CLINICAL PROTOCOL

PROSPECTIVE RANDOMIZED 12-WEEK CONTROLLED STUDY OF VISUAL FIELD CHANGE IN SUBJECTS WITH PARTIAL SEIZURES RECEIVING PREGABALIN OR PLACEBO

Compound:	PD-0144723; CI-1008
Compound Name (if applicable):	Pregabalin
EudraCT Number	2009-014269-25
US IND Number (if applicable):	49,393
Protocol Number:	A0081096
Phase:	Phase IV

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 5	25 September 2020	Sample size estimation changed based on the observed common standard deviation of mean deviation. Common SD changed from 5.6 dB based on literature at the time of the study design to 1.3 dB based on observed blinded data from study A0081096. Enrollment to be approximately 187. The following statement has been added to the Section 9.4 of the protocol: the expectation is that the Per Protocol subset will be close in the number of subjects to the number of subjects randomized.
Amendment 4	15 December 2015	Single Reference Safety Document (SRSD) for this study was changed from the Core Data Sheet (CDS) to the Investigators Brochure (IB). The IB contains more extensive information about pregabalin than the CDS. The protocol introduction was updated to include current marketing information on Lyrica. The following changes were made to comply with FDA and Neuropsychiatric and Abuse Potential Advisory Council (NAPAC) Guidance: • Suicidality assessment: the Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed instead of the Sheehan-Suicidality Tracking Scale (S-STS) for subjects screened following approval/initiation of Amendment 4. Subjects who are randomized under Amendment 3 will not switch to the C-SSRS. • Suicidal Behaviors Questionnaire–Revised (SBQ-R) will be performed at screening. • Scoring instructions for the PHQ8 have been inserted as well as a reference to the Instruction Manual. The following protocol exclusion has been inserted to increase subject safety:

		• Any subject at risk of suicide or self-harm based on investigator judgment and/or details of a mental health risk assessment (MHRA) by a qualified mental health professional. Instructions for completion of the PHQ-8 have been included. The Instruction Manual has been referenced. The following statement has been inserted into Section 4.3 to reinforce the requirement to include only subjects who have adequate baseline VFT. • Subjects may not be randomized prior to receiving confirmation of the validity of the Baseline VFT from the central reader. Sections presenting the Visual Field Testing (VFT) procedures were revised to clarify procedures or to amend the procedures to make it easier for the investigator to comply with the protocol: • Repeat VFT should be performed as soon as possible and within 2 weeks following notification from the central reader. • Section has been updated to reflect the electronic submission of the VFT results with subsequent faster response times. The number of sites to participate in the study has been deleted. This study has been ongoing for many years with waves of sites being initiated and terminated. The following changes were made to comply with the current protocol template and required language/wording: • Abbreviation list moved to an Appendix. • Updated terms study drug and study medication to investigational product for consistency. • Inserted Lifestyle Guidelines which includes template contraception language. • Inserted Sponsors Medically Qualified

		Personnel. • Updated Trial Treatments including insertion of new sections for Investigational Product Storage, Investigational Product Accountability and Destruction of Investigational Product Supplies. • Updated Drug Supplies. • Updated Investigational Product Storage. • Updated Quality Control and Quality Assurance. • Inserted Medication Errors. • Updated Exposure During Pregnancy. • Inserted Occupational Exposure. • Updated Publication of Results. The following changes were made to clarify potentially confusing language or to streamline the protocol: Clarified dose administration. Deleted samples of S-STS and PHQ-8 from Appendices. Subjects will be required to record all investigational product dosing in a dosing diary which is to be reviewed by site staff with the subject at each visit. This is expected to improve the ability of the investigative site to reconcile investigational product use.
Amendment 3	12 December 2011	To add new safety wording. To allow for rescreening of subjects. To add clarification around the timing of the visual field testing (VFT) and handling of the primary endpoint as an AE. Also clarification of prohibited and allowed concomitant medications; and documentation of adverse events related to changes from entry in vital signs, weight and on the physical exam. Background & Rationale, PASS language added, Subject Selection, Compliance, DMC text added.
Amendment 2	12 August 2009	See Appendix 4.

Amendment 1	17 October 2006	See Appendix 3.
Original protocol	25 May 2006	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, IRB/ERB, etc.

SUMMARY

Indication:

Epilepsy; adjunctive therapy in patients with partial seizures.

Rationale:

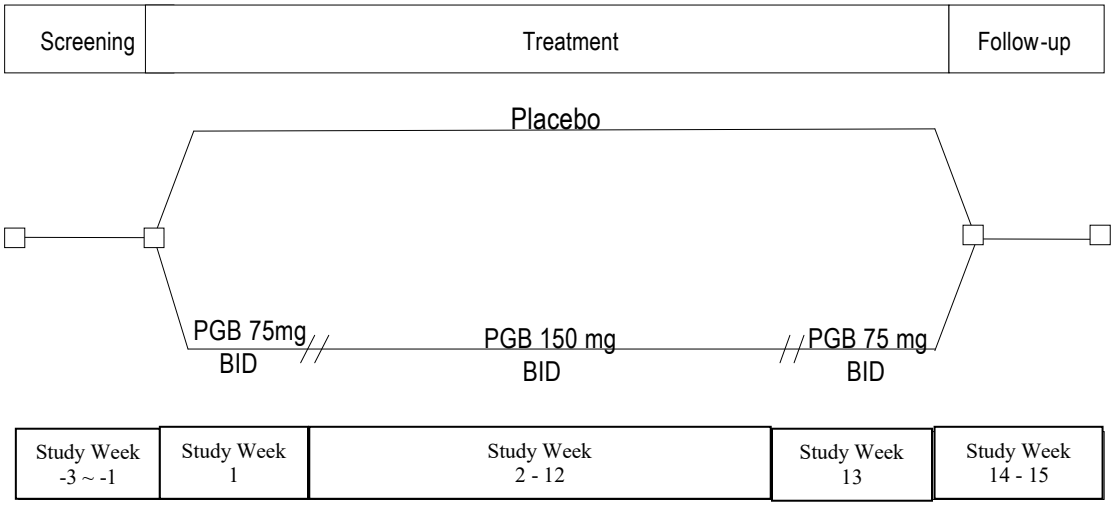
This study is being performed as a Phase IV commitment to assess visual fields in subjects taking pregabalin as compared to placebo when added to their existing antiepileptic therapy.

Objectives:

To evaluate visual fields in subjects with partial epilepsy receiving 12 weeks treatment of pregabalin compared to placebo.

Trial Design:

This is a Phase IV, multicenter, randomized placebo-controlled trial to further characterize visual fields in subjects with partial epilepsy dosed for 13 weeks, including a 1 week up titration and 1 week down titration from the target dose of pregabalin 300 mg/day versus placebo. Comprehensive ophthalmologic testing will be done at pre-treatment baseline to exclude those with pre-existing eye disease.



Approximately 187 subjects will participate in the study. Subjects will be randomized 1:1 to pregabalin or placebo, with approximately 93 randomized to pregabalin and 93 to placebo.

