may be adjusted up or down at clinic visits in increments no more than of 2.5 mg/kg/day. For pediatric subjects with body weight <30 kg, the daily dose will be adjusted by 40% to an initial daily dose of 3.5 mg/kg/day for a minimum of 1 week. Thereafter, dosing will be flexible, based on individual seizure response and tolerability. Doses may be adjusted up or down at clinic visits in increments of no more than 3.5 mg/kg/day.

Subjects <4 years of age at Visit 1 or participating from A0081042 will receive study medication TID in equally divided doses. Subjects who are ≥4 years of age at Visit 1 will receive study medication BID in equally divided doses. A TID dosing regimen accounts for a half life in youngest subjects shorter than in older pediatric and adult subjects. Subjects will maintain a BID or TID dosing regimen throughout study participation based on age at Visit 1 or past participation in A0081042 in order to avoid potential dosing errors/noncompliance related to regimen switch.

Adult subjects (17 to 65 years of age) who enroll in this study following participation in Study A0081105 will initiate dosing at 150 mg/day. Thereafter, dosing will be flexible, based on individual seizure response and tolerability. Doses may be adjusted up or down at clinic visits in increments of 150 mg/day.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

- To evaluate the long-term safety and tolerability of pregabalin in pediatric subjects 1 month through 16 years of age with partial onset seizures and pediatric and adult subjects 5 to 65 years of age with (PGTC) seizures.

2.2. Endpoints

Safety Endpoints:

- Adverse event (AE) data (occurrence, nature, intensity, and relationship to study drug).
- Physical and neurological examinations.
- Vital signs.
- Growth and development parameters (height, weight, Tanner stage).

- Clinical laboratory data (hematology, chemistry, urinalysis).
- Electrocardiograms (ECGs).
- 28-day seizure rate (number of seizures per 28 day period).
- Assessment of suicidal ideation and behavior.
- Cognitive assessment battery (POS pediatric subjects 4-16 years of age only).

3. STUDY DESIGN

Study A0081106 is a 12 month, open-label, flexible dose, multicenter study to evaluate the tolerability and safety of pregabalin (administered BID in subjects ≥4 years of age and TID in subjects <4 years of age) 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 (PGTC) seizures. Subjects who have completed the studies A0081041, A0081042, or A0081105 will be eligible for screening for this study. For subjects who have participated in, but did not complete Studies A0081041, A0081042, or A0081105, eligibility for Study A0081106 will be considered, after consultation with Study Clinician, on a case by case basis. A minimum of 4 weeks in the double-blind treatment phase of either Study A0081041 or Study A0081105 will be required for consideration of enrollment into Study A0081106.

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

3.1. Treatments and Visits

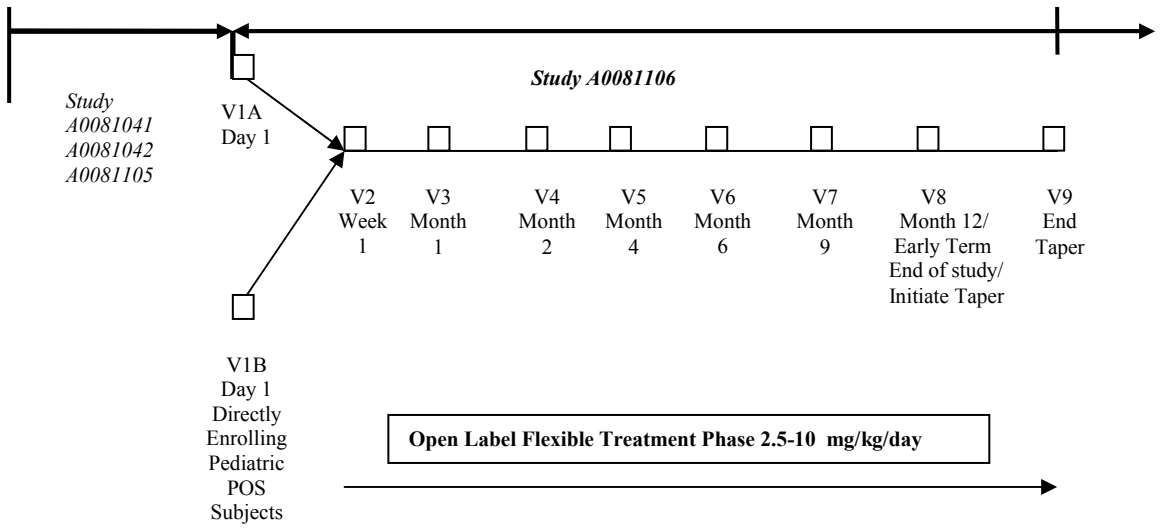
The day of the last visit (completion of taper phase) of Studies A0081041, A0081042, and A0081105 is designated as Day 1 (Visit 1A) of this study. Baseline values for analysis of change in safety endpoints will be the assessments made prior to initiating double-blind dosing at Visit 1 of Studies A0081041,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

For pediatric subjects, pregabalin dosing will initiate at the daily dose of 2.5 mg/kg/day (subjects ≥30 kg) or 3.5 mg/kg/day (subjects <30 kg) at this visit. Adult subjects who enroll in this study following participation in Study A0081105 will initiate dosing at 150 mg/day. All seizures experienced will be self-recorded by the subject or recorded by their parents/legally acceptable representative as appropriate, in a daily seizure diary beginning at Visit 1 and subsequently throughout the entire study.

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

At Visit 2 and subsequent visits thereafter, the investigator or designee will review seizure diary data and tolerability with the subject and may adjust the dose at his/her discretion. For pediatric subjects with body weight ≥30 kg (1 month to 16 years of age), doses may remain the same or be adjusted upward in increments of no more than 2.5 mg/kg/day to daily dose levels of 5.0, 7.5, or 10.0 mg/kg/day. For pediatric subjects with body weight <30 kg, doses may be adjusted in increments of no more than 3.5 mg/kg/day to daily dose levels of 7.0, 10.5, or 14.0 mg/kg/day. For adult subjects (17 to 65 years of age) doses may be adjusted in increments of 150 mg/day to daily dose levels of 300, 450, or 600 mg/day.

Figure 1. Study Design Schematic



Subjects who discontinue early and those who complete the study and do not continue treatment with pregabalin are recommended to taper off of study medication (see below for recommended tapering schedule), and will return for Visit 9 when the taper is completed.

For pediatric subjects ≥30 kg who taper off of pregabalin, the following schedule is recommended:

- Subjects receiving a dose of 10.0 mg/kg/day should receive 5.0 mg/kg/day for 4 days, then 2.5 mg/kg/day for 3 days, then discontinue study medication.

- Subjects receiving a dose of 7.5 mg/kg/day should receive 5.0 mg/kg/day for 4 days, then 2.5 mg/kg/day for 3 days, then discontinue study medication.

- Subjects receiving a dose of 5.0 mg/kg/day should receive 2.5 mg/kg/day for 7 days, and then discontinue study medication.

- Subjects receiving a dose of 2.5 mg/kg/day may discontinue study medication without any taper.

Table 1. End-of-Treatment Taper Schedule for Pediatric Subjects >30 kg

Day[1] / Total Daily Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7/ Follow up
10.0 mg/kg/day	5.0	5.0	5.0	5.0	2.5	2.5	2.5
7.5 mg/kg/day	5.0	5.0	5.0	5.0	2.5	2.5	2.5
5.0 mg/kg/day	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2.5 mg/kg/day	0	0	0	0	0	0	0

1. Days 1-7 post-Month 12/Early Termination visit.

For pediatric subjects <30 kg who taper off of pregabalin, the following schedule is recommended:

- Subjects receiving a dose of 14.0 mg/kg/day should receive 7.0 mg/kg/day for 4 days, then 3.5 mg/kg/day for 3 days, then discontinue study medication.

- Subjects receiving a dose of 10.5 mg/kg/day should receive 7.0 mg/kg/day for 4 days, then 3.5 mg/kg/day for 3 days, then discontinue study medication.

- Subjects receiving a dose of 7.0 mg/kg/day should receive 3.5 mg/kg/day for 7 days, and then discontinue study medication.

- Subjects receiving a dose of 3.5 mg/kg/day may discontinue study medication without any taper.

Table 2. End-of-Treatment Taper Schedule for Pediatric Subjects <30 kg

Day[1] / Total Daily Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7/ Follow up
14.0 mg/kg/day	7.0	7.0	7.0	7.0	3.5	3.5	3.5
10.5 mg/kg/day	7.0	7.0	7.0	7.0	3.5	3.5	3.5
7.0 mg/kg/day	3.5	3.5	3.5	3.5	3.5	3.5	3.5
3.5 mg/kg/day	0	0	0	0	0	0	0

1. Days 1-7 post-Month 12/Early Termination visit.

For adult subjects (17 to 65 years of age) who taper off of pregabalin, the following schedule is recommended:

- Subjects receiving a dose of 600 mg/day should receive 300 mg/day for 4 days, then 150 mg/day for 3 days, then discontinue study medication.

- Subjects receiving a dose of 450 mg/day should receive 300 mg/day for 4 days, then 150 mg/day for 3 days, then discontinue study medication.

- Subjects receiving a dose of 300 mg/day should receive 150 mg/day for 7 days, and then discontinue study medication.

- Subjects receiving a dose of 150 mg/day may discontinue study medication without any taper.

Table 3. End-of-Treatment Taper Schedule for Adult Subjects

Day[1] / Total Daily Dose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7/ Follow up
600 mg/day	300	300	300	300	150	150	150
450 mg/day	300	300	300	300	150	150	150
300 mg/day	150	150	150	150	150	150	150
150 mg/day	0	0	0	0	0	0	0

1. Days 1-7 post-Month 12/Early Termination visit.

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 for Subjects who have Participated in Studies A0081041, A0081042, or A0081105

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 subject (or a legally acceptable representative) has been informed of all pertinent aspects of Study A0081106. When there are 2 parents or 2 legally acceptable representatives, consent should be obtained from both of the child's parents/legal representatives if present at the meeting where the informed consent document is signed. Subject to local regulations whenever the minor is able to give assent, the minor's assent must be obtained.