Endpoints:

The primary endpoint is the proportion of subjects with a decrease in the threshold value from baseline to termination in five or more points (in either eye) at the p<.05 level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard).

Trial Treatments:

Subjects will receive oral pregabalin 75 mg twice daily (BID) (150 mg/day) or matching placebo for titration and taper. Subjects will receive oral pregabalin 150 mg BID (300 mg/day) or matching placebo for the treatment phase.

Statistical Methods:

The primary endpoint will be analyzed using a non- inferiority analysis. The difference in proportions between pregabalin and placebo in the per protocol population will be compared using a 2-sided 95% confidence interval (CI). Non-inferiority will be demonstrated if the upper CI bound is less than 0.10 (10%). The proposed sample size will have >90% power to detect non-inferiority on the primary endpoint, assuming a proportion of 1% for each group.

SCHEDULE OF ACTIVITIES

Protocol Activity		**Screening**	**Baseline**	**Wk 0 Randomization**	**Wk 1**	**Wk 6**	**Wk 12** (Or ET)	**Week 15** (Follow-Up)
Visit Number[n]		1	2	3[m]	4	5	6	7
Informed Consent		X						
Inclusion/Exclusion Criteria		X	X	X				
Review/document contraception use		X						
History/Diagnosis/Demographics		X						
Physical Examination[p]		X					X	
Concomitant Medication		X	X	X	X	X	X	X
Body Weight		X	X		X	X	X	X
Vital Signs (Sitting BP/HR)		X	X		X	X	X	
ECG (Singlet)		X						
EEG		X[a]						
CT or MRI		X[b]						
Clinical Laboratory	1) Hematology[c]	X					X	
	2) Chemistry[d]	X					X	
	3) Urinalysis[e]	X					X	
Urine Pregnancy Test[f]		X					X	
Urine Drug Screen		X						
Ophthalmic Examination	1) External Eye Exam	X					X	X[g]
	2) ETDRS Acuity	X	X			X	X	X[g]
	3) Intraocular Pressure	X						
	4) Dilated Funduscopic	X						
	5) VFT (24-2 SITA)	X[h,l]	X[h,l]			X[h]	X[h]	X[g,h]
Patient assessment of seizure frequency							X	

Protocol Activity	**Screening**	**Baseline**	**Wk 0 Randomization**	**Wk 1**	**Wk 6**	**Wk 12** (Or ET)	**Week 15** (Follow-Up)
Investigational product Dispensing			X[i,j]	X[k]	X[k]	X[j]	
Dispense Dosing Diary			X		X		
Review Dosing Diary with subject				X	X	X	X
Sheehan-Suicidality Tracking Scale (S-STS)[o,r]	X	X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)[o,r]	X	X	X	X	X	X	X
Suicidal Behaviors Questionnaire – Revised (SBQ-R)[r]	X						
Patient Health Questionnaire–8 (PHQ-8)	X						
Assessment of need to complete a risk assessment[q]	X	X	X	X	X	X	X
Adverse Events Report	X----------X						

a. Subjects who have not had a test within 2 years. See inclusion criteria 1.

b. Subjects who have not had a test within 3 years. See inclusion criteria 4.

c. Hemoglobin, hematocrit, RBC count, WBC count, platelet count.

d. Electrolytes (Na, K, Ca, Cl, bicarbonate), creatinine, BUN, glucose, AST, ALT, alkaline phosphatase, bilirubin, CK, uric acid, albumin, total protein.

e. Specific gravity, PH, Glucose (qual), Protein (qual), Blood (qual), Ketones, Nitrite and Microscopy if urine dipstick is positive for blood or protein.

f. Childbearing potential female subjects only.

g. Subjects who have had visual findings on Week 12 and subsequently confirmed.

h. A repeat may be necessary upon the confirmation from central reader.

i. Recommend subject to take first dose in the evening.

j. Titration/tapering dose.

k. Treatment dose.

l. Conduct 2 tests.

m. Usually occur between the 3rd – 7th day after Baseline (Visit 2) when the verification of VFT is available.

n. Screening procedures can be completed within 21 days prior to Baseline; Study Visits 4 – 7 have a ±3 days window.

o. The "Lifetime" assessment is completed at Screening and the "Since Last Visit" assessment is completed at **all** other visits.

p. Including neurological exam at screening.

q. A risk assessment must be performed and documented if the subject meets the criteria detailed in Protocol.

r. Subjects screened/randomized under Amendment 3 will continue the S-STS for assessment of suicidal ideation and behaviour. Subjects screened /randomized under Amendment 4 will have suicidal ideation and behaviour assessed by the C-SSRS and the SBQ-R.

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APPENDICES

1. INTRODUCTION

1.1. Background

Pregabalin (Lyrica®) has been approved in over 130 countries to date for varying neuropathic pain indications and for adjunctive treatment of patients with partial seizures and for generalized anxiety disorder. Lyrica is approved in the United States for management of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia, for the adjunctive treatment of adult patients with partial onset seizures, and for management of fibromyalgia.[1] Lyrica is approved in European Union countries for the treatment of peripheral neuropathic pain, adjunctive treatment of partial seizures with or without secondary generalization, and for the treatment of generalized anxiety disorder.[2] Since initial market approval of Lyrica in 2004 through 2014, it is estimated that more than 28.5 million 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, can be found in the current Investigator Brochure (IB).

Prospectively planned ophthalmologic assessments, including visual acuity testing, formal visual field testing and dilated funduscopic examination, were performed in the pregabalin clinical development program for all of the initial indications.

Formal visual field testing was conducted in over 2400 patients treated with pregabalin for neuropathic pain, chronic pain syndromes, intractable epilepsy, or generalized anxiety disorder in randomized controlled clinical trials of up to 3 months in duration and in over 3600 patients in open-label trials of up to 4 years in duration. Ophthalmologic assessments were included in the program due to concerns expressed at the time on emerging reports of visual field disturbances with the anticonvulsant vigabatrin, a gamma-aminobutyric acid (GABA)-transaminase inhibitor.[3-11] The mechanism of the visual field defects with vigabatrin is unknown but was considered as possibly related to its GABA mechanism. As a structural derivative of GABA, regulatory agencies considered similarity of pregabalin to vigabatrin as possible. Subsequently, it became clearer that the mechanism of action of pregabalin was not related to GABA-transaminase inhibition or to a GABA related mechanism. While the mechanism of action of pregabalin is not completely understood, results in animal models indicate that binding to the alpha-2-delta subunit of voltage-gated calcium channels may be involved in the activity of pregabalin.

In controlled pregabalin studies, a higher proportion of patients treated with pregabalin reported blurred vision (6%) than did patients treated with placebo (2%), which resolved in the majority of patients during treatment. In patients assessed with prospectively planned ophthalmologic testing, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated and 2% of placebo-treated patients.

This study is a Post-Authorization Safety Studies (PASS). It is being conducted as a commitment agreed upon with the United States Federal Drug Administration (FDA) regulatory agency.

1.2. Rationale

This study is being performed to further characterize visual fields with pregabalin as compared to placebo when added to their existing antiepileptic therapy. In this study, standardized test equipment, program and test procedures across all study sites will be used to optimize the data quality and the sensitivity of the test. Threshold visual fields will be performed using computerized static perimetry.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the pregabalin Investigator's Brochure (IB). The SRSD will be used in determining expected versus unexpected adverse events.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. Objective

To evaluate visual fields in subjects with partial epilepsy receiving 12 weeks treatment of pregabalin compared to placebo.

2.2. Endpoints

Primary endpoint:

- The proportion of subjects with a decrease in the threshold value from baseline to termination in five or more points (in either eye) at the $p<.05$ level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard).

Secondary endpoints:

- Change in mean deviation score from baseline to Week 12 from the Humphrey threshold test;

- Change in visual acuity from Baseline to Week 12 expressed by number identified in ETDRS visual acuity assessment.

3. TRIAL DESIGN

This is a Phase IV, multicenter, double-blind, randomized, placebo-controlled trial to measure visual field sensitivity in subjects with partial epilepsy dosed with pregabalin or placebo. Pregabalin will be dosed at 300 mg/day for 11 weeks after one-week initiation with 150 mg/day, followed by one-week tapering of 150 mg/day. Total treatment period will be 13 weeks. Comprehensive ophthalmologic testing will be done at pre-treatment baseline to exclude subjects with pre-existing eye disease.

A central reader will assure the quality of all visual field test results with pre-specified criteria. Any field failing this quality assurance criteria either due to poor subject compliance or due to failure to follow testing procedures will be repeated as soon as possible within 2 weeks following notification from the central reader. Prior to randomization subjects must

meet the pre-specified quality assurance criteria. Subjects failing to meet this criteria at Baseline either due to poor subject compliance or due to failure to follow testing procedures can be re-screened one additional time after 3 months and will keep their previously assigned ID number. Rescreening may also be allowed for subjects with non-lesional epilepsy who may have been screen failed for reasons other than those specified above, if correctable.

Approximately 187 subjects will participate in the study. Subjects will be randomized 1:1 to pregabalin or placebo, with approximately 93 randomized to pregabalin and 93 to placebo.

4. SUBJECT SELECTION

This clinical trial 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

Subjects must meet the following criteria to be eligible to participate in the study:

1. Diagnosis of epilepsy with partial seizures (as defined in the International League Against Epilepsy Classification of Seizures). Diagnosis must be established by subject's medical history (eg, seizures), family history, and the results of electroencephalogram testing done within 2 years prior to baseline (if none available, must be taken during Screening). Results must be consistent with the diagnosis of focal-onset epilepsy;

2. Seizures should not have occurred within 2 weeks of an acute neurological event (eg, a stroke);

3. Be currently taking 1 to 3 antiepileptic drugs (AEDs). Vagus nerve stimulator (VNS) device also will be considered an AED. AED should be continued without alteration of current dose during the study. Benzodiazepines and barbiturates will not be allowed as treatment regardless of indication;

4. Have magnetic resonance imaging (MRI) or computed tomography (CT) scan **with contrast** of the head within 3 years prior to randomization (if none available, must be taken during Screening) that demonstrates no progressive structural abnormality and non-lesional epilepsy;

5. Subjects who, in the opinion of the investigator, may benefit from treatment with pregabalin;

6. Be 18 to 65 years old;

7. Be male, or nonpregnant, nonlactating female who is postmenopausal, surgically sterilized, or premenopausal using a reliable method of contraception (including barrier or hormonal method) and have a confirmed negative urine pregnancy test prior to randomization;

8. Have a 12-lead electrocardiogram prior to randomization without clinically significant abnormal findings;

9. On both screening and baseline visual field exam, any eye has <20% false positives, <30% false negatives, <30% fixation loss;

10. Difference in mean deviation between screening and baseline visual field exams must be ≤2 decibels (dB) of mean deviation (MD) on both eyes;

11. Provide written informed consent signed by subject or legal guardian prior to entering the study;

12. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

4.2. Exclusion Criteria

Subjects may **not** participate in the study if they meet any of the following criteria:

- Known previous or current serious ophthalmologic disease (including uncorrected cataracts or history of cataract surgery <8 days), serious eye trauma or intra ocular or ocular surgery other than refractive (ie, lasik, cataract) surgery, or ophthalmologic finding that could affect the visual field;

- Amblyopia;

- Ptosis;

- Manifest nystagmus in primary gaze;

- On medications that could affect the visual field or pupil eg, chloroquine or miotics;

- Refractive error in either eye exceeding ±5 D (sphere) or ±2.5 D (cylinder);

- Best corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity worse than 20/25 in either eye;

- Intra ocular pressure (IOP) >22 mmHg in either eye at Screening;

- Have clinically significant abnormal findings on ophthalmologic examinations including external eye examination, visual acuity test, intraocular pressure, funduscopy and repeated visual field test (VFT). Repeat any test if there is a finding that is uncertain. For VFT – if one test is normal and another one abnormal a third test may be performed. Two of the three tests being normal is acceptable;

- Subjects with glaucoma or a history of glaucoma;

- Family history of inherited retinal or optic nerve disorders;

- Subject with a history of intolerability to pregabalin, or with a history of insufficient response (based on investigator's clinical judgment) to pregabalin in the treatment of partial seizure, or subjects with current pregabalin treatment;

- Subjects who currently have poorly controlled epileptic seizures which could interfere with test procedures;

- Childbearing potential female who is unable to take adequate contraceptive precautions, has a positive pregnancy test result within 24 hours prior to study entry, is otherwise known to be pregnant, plans to become pregnant in the next 3 months or is currently breastfeeding an infant;

- Creatinine clearance ≤60 mL/min (estimated from serum creatinine);

- Have a history or clinical evidence of cardiovascular, hematologic, hepatic, or renal disease (ALT, AST, bilirubin, urea, or creatinine values above twice the upper limit of normal [ULN] at Screening) or any physical conditions that, in the opinion of the investigator, would compromise participation in the study;

- With a mental condition rendering the subject unable to be cooperative with and complete study requirements;

- Have a significant psychiatric disorder, recurrent episodes of severe depression (any pharmacologic treatment or hospitalization for the illness within 1 year prior to Screening), or subjects with serious suicidal risk per criteria described in the Section 7.5.1 of the protocol. Subjects with mild, chronic depression without recent hospitalization who are being maintained on a stable dose of a single antidepressant are acceptable;

- Has received any investigational drug during the previous 60 days prior to first dose;

- Hypersensitivity to pregabalin or gabapentin;

- Meets criteria for alcohol or drug abuse within the past year;

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial;

- Any subject at risk of suicide or self harm based on investigator judgment and/or details of a mental health risk assessment (MHRA) by a qualified mental health professional, as specified in Section 7.5.