2. Subjects and/or parents/legally acceptable representative who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male and female subjects who have participated in and completed, or participated in Studies A0081041, A0081042, or A0081105. For subjects who have participated in, but did not complete Studies A0081041, A0081042, or A0081105, eligibility for Study A0081106 will be reviewed with a member of the Pfizer study team to determine further eligibility. Subjects are required to have completed a minimum of 4 weeks of double-blind treatment in Studies A0081041 or A0081105 to be considered potentially eligible for Study A0081106.

4. Male and female epilepsy subjects who have participated in either Study A0081041 or Study A0081042, 1 month to 16 years of age inclusive on the date of the Screening Visit with diagnosis of epilepsy with seizures classified as simple partial, complex partial or partial becoming secondarily generalized, according to the International League Against Epilepsy (ILAE 2010[3]) (See Appendix 1 for additional seizure types). The diagnosis must be established by:

    - Subject's history (eg, description of seizures excluding confounding disorders such as pseudoseizures, syncope etc) family history and neurological exam.

    - Subjects must have had a contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain and electroencephalogram (EEG) testing prior to Study A0081041 or Study A0081042. Results must have been consistent with the diagnosis of focal-onset epilepsy and must have demonstrated that no abnormality was likely to be progressive.

5. Male and female subjects 5-65 years of age who have participated in Study A0081105 with a diagnosis of epilepsy (ILAE 2010[3]) with PGTC seizures and who continue to satisfy seizure related inclusion criteria for that study (see Protocol A0081105). Subjects who have participated in study A0081105 and who reach the age limit of 66 years of age will still be allowed to enter this study.

6. Currently receiving a stable dose of 1 to 3 antiepileptic drugs at Visit 1. Benzodiazepine medication used on a regular basis will be considered 1 of the concurrent antiepileptic treatments. The vagus nerve stimulator (VNS) is allowed and considered 1 of the 3 antiepileptic treatments.

7. A 12-lead ECG at (the last visit of Studies A0081041, A0081042, A0081105) without significant abnormal findings.

4.1.1. Inclusion Criteria for Directly Enrolling Subjects (ie, partial onset seizure subjects who have not participated in either Studies A0081041 or A0081042)

In order for Direct Enrolling Subjects to be eligible, all of the following inclusion criteria must be met and confirmed prior to, or on, Visit 2:

1. Evidence of a personally signed and dated informed consent document indicating that the parent/legally acceptable representative has been informed of all pertinent aspects

of the study. When there are 2 parents or 2 legally acceptable representatives, consent should be obtained from both of the child's parents/legal representatives if present at the meeting where the informed consent document is signed. Subject to local regulations whenever the minor is able to give assent, the minor's assent must be obtained.

2. Subjects and/or parents/legally acceptable representative who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Subjects and/or parent/legally acceptable representative must be considered willing and able to complete daily seizure diaries and monitor seizure frequency.

4. Male and female epilepsy subjects, 1 month (44 weeks gestational age) to 16 years of age inclusive on the date of the Screening Visit with diagnosis of epilepsy with seizures classified as simple partial, complex partial or partial becoming secondarily generalized, according to the International League Against Epilepsy (ILAE 2010[3]) (See Appendix 1 for additional seizure types). The diagnosis must be established by:

    - Subject's history (eg, description of seizures excluding confounding disorders such as pseudoseizures, syncope etc.) family history and neurological exam.

    - Subjects must have had a contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain within 60 months of the Screening Visit and an EEG within 24 months of the screening visit. However, if clinical symptoms have emerged or a change in a clinical status has occurred such that an imaging study would be required, then a CT with contrast or MRI of the head should be performed regardless of the amount of time that has elapsed since the previous CT/MRI scan. Results must be available as soon as possible following screening and must be completed and reviewed prior to enrollment. Imaging results must be consistent with the diagnosis of focal-onset epilepsy and must demonstrate that no abnormality is likely to be progressive.

    - Subjects must have had an average of at least 3 seizures per month in the 3 months prior to screening.

5. Currently receiving a stable regimen of 1 to 3 antiepileptic treatments (stable within 28 days prior to screening). Benzodiazepine medication used on a regular basis at a stable dosage will be considered 1 of the concurrent antiepileptic treatments. Any PRN benzodiazepine use in addition to AEDs must be discussed with the Pfizer clinician and allowance will be decided on a case-by-case basis. The vagus nerve stimulator (VNS) is allowed and considered 1 of the 3 antiepileptic treatments.

6. A 12-lead ECG at screening without clinically significant abnormal findings as determined by the investigator.

4.2. Exclusion Criteria

These exclusion criteria apply to subjects who have participated in Studies A0081041, A0081042, or A0081105, as well as those subjects who have not. In order for Direct Enrolling Subjects to be eligible, all exclusion criteria should be confirmed prior to, or on, Visit 2.

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

1. Lennox-Gastaut syndrome, Infantile Spasms, Absence seizures for Direct Enrolling subjects, BECT (Benign epilepsy with centrotemporal spikes) and Dravet syndrome. A current diagnosis of febrile seizures, any febrile seizures within 1 year of screening, or seizures related to an ongoing acute medical illness.

   Prior history (ie, more than 1 year prior to screening) of febrile seizures may be allowed on a case by case basis following consultation with study clinician.

2. Status epilepticus within 1 year prior to Visit 1 of this study.

3. Seizures related to drugs, alcohol, or acute medical illness.

4. Progressive structural central nervous system (CNS) lesion or a progressive encephalopathy. Progressive inborn errors of metabolism.

5. Known or suspected chronic hematologic, hepatic or renal disease (aspartate aminotransferase –AST- and alanine aminotransferase –ALT- above 3 times the upper limit of normal; or bilirubin, BUN, or creatinine above 2 times the upper limit of normal within the previous 6 months for infants, children and adolescents aged 6 months or more, or at any postnatal period for infants younger than 6 months). Estimated creatinine clearance (CLcr) <60 mL/min for subjects ≥17 yr and <80 mL/min/1.73m^2 (using age appropriate equations) for subjects <17 years of age. For subjects who previously participated in A0081041, A0081042 or A0081105, it is assumed the subjects have already met entry criteria, therefore, the creatinine clearance exclusion is based upon results collected at the Screening Visit laboratory of A0081041, A0081042 or A0081105. The laboratory exclusion criteria noted above will be based upon data collected at the Last visit (Visit 9, Early Termination, or Unscheduled Visit) of the A0081041, A0081042 or A0081105.

6. Other severe acute or chronic medical (eg, genetic or chromosomal syndromes) or 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 results and, in the judgment of the investigator or the sponsor, would make the subject inappropriate for entry into this study.

7. Pregnant or nursing females (females who are menarchal must have a negative urine pregnancy test); menarchal females of childbearing potential who are unwilling or

unable to use an acceptable method of contraception, as outlined in the protocol, until completion of follow-up procedures.

8. Taking any non-antiepileptic (non-AED) medication that could alter the effectiveness of the subject's medication, response, seizure frequency or characteristics. Medications for Attention Deficit/Hyperactivity Disorder and other behavioral changes (eg, risperidone) will be permitted. A ketogenic diet will also be allowed given that the diet is adhered to for the duration of the study. Note: changes in the dose, regimen and type of these medications during study participation may be allowed upon discussion with the study clinician. Continued participation of the subject will be evaluated and decided on a case-by-case basis.

9. Taking or have taken any other investigational drug (aside from participation in Studies A0081041, A0081042 or A0081105) within the last 30 days prior to screening.

10. The concomitant use of gabapentin, felbamate and vigabatrin is prohibited.

11. Use of cocaine, phencyclidine (PCP), or other illegal or illicit drugs is prohibited. Use of marijuana, or its derivatives, including prescribed medical marijuana, is not allowed under any circumstances. Use of amphetamines, barbiturates, opiates, or benzodiazepines without a valid current prescription is prohibited.

12. Unwilling or unable to comply with the Life Style Guidelines.

13. Subjects not reasonably expected to complete the study.

14. Any subjects considered at risk of suicidal behavior based upon the Columbia Suicidality Rating Scale (C-SSRS) Lifetime (subjects ≥6 years of age) or Child Behavioral Check List (CBCL)(subjects <6 years of age) or responses obtained during the Modified International Neuropsychiatric Interview (MINI-KID). A subject should be excluded or a risk assessment should be done by a qualified mental health professional based on responses to assessment of suicidal ideation and behavior and if the subject has had suicidal ideation in the last 6 months prior to screening, suicidal behaviors or attempts in the past year, or current major psychiatric disorders that are not explicitly permitted in the inclusion/exclusion criteria. A risk assessment should also be performed in any child <6 years of age who has ever exhibited any potentially self-injurious or high-risk behaviors such as hurting himself or herself, or unusual behaviors such as running into traffic or using items as weapons (eg, knife, bat). Any concerns regarding such behaviors should be discussed with the Pfizer clinician prior to study participation or continuation.

15. For subjects who have not participated in Studies A0081041, A0081042, or A0081105 and enrolling directly into Study A0081106, treatment with pregabalin for any reason within 60 days prior to screening, or prior participation in a pregabalin clinical study is prohibited.

16. Known allergy or intolerance to pregabalin or its excipients, including lactose, or other α2δ ligands (eg, gabapentin).

17. Subjects, or subjects whose parents/legally acceptable representatives are investigational site staff members; and subjects, or subjects whose parents/legally acceptable representative are Pfizer employees directly involved in the conduct of the study.

4.3. Life Style Guidelines

Subjects should be advised that pregabalin may cause dizziness and somnolence. Accordingly, as age appropriate, subjects should be advised not to drive, consume alcohol or operate complex machinery until they have gained sufficient experience on study drug to assess its effects on performance.

4.3.1. Contraceptive Guidelines

The investigator should interview each subject to obtain his/her sexual and contraceptive history in order to give appropriate sexual counseling about conduct during the study. All subjects (male and female) with reproductive potential must agree to practice simultaneously 2 effective contraception methods or abstinence for at least 28 days prior to the first dose of study drug and for 28 days following the last dose of study drug. These may include:

- Barrier (condoms, diaphragm or cervical cap) with spermicide.
- Oral or other acceptable contraceptives which may include but is not limited to: injectable, implanted or patch hormone therapy, IUD, or documented surgical sterilization.
- Absolute sexual abstinence, without a second method.

A urine pregnancy test for female subjects who are menarchal will be collected at Visits 1, 6, 7, and 8. If the results of the urine pregnancy test are positive, the subject will not be eligible for study participation.

4.4. 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 located in the team Sharepoint.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects 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 subject directly and if a subject calls that number they will be directed back to the investigational site.

4.5. Rater Qualifications

The process of reviewing rater qualifications, approval of raters for training and the training of raters is administered by CCI as an agent of the Sponsor. All designated raters must complete a Rater Qualification Survey available through the study web-based workspace CCI in order to become qualified as a rater. All site personnel who require or request access to the workspace are granted access upon site activation. All qualified raters must also successfully complete protocol required training prior to the administration of any assessment (ie, Mini-Kid; CBCL; C-SSRS – please see Section 7-ASSESSMENTS- for additional details). The assessment instruments have been designed for use by professionals who have been trained on their administration. Therefore, all raters must complete the required assessment training, either during attendance at an Investigator Meeting, or through the study web-based workspace. All training materials and instructions are located on the workspace. The company CCI will issue a rater training completion certificate to qualified raters for training on each assessment instrument that has been completed. Qualified raters must have a valid rater training completion certificate on file in order to perform the assessment.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

Subjects who complete Visit 1 and meet the eligibility criteria will begin study treatment.

Subjects will be assigned sequentially a subject number at the time of screening (Visits 1A or 1B) by a telerandomization system. An IVRS drug supply management system will assign study medication by assigning appropriate container numbers.

Pediatric subjects with body weight ≥30 kg will initiate dosing of pregabalin at the daily dose of 2.5 mg/kg/day administered in 2 equally divided doses (BID) in subjects ≥4 years of age or in 3 equally divided doses (TID) in subjects <4 years of age for a minimum of 1 week. Thereafter, dosing will be flexible, based on individual seizure response and tolerability. Doses may be adjusted up or down at clinic visits in increments of no more than 2.5 mg/kg/day to daily dose levels of 5.0, 7.5, or 10.0 mg/kg/day. For pediatric subjects with body weight <30 kg, the daily dose will be adjusted by 40% to an initial daily dose of 3.5 mg/kg/day administered in 2 equally divided doses (BID) in subjects ≥4 years of age or in 3 equally divided doses (TID) in subjects <4 years of age for a minimum of 1 week. Thereafter, dosing will be flexible, based on individual seizure response and tolerability. Doses may be adjusted in increments of no more than 3.5 mg/kg/day to daily dose levels of 7.0, 10.5, or 14.0 mg/kg/day. Subjects will maintain a BID or TID dosing regimen throughout study participation based on age at Visit 1 (especially for subjects rolling over

from Study A0081042 who will remain on a TID regimen) to avoid potential dosing error/noncompliance related to regimen switch.

Adult subjects who enroll in this study following participation in Study A0081105 will initiate dosing of pregabalin at the level of 150 mg/day administered daily in 2 equally divided doses (BID) of 75 mg. Thereafter, dosing will be flexible and based on individual seizure response and tolerability. Doses may be adjusted in increments of no more than 150 mg/day to daily dose levels of 300, 450, or 600 mg/day.

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Study medication will be supplied by Pfizer as capsules of pregabalin (50, 75, 100, 150, 200, 225, and 300 mg), as well as 20 mg/mL solution. The pregabalin liquid oral solution formulation (20 mg/mL) and the pregabalin oral capsules are bioequivalent. The pregabalin capsules are formulated into size #0 gray/gray capsules. All study medication is to be packaged in bottles that are child-resistant.

Pregabalin capsules are composed of pregabalin, lactose monohydrate, cornstarch, and talc encapsulated in opaque hard gelatin capsule shells composed of gelatin and titanium dioxide. Pregabalin oral solution contains a sweetening agent (sucralose) and a flavor (artificial strawberry).

5.2.2. Preparation and Dispensing

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

The Sponsor will provide study medication that will be dispensed through an interactive voice response system (IVRS). 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 study medication will be dispensed at Visit 1 through Visit 8. The 1-week taper medication will be dispensed at Visit 8, or for those subjects who discontinue before completing the study, between Visits 3 and 7.

Additional bottles of placebo will be provided to each site for subjects to be able to test their ability to swallow the size #0 capsules. These bottles will be clearly labeled for this purpose.

5.2.3. Administration

Pregabalin will be administered orally daily in 2 equally divided doses (BID; approximately q12 hr) in subjects ≥4 years of age or in 3 equally divided doses (TID; approximately q8 hr) in subjects <4 years of age, as specified in Section 5.1- Allocation to Treatment. Subjects weighing <30 kg will receive pregabalin as a liquid formulation. Pediatric and adult subjects

with body weight ≥30 kg may choose either liquid or capsule formulation based on subject preference and ability to swallow the size # 0 capsules. Study medication formulation for administration will be as outlined below, with investigators (and subjects) determining the choice of solution or capsule for children and adults >30 kg.

If a subject missed a dose, subject should skip the dose and wait until the next scheduled dose for administration. No additional study medication administration (ie, double-dosing) is allowed at any time during the study.

Weight	Formulation
<30 kg	Liquid
Pediatric subjects ≥30 kg	Liquid or capsule
Adult subjects	Capsules or liquid

5.2.4. Compliance

Subjects will take the study medication according to the instructions provided, and should adhere to the dosing schedule as closely as possible, with study medication administered approximately every 12 hr (ie, q12 hours) in subjects ≥4 years of age or in 3 equally divided doses (ie, q8 hours) in subjects <4 years of age. 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.

For subjects who begin taking capsules, but can no longer comply with swallowing after starting, parents/caregivers should break open the capsules and sprinkle the study drug into food for ingestion until the next study visit. Sprinkling should only occur when the child is in danger of missing a dose due to inability to swallow the capsules and there is no liquid dose available at that time. All of the food that the capsule has been sprinkled on must be ingested. This should be noted in the Dosing Diaries and dosing log CRFs. At the next study visit, the site should record the days that the study drug was sprinkled, and then switch the subject to the liquid oral solution form of the study drug for the remainder of the study. An unplanned visit may be scheduled to switch from capsules to liquid if necessary.

If the subject regurgitates or spits out the study drug within 15 minutes after either liquid or capsule administration, the subject/parent/caregiver should re-administer the study drug. If more than 15 minutes have elapsed since drug was taken, no additional study drug should be administered until the next scheduled dose. This occurrence should be noted in the Dosing Diaries and dosing log CRFs.

Administration of the liquid oral solution 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 important to document.

5.3. 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 (CV) in the US, and therefore in the US must be stored according to US/Federal Drug Enforcement Agency (DEA) regulations. 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 must be stored at 15-25°C. Access to the stored study medication should be limited to the Investigator, 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. If the study medication is determined to have been stored or delivered outside the outlined temperature range, the information is to be brought to the appropriate study supply personnel for evaluation.

Storage conditions stated in the investigator brochure may be superseded by the label storage.

Study medication will be dispensed under the supervision of investigator site personnel. Each subject will complete a dosing diary and will bring the diary and the medication bottle(s) back to the clinic at each visit. For those subjects who are dispensed capsules, a pill count will be done by the site staff at each visit, and the subject/caregiver will be queried about any missed or extra doses taken. For those subjects who are dispensed liquid oral solution, 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 consumed. The subject/caregiver will be queried about any missed or extra doses taken or any volume discrepancies.

All dispensed study medication bottles will be locally kept available for checks by the study monitor.

The Investigator must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(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 investigational product, 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 study all drug supplies unallocated or unused will 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 study 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.

5.4. Concomitant Medication(s)

Prior and concomitant medication information will be collected for all subjects for a period of 30 days prior to screening (for subjects enrolling directly into Study A0081106) 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, reason for use, start date and stop date.

5.4.1. Permitted Medications

The Investigator must be informed of all medications the subject receives prior to the subject's 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 may be consulted for assistance in determining whether or not specific medications not contained on this list should be permitted or prohibited. Initiation of new medications, including AEDs, during study participation is allowed if medically indicated. Initiation of certain drugs, however, such as CNS active compounds, like Risperidone, should be discussed with the study clinician. If there are any questions about the start of a new drug, the study clinician should be contacted.

Anti-epileptic drugs (including VNS) are permitted and the number and dosages are at the discretion of the investigator. Changes in the dose, regimen and type of AED are allowed during the study participation upon the discretion of the investigator.

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).
- Non-steriodal anti-inflammatory drugs (NSAIDs).
- Over the counter medications (excluding medications such as Kava Kava or St. John's Wort).

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

- Antihypertensive agents.
- Lipid lowering agents.
- Medications to treat ADHD [ie, stimulants (eg, methylphenidate; amphetamine); selective norepinephrine reuptake inhibitors (eg, atomoxetine); alpha agonists (eg, clonidine; guanifacine)].
- Antiepileptic drugs.
- Aspirin.
- Bronchodilators.
- Inhaled steroids.
- Multivitamins.
- NSAIDs.
- Oral and depot contraceptives.