4.3. Randomization Criteria

Subjects will complete visual field testing (VFT) at baseline. Once the central reader confirms the validity of the VFT, the subjects will return to the site to be randomized to treatment and to receive the investigational product. Subjects may not be randomized prior to receiving confirmation of the validity of the Baseline VFT from the central reader.

4.4. Lifestyle Guidelines

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

- Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

- Correctly placed copper-containing intrauterine device (IUD).

- Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

- Male sterilization with absence of sperm in the postvasectomy ejaculate.

- Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

- Female partner who meets the criteria for non-childbearing potential, as described below:

  Female subjects of non-childbearing potential must meet at least one of the following criteria:

  - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

  - Have medically confirmed ovarian failure; or

  - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

  All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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, subject study numbers, contact information for the investigational site, and contact details for a contact center 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 subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only 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 the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. TRIAL TREATMENTS

Equal number of subjects will receive oral pregabalin or matching placebo. Pregabalin treatment period will be 11 weeks at the dose of 300 mg/day (150 mg BID). A one-week titration and one-week taper at 150 mg/day (75 mg BID) will be given prior to and following the 11 week period (total 13 weeks).

If the subject cannot tolerate 300 mg/day dose, they will be discontinued from the study. No down-titration on the dose is allowed.

It is recommended that the first dose of pregabalin be taken in the evening.

On the day of the ophthalmic testing it is recommended that the visual field test be performed in the morning (or when the subject is most alert). It is also recommended that the subject withholds the morning dose of investigational product until the ophthalmic tests are completed to reduce any potential effects of CNS events that may occur (eg, somnolence) with pregabalin which may interfere with testing. If the subject has taken the morning study dose of medication, testing should be performed when the subject is least probably affected by any potential CNS events that may occur to ensure the subject is optimally alert during the test.

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Prohibited/Allowable Medications or Precautions

Apart from the background antiepileptics, administration of psychotropic compounds is prohibited during the trial, with the exception of a single antidepressant. Benzodiazepine and barbiturate usage are not allowed in this study. Concurrent treatment with other investigational agents or devices is not allowed during the study. The prior or current use of vigabatrin is prohibited in this trial.

If it is necessary to alleviate insomnia during the study, zolpidem 10 mg or another non benzodiazepine hypnotic is permitted on an as needed (PRN) basis, but must not be taken for more than 4 nights per week, and must not be taken on a night before an ophthalmologic study visit.

5.2. Allocation to Treatment

Following the Baseline visit and after confirmation of the validity of the VFTs from the central reader, subjects will be randomized to receive either pregabalin or placebo. Subjects will be randomly assigned to treatment regimens in a 1:1 ratio according to a computer-generated random code. Each subject will receive the lowest randomization number available at the site.

5.3. Breaking the Blind

At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. The investigator should contact Pfizer before breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form. With the exception of such emergency code breaks, the blind for the study will be broken only after all subjects have completed or terminated from the study, data issues have been resolved, and the per protocol population has been determined.

5.4. Drug Supplies

5.4.1. Formulation and Packaging

Pregabalin capsules (75 mg and 150 mg) and matching placebo will be supplied by Pfizer. Investigational product will be assigned according to a randomization code prepared from specifications provided by the Clinical Statistics department.

Investigational product is formulated into size 0 grey/grey capsules and packaged into high-density polyethylene child-resistant bottles.

5.4.2. Preparation and Dispensing

The Sponsor will provide the investigational product that will be dispensed according to randomization code. The investigator must verify and acknowledge the receipt of clinical drug supplies and retain related documentation. A set of detailed dispensing instructions will be provided.

At Randomization, each subject will receive 1 bottle of investigational product capsules with the titration dose for the first week (pregabalin 75 mg BID (150 mg/day) or placebo BID). At Week 1, the subject will receive 5 bottles containing capsules of the treatment dose (pregabalin 150 mg BID (300 mg/day) or placebo BID). At Week 6, the subject will receive 6 bottles containing capsules of treatment dose (pregabalin 150 mg BID (300 mg/day) or placebo BID). At Week 12, the subject will receive 1 bottle containing capsules for the taper (pregabalin 75 mg BID (150 mg/day) or placebo BID). All bottles will contain 3 days overage except the taper bottle that will contain only enough capsules for seven days.

5.4.3. Administration

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

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

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

The subjects will be recommended to take their first dose of investigational product **the evening of** their randomization visit. Dosing is BID, therefore subjects should take one capsule 2 times per day, except on Day 1 when the subject should take their first capsule in the evening.

Subjects are to take a single capsule of investigational product from a single bottle at each dose. Subjects must not take more than 1 capsule per dose. Subjects should take study capsules only from one bottle at a time. Doses should be administered at approximately the same time of day, without regard to meals, preferably as close to 12 hours apart as possible. All doses should be taken with 6 to 8 ounces of water. Subjects must swallow the capsules intact. Blinding will be maintained within each group by administering the same number of capsules of investigational product per day and by the fact that all capsules are identical in appearance.

Subjects will document each dose in a diary at the time of the dose. Reasons for any missed doses should also be recorded in the diary. The dosing diary is to be brought to each study visit and reviewed by the study team at the site and any correction should be made by the subject while they are at the site.

5.4.4. Compliance

Subjects who are not fully compliant with investigational product as intended (<80% or >120% of doses taken) will be evaluated by the investigator for possible discontinuation from the study. If the subject fails to take investigational product for 7 consecutive days the subject should be considered non compliant, and the investigator should consider discontinuing the subject from the study after confirming the decision with Pfizer.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the Investigational Product Manual for storage conditions of the product. Pregabalin is a controlled substance in the United States and must be handled and stored in accordance with state and federal regulations for controlled substances.

Storage conditions stated in the single reference safety document (SRSD) (eg, investigator's brochure [IB]) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the proper storage requirements for take home investigational products.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. Subjects should bring all Investigational Product bottles to each study visit for review and accounting. Bottles no longer needed will be retained by the site. By the completion of the study all Investigational Product bottles are to be returned to the site. Do not transfer the investigational product from one bottle to another.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6. TRIAL PROCEDURES

6.1. Screening

At the Screening Visit (up to 21 days prior to Baseline), subjects will be eligible for the study after verification of the inclusion/exclusion criteria and the study has been explained to them. The following procedures will be completed at the screening visit:

- Obtain written informed consent (must be signed prior to the initiation of any study related activities);
- Verify inclusion/exclusion criteria;
- Record demographic information, medical history, and diagnosis;
- Record concomitant medications;
- Perform physical exam including neurologic exam;
- Collect vital signs (sitting blood pressure, heart rate);
- Perform electrocardiograph;
- Prescribe/perform EEG, CT and MRI if necessary (inclusion criteria 1 and 4);
- Collect body weight;
- Collect blood samples for clinical laboratories;
- Blood chemistry;
- Hematology;
- Urinalysis including drug screen;
- Urine pregnancy test (females of child-bearing-potential);
- Columbia-Suicide Severity Rating Scale (C-SSRS) Lifetime Assessment;
- Suicide Behaviors Questionnaire-Revised (SBQ-R);

- Patient Health Questionnaire – 8 (PHQ-8);
- Determine if mental health risk assessment (MHRA) is required (refer to Section 7.5);
- Ophthalmic Examination.

    1. External eye examinations.
    2. Best corrected ETDRS visual acuity.
    3. Intraocular pressure to be measured by a calibrated applanation tonometer such as Goldmann, Perkins, or Tonopen.® If more than one tonometer is available at the site, the same one should be used consistently throughout the study.
    4. Computerized automated perimetry (Humphrey 24-2 SITA standard) 2 times on both eyes with a minimum 5 minute break between each eye tested and minimum 10 minutes (may take longer break if needed) between 2 tests.
    5. Dilated funduscopic examination. Recommend subject to wear sunglasses for at least one hour after this procedure and to bring someone along for driving home.

6.2. Trial Period

6.2.1. Baseline

The following procedures will be completed at this visit:

- Verify inclusion/exclusion criteria;
- Vital signs (sitting blood pressure, heart rate);
- Body weight;
- Best corrected ETDRS visual acuity;
- Computerized automated perimetry (Humphrey 24-2 SITA standard) 2 times on both eyes with a 5 minute break between each eye tested and 10 minutes between 2 tests. A longer break may be taken if needed;
- Concomitant medications;
- Adverse events;
- C-SSRS Since Last Visit assessment (or C-SSRS Lifetime assessment if not completed at screening);
- SBQ-R if not completed at screening;
- Review C-SSRS to determine if a MHRA is required;

- Subjects who fail the VFT due to poor subject compliance or due to failure to follow the testing protocol can be re-screened one additional time after 3 months and will keep their previously assigned ID number**.** Rescreening may also be allowed for subjects with non-lesional epilepsy who may have been screen failed for reasons other than those specified above, if correctable.

6.2.2. Randomization (Week 0) Visit

At this visit, subjects will be randomized after verification that they continue to meet the inclusion/exclusion criteria. This visit occurs after the central reader confirms the validity of the VFTs, ie, usually between 3 and 7 days after the Baseline visit.

The following procedures will be completed prior to randomization:

- Verify inclusion/exclusion criteria;
- Confirmation from Central Reader that VFTs are valid and useable prior to dosing;
- Concomitant medications;
- Adverse events;
- Complete C-SSRS Since Last Visit assessment (or C-SSRS Lifetime assessment if not completed at prior visit);
- Complete SBQ-R if not completed at a prior visit;
- Determine if MHRA is required based on results of screening and subsequent assessments of suicidal ideation and behavior. No subject can be randomized until a risk assessment has been completed and documents eligibility to participate in the study in applicable subjects (refer to Section 7.5.5).
- Dispense investigational product (titration dose). Recommend subject take the first dose that evening.
- Provide dosing diary and instructions for use to the subject.

6.2.3. Week 1 Visit

- Review Dosing Diary with subject and assess dosing compliance;
- Dispense investigational product (treatment dose);
- Concomitant medications;
- Adverse events;
- Body weight;

- Vital signs (sitting blood pressure, heart rate);
- Complete C-SSRS Since Last Visit assessment;
- Review C-SSRS to determine if a MHRA is required.

6.2.4. Procedures During the Investigational product Treatment Period (Weeks 6 and 12)

Subjects will have the following assessments performed at 6 and 12 weeks following randomization (or at Early Termination if subject does not complete 12 weeks of study).

6.2.4.1. The Following will be Performed at Weeks 6 and 12 Visits

- Best corrected ETDRS visual acuity;
- Computerized automated perimetry (Humphrey 24-2 SITA) on both eyes with a 5 minute break between each eye tested;
- Body weight;
- Vital signs (sitting blood pressure, heart rate);
- Review Dosing Diary with subject and assess dosing compliance;
- Concomitant medications;
- Adverse events;
- Complete C-SSRS Since Last Visit assessment;
- Review C-SSRS to determine if a MHRA is required;
- Dispense Dosing Diary (Week 6);
- Dispense investigational product (treatment dose at Week 6, taper dose at Week 12).

6.2.4.2. The Following Additional Assessments will be Performed on Week 12 Only

- Physical exam;
- External eye exam;
- Collect blood samples for clinical laboratories.
    1. Blood chemistry.
    2. Hematology.

- Urinalysis;
- Urine pregnancy test (females of child-bearing-potential);
- Patient assessment of seizure frequency;
- Subjects will be recommended to withhold their morning dose of investigational product on testing days until ophthalmologic testing is completed.

6.3. Follow-up Visit (Week 15 Visit)

Subjects will have the following assessments performed 15 weeks following randomization (or 2 weeks after final dose of investigational product).

- Review Dosing Diary and assess dosing compliance;
- Concomitant medication;
- Adverse events;
- Body weight;
- Complete C-SSRS Since Last Visit assessment;
- Review C-SSRS to determine if a MHRA is required.

Subjects who have had visual findings on Week 12 and subsequently confirmed will also have ophthalmologic tests done at this visit.

- Ophthalmic Examination.
    1. External eye examinations;
    2. Best corrected ETDRS visual acuity;
    3. Computerized automated perimetry (Humphrey 24-2 SITA standard) on both eyes with 5 minutes break between 2 eyes.

Visual findings that require follow-up beyond Week 15 will be supported by Pfizer.

6.4. Subject Withdrawal

Subjects may withdraw from the trial 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. 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 trial and 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. If the subject withdraws early, all Week 12 activities are to be conducted:

- External eye exam;
- Best corrected ETDRS visual acuity;
- Computerized automated perimetry (Humphrey 24-2 SITA) on both eyes with 5 minutes break between 2 eyes;
- Body weight;
- Review Dosing Diary and assess dosing compliance;
- Concomitant medications;
- Adverse events;
- Physical exam;
- Vital signs (sitting blood pressure, heart rate);
- Collect blood samples for clinical laboratories.
    1. Blood chemistry;
    2. Hematology;
- Urinalysis;
- Urine pregnancy test (females of child-bearing-potential);
- Complete C-SSRS Since Last Visit assessment;
- Review C-SSRS to determine if a MHRA is required.

7. ASSESSMENTS

7.1. Ophthalmic Examination Procedures

7.1.1. External Eye Examinations

An external eye examination will be performed to assess the general appearance of the eye. It will look at ocular motility to detect deviations from strabismus or a convergence defect.

The external eye examination will be conducted at the Screening (Visit 1) and Week 12 (Visit 6) visits, and at the Week 15 (Follow-up, Visit 7) visits if deemed necessary.

7.1.2. Direct and Indirect Funduscopy

At Screening visit, direct and indirect funduscopy will be used to look at retinal morphology (dilated eyes). Indirect funduscopy will be performed using a biomicroscope (slit lamp) and a Volk 90 diopter lens allowing evaluation of maculae and optic nerve. A 20 or 28 diopter lens can be used to evaluate the peripheral fundus and providing an overall view of the pigment epithelium. Direct funduscopy may be performed using a manual ophthalmoscope and will examine the macular ocular disc vessels, looking especially for edema and alterations of the macular reflex. Results will be collected on the Case Report Form (CRF).