5.4.2. Prohibited Medications

Concurrent treatment with other investigational agents or devices is not allowed during the study. **Note:** a previously implanted Vagus Nerve Stimulator (VNS) is allowed but will be considered as a concomitant AED.

The use of felbamate, gabapentin or vigabatrin is prohibited during the study.

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

- Prescribed medications consistent with inclusion/exclusion criteria.
- Use of PRN benzodiazepines (See Section 5.5).

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.

5.5. Benzodiazepine Use as Needed for Occasional Seizure Exacerbation

Benzodiazepines may be used as needed (PRN) during this open-label study. Use of PRN benzodiazepines will be permitted for the occasional seizure exacerbation. PRN benzodiazepine use should not exceed a total of 6 dosage administrations in any given 3 month period.

If a benzodiazepine is prescribed for treatment on a regular basis (eg, weekly) then it is considered one of the 3 allowed AEDs. In such cases, additional benzodiazepines may also be used PRN as described above.

6. STUDY PROCEDURES

The study 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. Clinic Visit 1A (Day 1A): Screening for Subjects who have participated in Studies A0081041, A0081042, or A0081105

The last day of Studies A0081041, A0081042, and A0081105 will be designated Day 1 of this study. The subject may be screened, and if inclusion and exclusion criteria are met, enrolled into Study A0081106 after all procedures have been completed for Studies A0081041, A0081042, or A0081105. For subjects who have participated in, but did not complete Studies A0081041, A0081042, or A0081105, eligibility for Study A0081106 will be reviewed with a member of the Pfizer study team to determine further eligibility. Subjects are required to have completed a minimum of 4 weeks of double-blind treatment in Studies A0081041 or A0081105 to be considered potentially eligible for Study A0081106. The following activities will be performed at Visit 1:

- Obtain written informed consent from both (if available) of the child's legal representatives (parents or guardians) and obtain the child's assent (if applicable). For adult subjects written informed consent will be obtained from the subject, or if necessary, a legally acceptable representative (parent or guardians).
- Review eligibility per inclusion/exclusion criteria.
- Record demographic data (eg, date of birth, sex [at birth], race, etc).
- Record medical history including primary diagnosis.
- Record seizure history including classify seizure type.
- Record ongoing adverse events from Studies A0081041, A0081042, or A0081105 if appropriate.
- Record all ongoing concomitant medications and non-drug treatments/procedures from Studies A0081041, A0081042, or A0081105 if appropriate.
- Evaluate study medication compliance from Studies A0081041, A0081105 and A0081042.
- Assign subject number and dispense study medication via telerandomization system.
- Dispense subject daily seizure and dosing diary.

- The following assessments are not required to be completed at this visit as the results from Studies A0081041, A0081042, or A0081105 will be used: medical history including seizure related history and antiepileptic medication history; all prior medications; blood samples for hematology and chemistry; urine sample for urinalysis; full physical examination to include height, weight and vital signs and assessment of Tanner Stage for pediatric/adolescent subjects less than 16 years of age; full neurological examination; urine pregnancy test for female subjects who are menarchal, if the results of the urine pregnancy test are positive, the subject will not be eligible for study participation; 12-lead electrocardiogram; CogState battery (completed as part of the last visit of Study A0081041 only); assessment of suicidal ideation and behavior (C-SSRS Since Last Visit version or CBCL) using appropriate test for subject's age.

  Note: From Visit 1 onwards, weight of subjects will be recorded in the IVRS at every visit during the course of the study in order to adjust the volume and/or dose of study medication dispensed according to weight change to ensure appropriate study medication administration.

6.2. Clinic Visit 1B (Day 1B): Screening for Subjects Directly Enrolling into Study A0081106 who have <u>not</u> Participated in Studies A0081041, A0081042, or A0081105

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

- Obtain written informed consent from both parents (if available), or the child's legally acceptable representatives and obtain the child's assent (if applicable).
- Review eligibility per inclusion/exclusion criteria.
- Review and record adverse events.
- Record demographic data (eg, date of birth, sex [at birth], race, etc).
- Record medical history including primary diagnosis.
- Record seizure history including classify seizure type.
- Verify subjects have had an average of at least 3 seizures per month in the 3 months prior to screening. There must not be any seizure free months in the 3 months prior to screening.
- Record complete medical history including seizure related history and antiepileptic medication history.
- Perform complete full physical exam which includes vital signs, including blood pressure (BP) (sitting), pulse and assessment of Tanner Stage for pediatric/adolescent subjects <16 years of age.

- Record height and weight.

  Note: From Visit 1 onwards, weight of subjects will be recorded in the IVRS at every visit during the course of the study in order to adjust the volume and/or dose of study medication dispensed according to weight change to ensure appropriate study medication administration.

- Perform full neurological examination.

- Perform electroencephalogram (EEG) (unless the procedure has been performed within 24 months prior to the Screening Visit).

- Perform contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain if it has not been performed within 60 months prior to the Screening Visit or if it is clinically warranted.

  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 on the day of this visit and must be completed and reviewed prior to Visit 2.

- Record all concomitant medications and non-drug treatments/procedures currently and within 30 days of Visit 1.

- Perform, review and transmit 12-lead ECG to central reader.

- Administer CogState battery (POS subjects 4-16 years of age).

- Perform urine pregnancy test for female subjects who are menarchal. If the results of the urine pregnancy test are positive, the subject will not be eligible for study participation.

- 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 exclusionary abnormal screening laboratory value (see Exclusion Criteria 5) the laboratory test should be repeated. If the repeated test is still abnormal, the subject should be withdrawn from the study at Visit 2. In the event that the subject has an abnormal laboratory value that the investigator determines is significant and exclusionary, the subject should be contacted to stop taking study medication and return to the clinic for an early termination visit.

- Administer the MINI-KID and C-SSRS Lifetime or Child Behavioral Checklist (CBCL) as appropriate for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization.

- Assign subject number and dispense study medication via tele-randomization system.

- For direct-enrolling subjects that will receive liquid solution, train parents on dosing administration and demonstrate use of oral syringe/bottles. Have subject and/or child's parents/legally acceptable representative practice dosing in office to verify comprehension of dosing instructions.

- Administer first dose of study medication in office.

  Note: all screening procedures must be completed before subject is administered the first dose of study medication. All eligibility criteria should be confirmed prior to, or on Visit 2. If a subject is not deemed eligible, subject should be notified by phone to discontinue study medication, and should come back for an Early Termination visit as soon as possible.

- Dispense subject daily seizure and dosing diary and train subject and/or child's parents/legally acceptable representative on its use and completion.

6.3. Clinic Visit 2 (Week 1/Day 8 ±1 day)

At this visit, the investigator will review dosing with the subject and/or child's parents/legally acceptable representative and may adjust the dose based on seizure response and tolerability.

The following activities will be performed at Visit 2:

- Review and record adverse events.

- Review and record all concomitant medications and non-drug treatments/procedures.

- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate version or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).

- Collect and review daily seizure and dosing diary and record number and type of seizure.

- Adjust the dose if needed based on seizure response and tolerability.

- Evaluate and record study medication compliance.

- Dispense study medication via tele-randomization system.

- For direct-enrolling subjects assigned liquid solution, verify accurate dose administration via syringe/bottles. Have subject and/or child's parents/legally

acceptable representative demonstrate dosing in office to verify continued comprehension of dosing instructions.

- Dispense seizure and dosing diary and review instructions for completion.

6.4. Clinic Visit 3 (Month 1/Day 30 ±4 Days)

The following activities will be performed at Visit 3:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Adjust the dose if needed based on seizure response and tolerability.
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate versions or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).
- Evaluate and record study medication compliance.
- Dispense study medication via tele-randomization system.
- Dispense subject daily seizure and dosing diary.

6.5. Clinic Visit 4 (Month 2/Day 60 ±4 Days)

The following activities will be performed at Visit 4:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Adjust the dose if needed based on seizure response and tolerability.
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate version or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).

- Collect and record vital signs.
- Evaluate and record study medication compliance.
- Dispense study medication via tele-randomization system.
- Dispense subject daily seizure and dosing diary.

6.6. Telephone Contact (Month 3/Day 90 ±4 Days)

The Investigator (or designee) will contact the parent/subject by telephone to ensure medication compliance and provide guidance for accurate dosing as required.

- Review subject's compliance with dosing regimen.
- Review compliance with completion of dosing and seizure diary.
- Review concomitant medications and non-drug treatments/procedures.
- Assess adverse events.

6.7. Clinic Visit 5 (Month 4/Day 120 ±4 Days)

The following activities will be performed at Visit 5:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate version or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).
- Evaluate and record study medication compliance.
- Dispense study medication via tele-randomization system.
- Dispense subject daily seizure and dosing diary.

6.8. Telephone Contact (Month 5/Day 150 ±4 Days)

The Investigator (or designee) will contact the parent/subject by telephone to ensure medication compliance and provide guidance for accurate dosing as required.

- Review subject's compliance with dosing regimen.
- Review compliance with completion of dosing and seizure diary.
- Review concomitant medications and non-drug treatments/procedures.
- Assess adverse events.

6.9. Clinic Visit 6 (Month 6/Day 180 ±4 Days)

The following activities will be performed at Visit 6:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Evaluate and record study medication compliance.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Adjust the dose if needed based on seizure response and tolerability.
- Complete brief physical and neurological exams to include height, weight, vital signs.
- Collect blood samples for hematology, biochemistry.
- Collect urine samples for urinalysis and a urine pregnancy test (for female subjects who are menarchal).
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate version or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).
- Dispense study medication via tele-randomization system.
- Dispense subject daily seizure and dosing diary.

6.10. Telephone Contact (Month 7/Day 210 ±4 Days)

The Investigator (or designee) will contact the parent/subject by telephone to ensure medication compliance and provide guidance for accurate dosing as required.

- Review subject's compliance with dosing regimen.
- Review completion of dosing and seizure diary.