Funduscopy will be conducted at Screening visit.

7.1.3. Best Corrected Visual Acuity

The best corrected visual acuity (with glasses or best possible glasses prescription) will be measured using the ETDRS charts. The letters on chart A are read using the right eye and chart B using the left eye.

The subject starts the top of the chart and begins to read down the chart. The subject reads down the chart until they reach a row where a minimum of three letters on a line cannot be read. The subject is scored by how many letters could be correctly identified.

The number of correct letters identified by each eye will be collected into the CRF.

Visual acuity will be measured at Screening (Visit 1), Baseline (Visit 2), Week 6 (Visit 5), and Week 12 (Visit 6) visits, and at Week 15 (Follow-up, Visit 7) visit if deemed necessary. The best corrected visual acuity should be obtained at each scheduled visit or repeat visit. It should not be copied from a previous visit.

7.1.4. Visual Field Test

All investigators will receive extensive training at the investigator's meeting and periodically throughout the study to improve the reliability of measurements by monitoring subject compliance and recognizing artifact in visual field examination. Investigators should repeat/reschedule sessions when subjects have poor compliance or any difficulties which interferes with visual field testing. Ophthalmologists/ VFT technician should inquire prior to testing when the subject's last seizure occurred to assess the possibility of ictal or post-ictal state to avoid interference with testing; the time of last dose of investigational product (it is

recommended that the subject withholds the morning dose of investigational product until after the VFT has been completed to reduce any potential effects of CNS events that may occur (eg, somnolence) with pregabalin which may interfere with testing). If the subject has taken the morning study dose of medication, testing should be performed when the subject is least probably affected by any potential CNS events that may occur to ensure the subject is optimally alert during the test.

Prior to performing the computerized automated perimetry (Humphrey 24-2 SITA), pupil size will be measured and recorded and must be 3 mm or greater for VFT, otherwise the pupil must be dilated. Visual fields will be measured using the Humphrey 24-2 SITA and analyzed using STATPAC according to the guidelines. A detailed guideline is provided in the Appendix 2 of this document. Because visual field results are strongly affected by experience, visual field tests will be repeated on two occasions at Screening and at Baseline visits. A pre-test is recommended for all subjects who have never performed VFT.

All automated perimetry results will be read by a central reader within 3 working days of the examination. If the central reader assesses the visual field exam to be of poor quality, the exam should be repeated as soon as possible within 2 weeks of being notified. The repeat test will be performed only on the eye whose test was considered to give a poor result.

Any subject who has a new loss of sensitivity at the $p<.05$ level in five or more points in the visual field will have a repeat exam as soon as possible within 2 weeks of receiving confirmation from the central reader.

VFT will be conducted at the Screening (Visit 1), Baseline (Visit 2), Week 6 (Visit 5), and Week 12 (Visit 6) visits as well as at the Week 15 (follow-up, Visit 7) visit if deemed necessary.

If a subject complains about their vision at the site it should be recorded as an adverse event like every other adverse event regardless of central reading.

If the subject does not complain about the vision and the central reader shows confirmed deterioration based on the VFT this should not be collected as an adverse event because this is the study endpoint.

7.2. Clinical Laboratory Tests

Laboratory

The following safety laboratory tests will be performed at the Screening (Visit 1) and Week 12 (Visit 6).

Safety Laboratory

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC Count Platelet Count WBC Count	Creatinine BUN Glucose Ca^{++} Na^{+}, K^{+}, Cl^{-} Total CO_2 (Bicarbonate) AST, ALT Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein Creatine phosphokinase	PH Color Clarity Specific gravity Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Microscopy[b]	Urine Pregnancy test[a] Urine drug testing[c] (amphetamines, antidepressants, barbiturates, benzodiazepines, canabinoids, cocaine, methadone, methaqualone, opiates, phenothiazines, propoxyphene and alcohol)

[a] Childbearing potential females only.
[b] Only if urine dipstick is positive for blood or protein.
[c] Only at Screening.

Results of the urine drug tests at screening (V1) must be negative for the subject to receive trial medication on Day 1.

- Safety laboratory tests from Screening must have no clinically significant findings, as judged by the investigator, in order for a subject to receive trial medication on Day 1.

  - CLcr (must be >60 ml/min) will be estimated from serum creatinine at screening to determine eligibility using the equations that follow.[13]

$$\text{Male } CL_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}$$

$$\text{Female } CL_{cr} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}\right] \times 0.85$$

In order to use SI units for creatinine (μmol/L), use the following formulas:

$$\text{Male } CL_{cr} \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{\text{Serum Creatinine}} \quad \text{x} \quad 1.23$$

$$\text{Female } CL_{cr} \text{ (mL/min)} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{\text{Serum Creatinine}}\right] \times 1.23 \times 0.85$$

7.3. Vital Sign, Body Weight and Physical Examination

Vital signs (sitting heart rate and blood pressure) will be obtained at Screening (Visit 1), Baseline (Visit 2), Week 1 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6) and Early Termination (ET). BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. The same arm (preferably the dominant arm) will be used throughout the trial. BP and heart rate will be measured after at least 5 minutes in sitting position. When done manually, heart rate will be measured in the brachial/radial artery for at least 30 seconds. The use of automated devices for measuring BP and heart rate are also acceptable. Any clinically significant negative changes (increase or decrease) in vital signs from the entry examination should be recorded as an adverse event and/or based on the clinical judgment of the PI.

Body weight will be collected at Screening (Visit 1), Baseline (Visit 2), Week 1 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6), Week 15 (Visit 7) and Early Termination (ET). Any clinically significant negative changes (increase or decrease) from the entry examination should be recorded as an adverse event for weight and/or based on the clinical judgment of the PI.

To reduce measurement variability of body weight, subjects should be weighed on the same scale at each visit that body weight is assessed; should not carry extraneous items such as purses, blackberries, and cell phones onto the scale; should remove their coats and shoes before being weighed, and should empty their pockets of any heavy items.

A physical exam will be performed at Screening (V1) and Week 12 (Visit 6). Items included will be:

- General appearance – including height (at Screening only);
- Skin – Examination for the presence of rash;
- HEENT – Examination of extraocular movements, pupillary response, determination of nystagmus, and visual field examination by confrontation;
- Lungs and Cardiovascular – Auscultation of lung fields, determination of BP, cardiac rhythm and rate auscultation for the presence of murmurs, gallops, or rubs;
- Neurologic – Including mental status, station and gait, cranial nerves, motor and sensory function, reflexes, and coordination;
- Abdominal – Palpation and auscultation performed.

Additional physical assessment will be made as necessary to evaluate symptoms or adverse experiences at the discretion of the investigator. Any clinically significant negative changes on the physical examination from the entry examination should be recorded as an adverse event and/or based on the clinical judgment of the PI.

7.4. Electrocardiogram (ECG)

A 12-lead ECG (singlet) will be performed at Screening (Visit 1). ECG should be performed after the subject has rested quietly for at least 10 minutes in a supine position. ECG tracing will be evaluated by the investigator in a real time for the safety monitoring of the subjects. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

7.5. Assessment of Suicidal Ideation and Behavior

Three tools are being used to assess for suicidal ideation and behavior during the study; the Sheehan-Suicidality Tracking Scale (S-STS), the Columbia-Suicidality Severity Rating Scale (C-SSRS) and the Suicidal Behaviors Questionnaire – Revised (SBQ-R). Subjects randomized prior to Amendment 4 will only complete the S-STS.

7.5.1. Sheehan-Suicidality Tracking Scale (S-STS)

The Sheehan-Suicidality Tracking Scale (S-STS) is an 8-item prospective rating scale that tracks treatment-emergent suicidal ideation and behaviors. This scale was adapted from the Suicidality Module of the Mini International Neuropsychiatric Interview (MINI) Structured Diagnostic Interview for DSM-IV. Items 1a, 2-6, 7a, and 8 are scored on a 5-point Likert scale (ranging from 0= not at all to 4=extremely). Items 1, 1b, and 7 require yes or no responses. This scale can be administered either by a clinician (ie, MD or a PhD level clinical Psychologist) or patient through self-report. The baseline Lifetime Assessment will be completed at Screening and the "Since Last Visit" version will be completed at Baseline (Visit 2), Randomization (Visit 3), Week 1 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6), Week 15 (Visit 7) and ET.

Subjects randomized prior to Amendment 4 will complete the S-STS and not the C-SSRS or SBQ-R. Subjects enrolled/randomized after implementation of Amendment 4 will not complete the S-STS but will instead complete the C-SSRS and SBQ-R.

7.5.2. Columbia-Suicidality Severity Rating Scale (C-SSRS)

The Columbia-Suicidality Severity Rating Scale (C-SSRS) is a semi-structured interview developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and track suicidal events through any treatment.[14] The C-SSRS is being used in the current study to provide a summary measure of suicidal risks. This scale is to be completed by a trained clinician. Training materials on the scale will be provided to investigator sites by Pfizer. The Lifetime version is completed during the first visit and the Since Last Visit version will be completed at subsequent visits.

7.5.3. Suicide Behaviors Questionnaire – Revised (SBQ-R)

The SBQ-R is a 4-item; self-report questionnaire that assesses behaviors associated with suicidality. The SBQ-R will be completed at Screening (V1) following implementation of Amendment 4. Subjects screened under Amendment 3 but continue under Amendment 4 should complete the SBQ-R at the baseline or randomization visit.

7.5.4. Patient Health Questionnaire-8 (PHQ)

The PHQ-8 is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as 0 (not at all) to 3 (nearly every day).[15] The PHQ-8, a validated subset of the PHQ-9, which comprises the first 8 items of the measure, will be completed by subjects at Screening (Visit 1).

The score is the sum of items 1-8. A total score ≥15 indicates significant depression and requires mental health risk assessment.[16]

When scoring the PHQ-8, if more than one response is given on an item and two consecutive numbers are checked, score the higher (more distress) number; however, if the numbers are not consecutive, do not score the item. If more than 1 item is missing, the PHQ-8 should be reported as Not Done.

7.5.5. Assessment of Suicidal Ideation and Behavior During Screening

The Investigator will review the results of the STS (Lifetime), C-SSRS (Lifetime), SBQ-R, PHQ-8 and medical history. The following criteria would indicate a potential risk:

- Positive subject's responses (score ≥1) on any of these S-STS questions:
  - 1a (To what extent did you plan or intend to hurt yourself?),
  - 1b (Did you intend to die as a result of this accident?),
  - both 3 and 4 (How seriously did you ever want to harm yourself or to hurt or to injure yourself? and Did you think about suicide?),
  - 5 (How seriously did you ever plan for a suicide?),
  - 6 (How seriously did you ever take active steps to prepare for a suicide attempt in which you expected or intended to die?),
  - 8 (How seriously did you ever attempt suicide?).
- Suicidal ideation associated with actual intent and/or method and/or plan in the past year based on C-SSRS assessment (ie, 'yes' response to C-SSRS items 4 (Active suicidal ideation with some intent to act, without specific plan) or 5 (Active suicidal ideation with specific plan and intent)).

- Any previous history of suicidal behaviors reported or documented within the past 10 years.

- For events that occurred within the past 10 years, an answer of "yes" to any of the suicidal behavior items of the C-SSRS.

- SBQ-R total score ≥8.

- Clinically significant depression: PHQ-8 total score ≥15.

- The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.

- In the investigator's judgment a risk assessment or exclusion is required.

If any of these criteria are met and the subject is being considered for study participation, a risk assessment must be completed to determine whether it is appropriate for the subject to be enrolled.

Risk assessments should be done by a qualified mental health professional (MHP). A qualified MHP is a clinically-qualified MHP with appropriate training in the assessment of suicide risk, according to local clinical practice standards and regulations, who would normally evaluate the risk for suicidal ideation or behavior in a patient. In the United States, in addition to psychiatrists (board certified or board eligible), clinically qualified MHPs include the following: (1) Psy.D. or Ph.D. level Clinical Psychologists, (2) licensed Master's level Clinical Social Workers (LCSW), or (3) licensed Psychiatric Nurse Practitioners (PNP), who have specific training and experience in the assessment and management of acutely suicidal patients.

The MHP may be a member of study site team. If an MHP is not available within the study team, the Investigator should make the necessary referral.

The Investigator must obtain and review the risk assessment prior to the subject continuing in the study. A written copy of the risk assessment should be included in the subject's clinical record (source documentation).

7.5.6. Assessment of Suicidal Behavior and Ideation During the Clinical Trial

Beginning with Visit 2, if there are any positive response:

- On the S-STS (Since Last Visit version) items 1a, 1b, both 3 and 4, 5, 6, or 8;

or

- On items 4, 5, or on any behavioral question of the C-SSRS (Since Last Visit version).

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 trial.

Suicidal risk should be managed appropriately by the Investigator together with a qualified MHP (or the Investigator alone if the Investigator is a qualified MHP). In addition, the Investigator should consult with the Pfizer medical monitor to determine whether the subject can continue the trial.

A narrative should be prepared for subjects who have undergone any post-baseline risk assessment, using relevant information from the STS, C-SSRS and risk assessment.

7.6. Patient Assessment of Seizure Frequency

Global change of seizure frequency will be rated as increased, no change or decreased by patient at Visit 6 (Week 12) or Early Termination (ET).

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. 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 SAEs, 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. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product 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 investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE 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 AEs 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 (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, 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 CRF, which is a specific version of the 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 is captured on the medication error version of the 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 AE 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 or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient 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 AE when it is associated with an SAE.