- Review concomitant medications and non-drug treatments/procedures.
- Assess adverse events.

6.11. Telephone Contact (Month 8/Day 240 ±4 Days)

The Investigator (or designee) will contact the parent/subject by telephone to ensure medication compliance and provide guidance for accurate dosing as required.

- Review subject's compliance with dosing regimen.
- Review completion of dosing and seizure diary.
- Review concomitant medications and non-drug treatments/procedures.
- Assess adverse events.

6.12. Clinic Visit 7 (Month 9/Day 270 ± 4 Days)

The following activities will be performed at Visit 7:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Adjust the dose if needed based on seizure response and tolerability.
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate version or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).
- Evaluate and record study medication compliance.
- Collect urine samples for a urine pregnancy test (for female subjects who are menarchal).
- Collect and record vital signs.
- Dispense study medication via tele-randomization system.
- Dispense subject daily seizure and dosing diary.

6.13. Telephone Contact (Month 10/Day 300 ±4 Days)

The Investigator (or designee) will contact the parent/subject by telephone to ensure medication compliance and provide guidance for accurate dosing as required:

- Review subject's compliance with dosing regimen.
- Review completion of dosing and seizure diary.
- Review concomitant medications and non-drug treatments/procedures.
- Assess adverse events.

6.14. Telephone Contact (Month 11/Day 330 ±4 Days)

The Investigator (or designee) will contact the parent/subject by telephone to ensure medication compliance and provide guidance for accurate dosing as required:

- Review subject's compliance with dosing regimen.
- Review completion of dosing and seizure diary.
- Review concomitant medications and non-drug treatments/procedures.
- Assess adverse events.

6.15. Clinic Visit 8 (Month 12/Early Termination Day 365 ±7 Days)

The 12 month treatment phase is completed. Subjects who will not continue treatment with pregabalin, whether they complete, or require early termination prior to the completion of 12 months of treatment, should begin the taper as described in Section 3 (Table 1) and follow the procedures for Visits 8 and 9. Subjects who continue on pregabalin following completion of the study will not require a taper.

The following activities will be performed at Visit 8:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Perform 12-lead electrocardiogram (ECG).
- Complete brief physical examination to include height, weight, vital signs and assessment of Tanner stage (pediatric subjects only, but not applicable to subjects who participated to study A0081042).

- Complete full neurological examination.
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate version or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).
- Administer CogState battery (POS pediatric subjects 4-16 years of age).
- Collect blood samples for hematology, biochemistry.
- Collect urine sample for urinalysis and a urine pregnancy test (for female subjects who are menarchal).
- Evaluate and record study medication compliance.
- Dispense taper medication if required via tele-randomization system.
- Dispense subject daily seizure and dosing diary if subject will begin taper.

6.16. Visit 9 (Follow-up/End of Taper Visit-7 days Post-Completion/ Discontinuation±3 Days)

This visit is not required for subjects that do not enter the taper phase.

The following activities will be performed at Visit 9:

- Review and record adverse events.
- Review and record all concomitant medications and non-drug treatments/procedures.
- Collect and review seizure and dosing diary and record number and type of seizure.
- Collect urine sample for a urine pregnancy test (for female subjects who are menarchal).
- Evaluate and record study medication compliance.
- Complete assessment of suicidal ideation and behavior (C-SSRS or CBCL) using appropriate versions or test for subject's age. If CBCL is administered, scores must be obtained as soon as possible. If positive scores are obtained on the CBCL or CSSRS, a mental health risk assessment must be performed by a qualified mental health professional prior to randomization (please refer to Section 7 - ASSESSMENTS).

6.17. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. Events to consider could include but are not limited to:

- Adverse events.
- Intercurrent illness.
- Loss to follow-up.

  Note: All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

- Lack of efficacy.
- Pregnancy.
- Non-compliance with study drug, protocol requirements, or study-related procedures.
- Serious eligibility or on-study violations of the protocol (e.g., the subject does not have the disease under study).
- Study termination by Sponsor or regulatory authorities.
- Subject's decision to withdraw/withdrawal of consent.

  Note: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw

consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

- 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.

For subjects who have participated in Study A0081105, subjects must be withdrawn at any time during Study A0081106 if any 1 of the following predetermined subject exit criteria is met:

- An episode of status epilepticus.
- A 28-day PGTC seizure rate during open-label treatment that is greater than 2-times the maximum 28-day study seizure rate during the Study A0081105 baseline phase (a 28-day period is defined as a minimum of 4 consecutive study weeks).

Subjects with any of the following should be discussed with the Pfizer Study Clinician or representative for potential withdrawal:

- An episode of a newly emergent generalized seizure type during open-label treatment compared with the subject's history.
- An increase in the rate or intensity of PGTC or other generalized seizure activity that, according to the investigator, is clinically significant.

Protocol-specified withdrawal procedures are the same as those to be performed at Visit 8 and 9.

Note: under certain circumstances, when subjects leave the study early (early termination), 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 8 should be conducted where possible.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events. If the subject withdraws from the study 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 (eg, a subject may not be able or willing to comply due to neurological compromise, motor deficits or cognitive impairment). In these cases if an assessment cannot be performed the investigator will take all steps necessary to ensure the safety and well being of the subject. This may include gathering assessment data from a parent or legally acceptable representative who may answer assessment questions on behalf of the subject based upon their knowledge and observations of the subject. When a protocol required assessment 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, if feasible.

7.1. 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 Visits 1A and 1B. An abbreviated physical exam and full neurological exam will be performed at Visit 6 and 8 (i.e., at the completion of the study or early termination).

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. For pediatric subjects Tanner Stage will also be assessed at screening (Visit 1A or 1B) and at completion/early termination (Visit 8).

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.

Any clinically significant changes from the entry physical or neurological examinations will be recorded as adverse events. A physical and neurological exam will be performed at the screening and at the completion of study visit or early termination.

7.2. Vital Signs, Height and Weight

Sitting blood pressure and pulse are to be recorded at the Screening Visit (Visit 1A or 1B), Visits 4, 6, 7 and at the completion of the study. Height (using stadiometer when appropriate) will also be recorded at the Screening Visit (Visit 1A or 1B), Visit 6 and at the

completion of the study. Weight will be recorded at Visits 1A or 1B, 6, and 8. Weight recorded at Visit 1A or 1B and Visit 6 will be used to calculate the dose for subsequent visits.

7.3. Clinical Laboratory Assessments

Samples for clinical laboratory measurements will be analyzed by a central laboratory.

Estimated Creatinine Clearance (ml/min)

Estimated Creatinine Clearance will be calculated at Screening (Visit 1A or 1B) only. For subjects who previously participated in A0081041, A0081042 or A0081105, it is assumed the subjects have already met entry criteria, therefore, the Creatinine Clearance exclusion is based upon the Screening visit of A0081041, A0081042 or A0081105. For those subjects directly enrolling into A0081106, this assessment is to be performed at Screening Visit 1B only. The estimation will be calculated by the central laboratory using the following equation, the subject's age in years and the serum creatinine value (mg/dL).

Converting Serum Creatinine Concentration from μmoles/L to mg/dL

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

For subjects ≥12 years of age

$$\text{Male } CL_{CR} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} \times 1.73 m^2/\text{BSA}$$

$$\text{Female } CL_{CR} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}}\right] \times 0.85 \times 1.73 m^2/\text{BSA}$$

$$\text{BSA (Body Surface Area)} = 0.007184 \times \text{Height(cm)}^{0.725} \times \text{Weight(kg)}^{0.425}$$

For Subjects ≥1 year of age and <12 years of age

Cl_{CR} = 0.55 × length (cm)/serum creatinine (mg/dL)

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

Cl_{CR} = 0.45×length (cm)/serum creatinine (mg/dL), for infants 1 to <12 months old

7.3.1. Pregnancy Test

A urine pregnancy test for female subjects who are menarchal will be collected at Screening (Visit 1A and B). If the results of the urine pregnancy test are positive, the subject will not be eligible for study participation, or will need to withdraw from the study. A urine pregnancy test will also be performed at Visits 6, 7, 8, and 9. In the case of a positive urine pregnancy test, the subject can have a second confirmatory urine pregnancy test conducted locally prior to exclusion from the study. Pregnancy tests may also be performed more

frequently as per Institutional Review Board (IRB's)/Independent Ethics Committee (IEC's) or as required based upon local regulations.

7.3.2. Hematology

Blood samples will be collected at Screening Visit 1A and 1B (for direct enrolling subjects only), 6 and 8 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, basophils, and eosinophils.

Blood volumes to be obtained, per visit, are as follows:

Screening:	10.5 mL
V6:	4.5 mL
V8/ET:	10.5 mL
Unscheduled visit:	12.3 mL maximum (all testing optional)

7.3.3. Clinical Chemistry

Blood samples will be collected at Screening Visit 1A and 1B (for direct enrolling subjects only), 6 and 8 to assess clinical chemistries, including: total bilirubin, direct and indirect bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyl transferase (GGT), 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 will be assessed at Visit 1B and 8 only.

7.3.4. Urinalysis

Urine samples will be collected at Visit 1A and 1B (for direct enrolling subjects only), 6 and 8 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 the lack of a sample must be recorded and documented in source documentation.

7.4. Electrocardiogram (ECG)

12-lead electrocardiographic assessments (ECG) will be performed at Visit 1B (for direct enrolling subjects only) and Visit 8 (Month 12/Early Termination). The following parameters will be assessed: PR interval, RR interval, QRS complex/duration, QT interval, QTc, and heart rate.

7.5. Seizure Counts

Subjects, parents or guardians will be responsible for completing a daily seizure diary throughout the subjects' study participation. The diary will enumerate the number of seizures experienced each day, and the seizure type for each seizure event.

7.6. Assessment of Suicidal Ideation and Behavior (SIB)

In addition to the information provided below, please refer to the study web-based workspace for additional details regarding the administration of the SIB assessments; training materials and instructions are located at the A0081106 workspace CCI [redacted]. All site personnel who require or request access to the workspace are granted access upon site activation.

7.6.1. Child Behavior Checklist (CBCL); Subjects 4 to <6 Years of Age

There are currently no validated scales to assess suicidal ideation and behavior in children below age 6, and suicidal ideation and behavior is an extremely rare occurrence in this age group. Children in this age group and young school-aged children are more likely to demonstrate aberrant behaviors that place them at-risk for self-injurious behaviors. Therefore, the Child Behavior Checklist (CBCL) will be implemented to assess behaviors in young children that may place them at-risk for self-injury. The CBCL is a 100-item questionnaire designed to assess behavioral problems and social competency in children and has been used in studies of children with epilepsy.[14] A parent or legally acceptable representative will complete the scale using pen and paper to rate the subject's problem behaviors and competencies. All items are rated on a 3-point scale (0 = Not true for that child; 1 = somewhat or sometimes true; and 2 = Very or often true) based on the subject's behavior in the past 2 months at Screening, and then since last visit at all other study visits (Visit 2-10). For this study, scores on the Withdrawn, Internalizing Problems subscales and the Total Problem scales will be obtained. Higher scores on the CBCL subscales indicate higher levels of problematic behaviors or dysfunction. The CBCL scoring algorithm allows for a subject's scores to be standardized using scores from a normal population. These standardized scores are referred to as T-scores. CBCL T-scores will be obtained utilizing a standardized computerized scoring system provided to the Sponsor by CCI [redacted]. For this study, a cut-off of ≥68 on the T-scores for the Withdrawn, Internalizing Problems subscales and the Total Problem scales will be used to determine whether a child is at-risk for SIB and requires a mental health risk assessment.

The CBCL will be used in this study for children who are 4-<6 years of age beginning at Visit 1. The CBCL will be completed at Visit 1 and for each subsequent visit through Visit 9 or Early Termination. The CBCL will be performed to assess for behavioral and emotional issues, including those that may be associated with suicidal ideation and behavior. See the Schedule of Activities for the visits at which the CBCL will be completed by a parent or legally acceptable representative.

Please note that for Greek and Cebuano speaking subjects/parents, there is no available translation of the CBCL. Therefore, subjects in the age range of 4-<6 years whose parents

are fluent only in these languages will be administered the CSSRS, which can be answered by the parents or legally acceptable representative.

The CBCL, once administered, must be scanned and emailed or faxed to the designated Pfizer clinician for scoring as soon as possible, utilizing the CBCL study cover sheet provided to each site. A subject should not be enrolled into the study until the site has received the CBCL scores and a signed approved cover sheet for study entry from the Pfizer clinician. Furthermore, the subjects' CBCL scores must be obtained as soon as possible at each study visit for study continuation. Sites should work with their study monitor to ensure that this process is followed correctly.

7.6.2. Mini International Neuropsychiatric Interview (MINI-KID) – Version 6.0 (Subjects 6-<17 Years of Age)

The MINI-KID is a structured diagnostic interview evaluating 23 psychiatric conditions.[15] It is divided into modules corresponding to different diagnostic categories. The interview questions are designed to elicit information relevant to specific diagnostic criteria. The questions should be read verbatim to the subject or the subject's parent or legally acceptable representative. If during an interview a particular word or concept is not understood, the rater may explain what it means or give examples that capture its essence. If a responder is unsure if the subject has a particular symptom, the interviewer may ask for an explanation or example to determine if it matches the criterion being investigated. If a subject is unwilling or unable to respond, the parent or legally acceptable representative may answer any or all questions based upon their knowledge of the subject and observations of the subject's behavior. Subjects may be interviewed alone or with the parents or legally acceptable representative present based upon discretion of the interviewer. The MINI-KID is derived from the validated MINI and will be administered by the designated rater at Visit 1/Screening only. Raters/interviewers must successfully complete required training and must have a valid rater training completion certificate in order to perform the assessment.

The MINI-KID will be used in this study to assess the presence or absence of psychiatric symptoms in subjects 6-<17 years of age at Screening (Visit 1B) for subjects who have not participated in Studies A0081041, A0081042, or A0081105 or for subjects ages 6-<17 who have not had the MINI-KID administered during prior participation in the studies above. However, subjects who have severe psychiatric illness (ie, current major depression, bipolar disorder, schizophrenia or other psychoses) based upon history or current diagnosis should be excluded from the study. Since the C-SSRS is administered, the Suicidality Module of the MINI-KID does not have to be administered, unless there is indication of significant depression or other severe psychopathology, during the MINI-KID assessment.

7.6.3. Columbia-Suicide Severity Rating Scale (C-SSRS)- Subjects 6-65 Years of Age

The C-SSRS is a prospective semi-structured interview comprised of the following areas of assessment: Ideation, Intensity of Ideation, Behavior and Lethality. It has been used extensively in global clinical studies (academic and industry sponsored) and in a range of therapeutic areas, disorders and indications, including psychiatry, neurology, obesity, urology and endocrinology and is FDA-approved. It has been translated into multiple languages.

The C-SSRS will be used to determine eligibility to enroll at Screening and at every follow-up visit to prospectively monitor suicidal ideation and behavior during the study. If a subject is unwilling or unable to respond, the parent or legally acceptable representative may answer any or all questions based upon their knowledge of the subject and observations of the subject's behavior. Subjects may be interviewed alone or with the parents or legally acceptable representative present based upon discretion of the interviewer.

The C-SSRS will be utilized for all subjects who are 6-65 years of age at Visit 1. The "Lifetime" version will be completed at Screening for those subjects who have not had it administered during participation to study A0081041 or at Visit 1B for direct enrolling subjects. The "Since Last Visit" version of the C-SSRS will be completed at Visits 1A, 2, 3, 4, 5, 6, 7, 8, and 9 or Early Termination. The "Since Last Visit" version will also be completed at any unscheduled clinic visits (ie, clinic visits not included in the Schedule of Activities). C-SSRS raters must demonstrate successful completion of required training and must have a valid rater training completion certificate in order to perform the assessment.

7.6.4. Assessment of Suicidal Ideation and Behavior at Screening

Any subjects considered at risk of suicide based on the C-SSRS Lifetime (subjects 6-65 years of age), or demonstrating at-risk behaviors on the CBCL (subjects 4-<6 years of age) or MINI-KID (6-<17 years of age), or are likely to self harm based on clinical judgment of the investigator, should be excluded from the study or a risk assessment should be done by a qualified mental health professional (MHP – eg, licensed clinical psychologist or psychiatrist; psychiatric nurse practitioner; licensed clinical psychiatric social worker) to determine if the subject is appropriate for study inclusion. A risk assessment should be performed based on responses to suicidal ideation and behavior assessments and if the subject has had suicidal ideation in the last 6 months prior to screening, suicidal behaviors or attempts in the past year, or current major psychiatric disorders that are not explicitly permitted in the inclusion/exclusion criteria. Any positive response on the C-SSRS or a previous history of suicide behaviors should trigger a risk assessment. A risk assessment should be performed in any child <6 years of age who the Investigator has knowledge of him/her exhibiting any potentially self-injurious or high-risk behaviors (eg, hurting himself or herself, running into traffic, or using potential weapons such as knives or bats for self or other injury). A written risk assessment provided by a qualified mental health professional with approval for study participation must be documented prior to subject inclusion for at-risk subjects.

7.6.5. Assessment of Suicidal Ideation and Behavior During the Clinical Study

The correct age appropriate scale to assess suicidal ideation and behavior risk should be used based on the guidance in previous sections of this protocol. At the interim baseline, randomization and post-baseline visits, if there are any positive responses on the C-SSRS or scores ≥68 on the Withdrawn, Internalizing Problems or Total Problems standardized scores from the CBCL (4-<6 years of age), a risk assessment should be done by a qualified MHP to determine whether it is safe for the subject to continue to participate in the study. Subjects who meet these criteria (either CSSRS or CBCL) on more than one occasion during a study must have their potential suicidal ideation and behavior managed appropriately by the

investigator together with a qualified MHP (or the investigator alone if the investigator is a qualified MHP), or be discontinued from the study. The investigator should consult with the Pfizer medical monitor regarding this issue.

For subjects <6 years of age , any lifetime history of exhibiting any potentially self-injurious or high-risk behaviors such as hurting himself or herself, should result in a risk assessment by a MHP to determine if it is safe for the subject to enroll in the study. At post-baseline visits, if the subject has exhibited any potentially self-injurious or high-risk behaviors since the last visit such as hurting himself or herself, a risk assessment by a qualified MHP should be obtained to determine if it is safe for the subject to continue in the study. A written risk assessment from a qualified MHP with approval for study participation must be documented for study continuation for at-risk subjects.

7.7. Cognitive Testing

Measures of psychomotor and attentional function before and after treatment with pregabalin will be used to determine the extent to which the compound is associated with any adverse cognitive outcome. Two tests will be used to measure psychomotor function and attention; these are the CogState Detection (psychomotor function) and CogState Pediatric Identification (Go-No Go: attention) tasks. Both of these tasks have demonstrated sensitivity to the effects of antiepileptic drugs, benzodiazepines and alcohol[4, 5, 6] and can be used unchanged in children from ages 5 to adults,[7, 8] they are rapid to administer, they can be given repeatedly without engendering practice effects[7] and performance on these tests is not influenced by the cultural, language or educational background of patients.[9, 10] Importantly, many children, adolescents and young adults with epilepsy do show impairments in attentional and psychomotor function prior to any treatment and these problems are associated with educational and behavioral difficulties. Therefore, tracking these functions is important.

7.7.1. The CogState Battery

The CogState brief battery to be used in this study consists of 2 tasks. Each task is summarized below.[7, 11] The test battery is presented on a laptop computer with external response buttons. At the beginning of each task, written instructions are presented on the screen to indicate the task rules. Each subject is then given an interactive demonstration and, once they have successfully completed a sufficient number of practice trials to demonstrate their awareness of the rules, the task begins. The CogState tasks are in the form of card games. For each task, subjects respond "yes" at the presentation of each stimulus using a response button. "Yes" responses are made with the dominant hand. At the beginning of each task subjects are instructed to "respond as fast and as accurately as possible." The tasks employed in this study, in their order of presentation, are described below:

- Detection task: The CogState Detection task is a measure of simple reaction time and has been shown to provide a valid assessment of psychomotor function in healthy children and adults. For this test, the subject must press a "YES" response key as soon as they detect an event (ie, a card turning face up presented in the center of the

computer screen). The software measures the speed and accuracy of responses to each event.

- Pediatric Identification task (Go-No Go task: GONG): The CogState Pediatric Identification task is a measure of choice reaction time and has been shown to provide a valid assessment of visual attention. In this task an event (a card turning face up) occurs in the center of the computer screen and the subject must decide whether this event meets a predefined and unchanging criterion (is the color of the card black?) and answer "YES" when the criterion is met. The software measures the speed and accuracy of each response.

- Total administration time is approximately 10 min.

The time required for performance of these tests is given in Table 4:

Table 4. Trials and Timing of each task in CogState- Cognitive Battery

Task	N Trials/ screens	Maximum Time allowed	Average time req'd in pediatric clinical trials
Subject demographic screen	1	Unlimited	1 min
Detection task instructions	1	Unlimited	0.5 min
Detection task practice	3	1 min	0.5 min
Detection task	30	5 min	3 min
Identification task instructions	1	Unlimited	0.5 min
Identification task practice	6	1 min	0.5 min
Pediatric Identification Task (GONG)	50	7.5 min	4 min

The CogState battery will be performed twice at Visit 1A and 1B and once at Visit 8 (Month 12/Early Termination) **for POS pediatric subjects 4-16 years of age**.

The CogState battery is easy enough to perform for the majority of subjects participating in this study. For those subjects who are uncooperative or incapable of performing the task, for example due to motor or cognitive impairments, the task does not need to be administered. The reason for task omission should be appropriately documented.

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 for 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 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 breast feeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

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 medication error case report form (CRF) which is a specific version of the adverse event (AE) page, and on the 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 should be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. 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.

8.6. 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;

- Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

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.

8.6.1. 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).

8.6.2. 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 ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

- **Concurrent with**

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

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 history, 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 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.

8.7. 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 out-patient/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

8.8. Severity Assessment

If 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 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.

8.9. 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.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as in-utero [EIU] occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed to (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;

2. A male has been exposed (eg, due to treatment or environmental exposure), to the investigational product prior to or around the time of conception or is exposed during his partner's pregnancy.

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event Form and Exposure in Utero (EIU) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIUreports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as serious adverse events follows:

- Spontaneous abortion includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays**).**

In the case of paternal exposure, the investigator will provide the study subject with the Exposure in Utero Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the Exposure in Utero Form that the subject was given this letter to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the study master file.

8.12. 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.

8.13. Eliciting Adverse Event Information

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

8.14. 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.

8.14.1. 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 as well as to the initial and follow-up reporting of exposure during pregnancy and exposure during breast feeding cases.

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.

8.14.2. 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.

8.14.3. 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

A 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.

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

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

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

20. Direct Pregabalin: pregabalin only in this study.

Additionally, all pregabalin data in this study will be combined "Overall".

Other than baseline, where relevant, information will be presented only for this study. Baseline values will be the last observation made prior to initiating double-blind dosing in

Studies A0081041, A0081042, and A0081105. Subjects entering Study A0081106 directly will have baseline observations made at screening (Visit 1B).

Cohort analysis will consist of an age cohort defined as either pediatric (1 month to 16 years of age) or non-pediatric; and a primary seizure type cohort (partial onset seizures or PGTC seizures).

9.1. Sample Size Determination

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

9.2. Efficacy Analysis

All seizure information will be addressed in safety.

9.2.1. Analysis of Primary Endpoint

Not applicable.

9.2.2. Analysis of Secondary Endpoints

Not applicable.

9.3. Analysis of Other Endpoints

Not applicable.

9.4. Safety Analysis

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

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

Twenty-eight-day seizure rate will be calculated from the seizure diaries and will be reviewed as a means of determining seizure control. Seizure frequency for each seizure type will be summarized using descriptive statistics every 4 weeks thereafter until the end of the study by treatment group and overall. No statistical inferences will be performed.

Subgroup analysis will be done on the safety data and seizures rates for each age cohort and primary seizure type.

9.5. Data Monitoring Committee

This study will not use a Data Monitoring Committee.

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 Pratices (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 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 case report form (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 forms, 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 Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement, 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. 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 forms, 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 and 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation 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 or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must be re-consented as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal

guardian and the subject's assent, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent/assent 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 (i.e., 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 Study 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 Participating Countries

End of Trial in all 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) www.pfizer.com, and/or the

European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer registers study protocols and posts Basic Results on ClincialTrials.gov for Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product. 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 after 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 after such discontinuation of the program (if there are no plans for outlicensing or within 2 years if outlicensing plans have not completed).

Primary Completion Date (PCD) 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 prespecified protocol or was terminated.

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

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

1. Hermann BP, Austin J. Psychosocial status of children with epilepsy and the effects of epilepsy surgery. In: Wylie E, editor. The treatment of epilepsy: principles and practices. Philadelphia: Lea & Febiger; 1993: p. 1141-8.

2. Ott D, Siddarth P, Gurbani S, et al. Behavioral disorders in pediatric epilepsy: unmet psychiatric need. Epilepsia 2003; 44(4):591-7.

3. Berg AT, Berkovic SF, Brodie MJ, et al. Revised Terminology and Concepts for Organization of Seizures and Epilepsies. Epilepsia 2010; 51: 676-685.

4. Pietrzak RH, Fredrickson A, Snyder PJ, Maruff P. A comparison of statistical approaches used to evaluate change in cognitive function following pharmacologic challenge: an example with lorazepam. Hum Psychopharmacol. 2010 Jun;25(4):335-41.

5. Cromer JR, Cromer JA, Maruff P, Snyder PJ. Perception of alcohol intoxication shows acute tolerance while executive functions remain impaired. Exp Clin Psychopharmacol. 2010 Aug;18(4):329-39.

6. Maruff P, Werth J, Giordani B, Caveney AF, Feltner D, Snyder PJ,. A statistical method for measuring cognitive response to treatment in individual patients. Psychopharmacology.2006; 186:7-17.

7. Maruff P, Thomas E, Cysique L, Brew B, Collie A, Snyder P, Pietrzak RH. Validity of the CogState brief battery: relationship to standardized tests and sensitivity to cognitive impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex. Arch Clin Neuropsychol. 2009 Mar;24(2):165-78.

8. Mollica CM, Maruff P, Collie A, Vance A (2005) Repeated assessment of cognition in children and the measurement of performance change. Neuropsychol Dev Cogn C Child Neuropsychol. 11, 303-10.

9. Dingwall KM, Lewis MS, Maruff P, Cairney S. Assessing cognition following petrol sniffing for Indigenous Australians. Aust N Z J Psychiatry. 2010 Jul;44(7):631-9.

10. Yamashita Y, Mukasa A, Anai C, Honda Y, Kunisaki C, Koutaki J Tada Y, Egami C, Kodama N, Nakashima N, Nagamitsu S and , Matsuishi T (in press) Summer treatment program for children with attention deficit hyperactivity disorder: Japanese experience in 5 year. Brain and Development DOI: 0.1016/j.braindev.2010.09.005.

11. Collie A, Maruff P, Snyder PJ, Darekar MA, Huggins JP. Cognitive testing in early phase clinical trials: outcome according to adverse event profile in a Phase I study. Hum Psychopharmacol. 2006 Oct;21(7):481-8.

12. Vartanian, M.G., Radulovic, L.L., Kinsora, J., Serpa, K.A., Vergnes, M., Bertram, E. & Taylor, C.P. Activity profile of pregabalin in rodent models of epilepsy and ataxia. Epilepsy research 68, 189-205 (2005).

13. Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J. Glossary of Descriptive Terminology for Ictal Semiology: Report of the ILAE Task Force on Classification and Terminology. Epilepsia 2001 42(9): 1212-1218.

14. Achenbach, T. M. (1991). Manual for the Child Behavior Checklist/4-18 and 1991 Profile. Burlington, VT: University of Vermont, Department of Psychiatry.

15. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. J Clin Psychiatry. 1998; 59 Suppl 20:22-33.

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 2001[13]) (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. *Simple partial seizures* (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 (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) (a) Somatosensory (b) Visual (c) Auditory (d) Olfactory (e) Gustatory (f) Vertiginous		
3. With autonomic symptoms or signs (including epigastric sensation, pallor, sweating, flushing, piloerection 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 (a) Dysphasic (b) Dysmnesic (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
(e) Illusions (e.g., macropsia) (f) Structured hallucinations (e.g., music, scenes)		
B. *Complex partial seizures* (with impairment of consciousness; may sometimes begin with simple symptomatology) 1. Simple partial onset followed by impairment of consciousness (a) With simple partial features (A.1.–A.4.) followed by impaired consciousness (b) With automatisms 2. With impairment of consciousness at onset (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
C. *Partial seizures evolving to secondarily generalized seizures* (This may be generalized tonic-clonic, tonic, or clonic) 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. *Absence seizures*	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. *Atypical absence*	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. *Tonic-clonic seizures*	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. *Atonic seizures* (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 Administration of the Liquid Oral Solution Formulation:

Oral solution

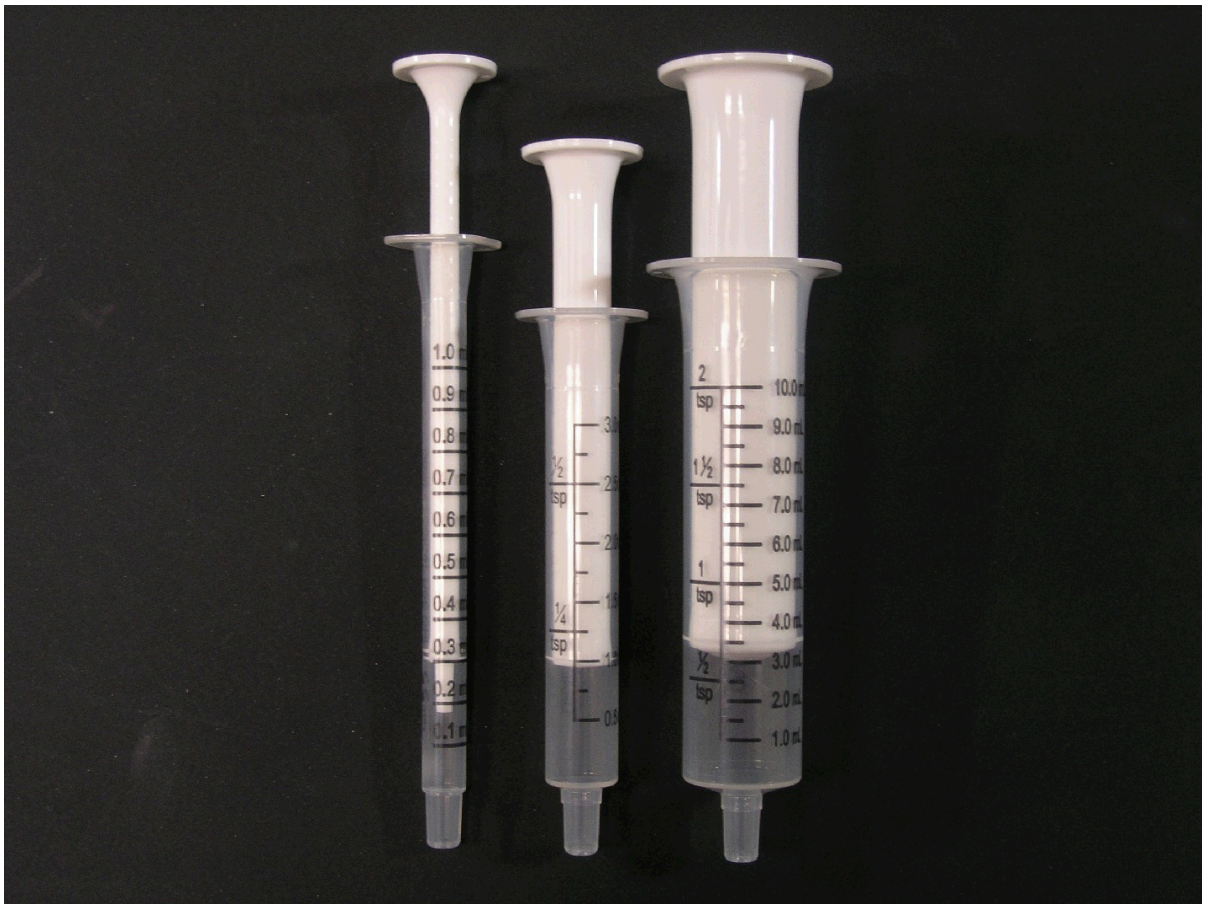
Pregabalin 20 mg/mL and matching placebo oral solutions are provided as clear, colorless, flavored solutions bottles. To accommodate the broad dose range that may be encountered during clinical studies, pregabalin 20 mg/mL and matching placebo oral solutions can be administered using a variety of oral dosing syringes (1, 3, and 10 mL). An example of the syringes and dosing tables are provided in this document for reference. Subjects/parents/guardians should receive training on dose preparation, administration, storage, and disposal prior to release for outpatient dosing.

DOSING:

Dosing is accommodated by the use of either a 1, 3, or 10 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 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 3.5-10.0 mL in 0.5 mL increments.

Illustrations of the oral dosing syringes are provided in Figure 2.

Figure 2. Oral Dosing Syringes (1, 3, and 10 mL left to right)



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). Note: the plunger on the 1 mL oral dosing syringe has 2 fins on the plunger and the fin closest to the syringe tip should be used to measure the dose.

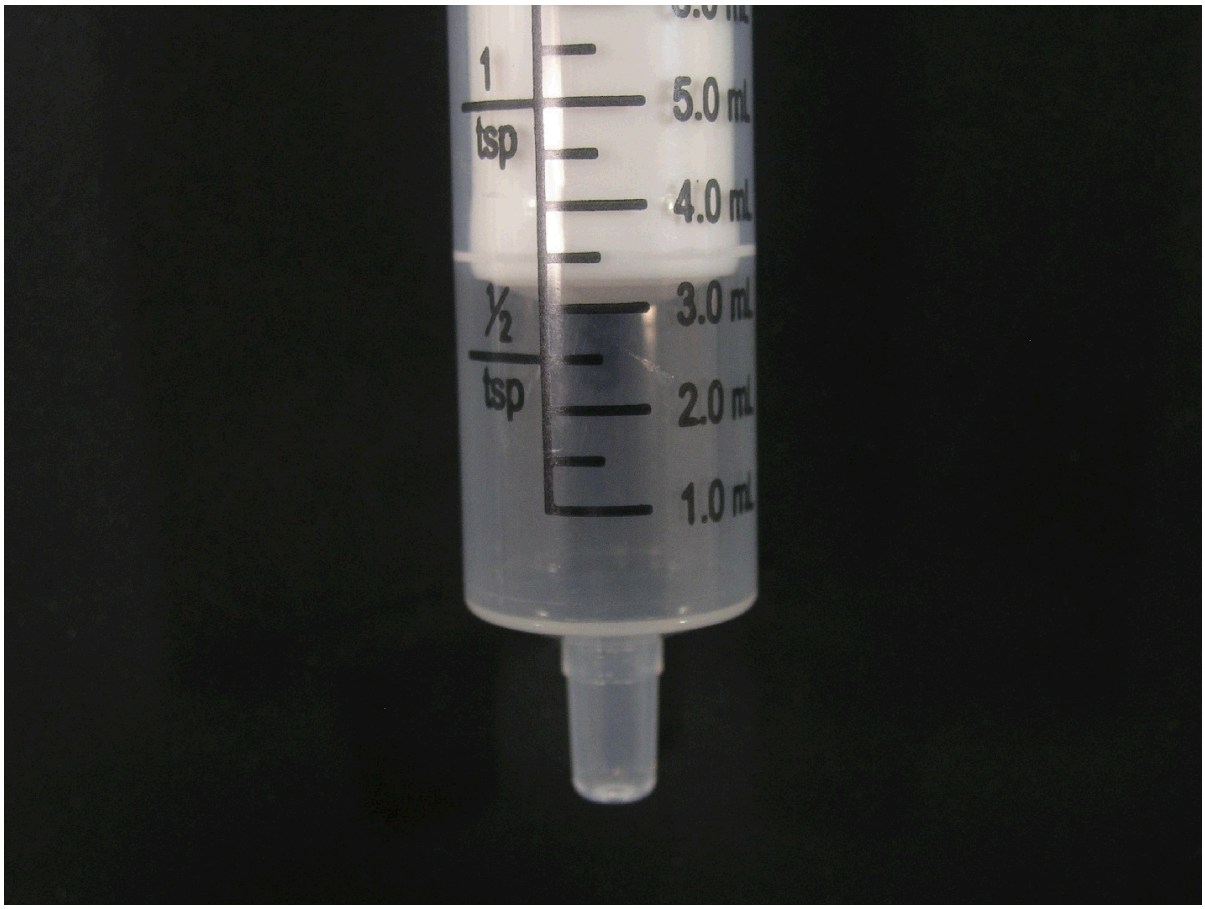
4. Place the oral dosing syringe down onto a clean surface and securely close the bottle.

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 3. Dosing Example



DOSE CALCULATIONS/SUPPLIES:

Subjects will be supplied with a suitable oral dosing syringe for self-administration.

STABILITY AND STORAGE:

A single dose that has been prepared in an oral dosing syringe should be administered within 1 hour. 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
B	
BID	Twice Daily
BP	Blood Pressure
C	
CBCL	Child Behavioral Check List
CLcr	Creatinine Clearance
C_{max}	Maximum Concentration
CNS	Central Nervous System
CP	Complex Partial
CRF	Case Report Form
C-SSRS	Columbia Suicidality Rating Scale
CT	CAT Scan (Computerized Tomography Scan)
CTA	Clinical Trial Application or Clinical Study Application
D	
DMC	Data Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Version IV
E	
ECG	Electrocardiogram
EEG	Electroencephalogram
EIU	Exposure in Utero
ET	Early Termination
F	
FSFV	First Subject First Visit
G	
GCP	Good Clinical Practice
I	
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
L	
LSLV	Last Subject Last Visit
M	
MHP	Mental Health Professional
MINI-KIDS	Mini International Neuropsychiatric Interview
mL	Milliliter
MRI	Magnetic Resonance Imaging

P	
PBO	Placebo
PGTC	Primary Generalized Tonic-Clonic Seizure
PI	Principal Investigator
PK	Pharmacokinetic/Pharmacokinetics
R	
RBC	Red Blood Cell
S	
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SE	Status Epilepticus
SGTC	Secondarily Generalized Tonic-Clonic Seizures (a type of Partial Epilepsy Seizure)
SP	Simple Partial
SSID	Single Subject Identification Number
T	
TID	Three Times A Day
V	
V	Visit
VNS	Vagus Nerve Stimulation
W	
WBC	White Blood Cell