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 AE 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 the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level 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 values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤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 level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (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 measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for 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 SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. 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, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

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

- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE 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 examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These 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 AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. 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 AE. A severe event is not necessarily an SAE. 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 SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (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 AE; 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 an SAE 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 SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

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

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

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

If a 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 an SAE report form and an EDP 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 EDP supplemental form. This must be done irrespective of whether an AE 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 general information on the pregnancy and its outcome for all EDP reports 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 EDP supplemental 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 preprocedure 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 baby, 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 SAEs follows:

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

Additional information regarding the EDP 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 Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form 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 AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the 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 CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also Section 6.4 Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE 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 AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE 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 AE.

For all SAEs, 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 SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE 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, vaccines and/or 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 AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

The study will be powered to show non-inferiority of pregabalin with respect to placebo on the mean deviation score from the Humphrey threshold test, a secondary endpoint. Non-inferiority from placebo will be declared with respect to mean deviation if the lower bound of the 95% 2-sided confidence interval of the difference in mean deviation scores between pregabalin and placebo is greater than -2.0 decibels (dB). Assuming the mean deviation scores to be equal and assuming estimated common standard deviation of 1.3 dB, then the proposed sample size of 187 subjects will provide greater than 85% power to show non-inferiority of pregabalin to placebo.

The estimated common standard deviation of 1.3 dB, from the 15 March 2019 dataset prepared for the annual Internal Review Committee (IRC) blinded review (refer to Section 9.6), was used to re-estimate the sample size for the secondary endpoints. Previously, at the time of study design, a common standard deviation of 5.6 dB had been used for the sample size determination based on literature.[12] Table 1 below used common standard deviation (1.3) and the number of enrolled subjects (n=187) to estimate the study power.

Table 1. Study 1096 Sample Size and Power for the Secondary Endpoint

Total Number of enrolled subjects	Common Standard Deviation	Non-inferiority Margin	Power
187	1.3	-2.0	>99.9%

For the primary endpoint, the proposed sample size will provide >99.9% power to show non-inferiority of pregabalin to placebo with respect to the proportion of subjects with a repeated decrease in the same 5 visual field points, with non-inferiority declared if the upper bound of the 95% confidence interval for the difference between pregabalin and placebo does not exceed 10% and assuming a proportion of subjects meeting primary endpoint definition of 1% for both groups. Table 2 below provided the estimated power for the primary endpoint.

Table 2. Study 1096 Sample Size and Power for the Primary Endpoint

Total Number of enrolled subjects	Proportion of Subjects Meeting Primary Endpoint Definition	Non-inferiority Margin	Power
187	1%	10%	>99.9%

9.2. Efficacy Analysis

Not Applicable.

9.3. Analysis of Other Endpoints

Not Applicable.

9.4. Safety Analysis

9.4.1. Analysis of Primary Endpoint

- **Definition**: The primary endpoint is the proportion of subjects with a decrease in the threshold value from baseline to termination in five or more points (in either eye) at the p<.05 level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard).

- **Baseline**: Baseline is determined from the last VFTs prior to receiving investigational product. A point will be considered abnormal at baseline only if it was abnormal (<0.05) at both baseline tests.

- **Termination:** Termination is the VFT done at Week 12 (including a repeat test if applicable). For subjects who did not complete the study, the last available test(s) after Day 1 will be used. Data will not be imputed for subjects who do not have any VFTs after baseline; rather, such subjects will be treated as missing values.

- **Comparison**: The difference in proportions between pregabalin and placebo will be compared using a 2-sided 95% confidence interval (CI). Non-inferiority will be demonstrated if the upper CI bound is less than 0.10 (10%).

- **Populations:** The intent-to-treat (ITT) population is defined as all subjects randomized to treatment who received at least one dose of investigational product. The Per Protocol population is a subset of the ITT population, and excludes subjects who had a decrease in at least 5 points at termination but did not return for a repeat test. The Per Protocol population may also exclude subjects with major protocol violations; the list of subjects excluded will be determined prior to breaking the blind. The primary analysis will be performed on the Per Protocol population, the expectation is that the Per Protocol subset will be close in the number of subjects to the number of subjects randomized. A supplementary analysis of the primary parameter will be performed using the ITT population.

9.4.2. Analysis of Secondary Endpoints

9.4.3. Mean Deviation

Change in mean deviation from baseline to termination will be computed for each subject. Baseline mean deviation will be the average of the two mean deviations from the Baseline visit, and termination mean deviation will be the mean deviation at the Week 12 visit (or the last available after Day 1 for subjects who terminate early). If a repeat test was done at termination, the mean deviation from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in mean deviation) will be used in the analysis. Change in mean deviation will be analyzed for the ITT population using analysis of covariance (ANCOVA), with treatment and center in the model and the baseline mean deviation as the covariate. Least squares means will be obtained from the model and a

2-sided 95% confidence interval will be constructed on the difference in least squares means between pregabalin and placebo. Non-inferiority with respect to mean deviation will be demonstrated if the lower bound of the CI is greater than –2.0 dB.

9.4.4. Visual Acuity

Visual acuity (best-corrected, measured using ETDRS charts) is expressed in terms of number of letters correctly identified. Change in visual acuity from baseline to termination will be computed for each subject. Baseline will be defined as the last visual acuity assessment prior to receiving investigational product, and termination will be the visual acuity assessment at the Week 12 visit (or the last available after Day 1 for subjects who terminate early). If acuity was assessed at a repeat visit at termination, the acuity from the repeat test will be used. For each subject, the worst eye (ie, the eye with the greatest decrease in visual acuity) will be used in the analysis. Change in visual acuity will be analyzed for the ITT population using ANCOVA, with treatment and center in the model and the baseline acuity as the covariate.

9.4.5. Other Safety Measurements

Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking investigational product, and C-SSRS/S-STS, will be summarized by treatment group, but not analyzed inferentially.

9.5. Interim Analysis

N/A.

9.6. Data Monitoring Committee

This study will use an Internal Review Committee (IRC).

The IRC will be responsible for ongoing monitoring of safety of subjects in the study according to the Charter. The recommendations made by the IRC to alter the conduct of the study will be forwarded to the clinical lead or delegate for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during trial conduct to ensure that the protocol and Global Clinical Practices are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), 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.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

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 trial.

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.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, Pfizer and the investigator must prospectively document which items will be recorded in the source documents and for which items 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, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the trial, Pfizer should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to 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 trial protocol, protocol amendments, informed consent forms, and other relevant documents, eg, 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 within 5 working days after the implementation.

12.2. Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be agreed to by Pfizer and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each trial subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any trial-specific activity is performed. The informed consent form used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and Pfizer before use. The investigator will retain the original of each subject's signed consent form.

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in all Participating Countries

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

13.2. End of Trial in a Member State of European Union

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.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. If a trial is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects within 72 hours. As directed by Pfizer, all trial materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF TRIAL 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), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication 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, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. 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, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the 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 (CSA) between Pfizer and the institution. In this section entitled PUBLICATION OF TRIAL RESULTS, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations/Definitions

AED	Anti-Epileptic drug	IRB	Institutional Review Board
ALT	Alanine Aminotransferase	ITT	Intent-to-treat
ANCOVA	Analysis of Covariance	kg	Kilogram
AST	Aspartate Aminotransferase	lb	Pound
BID	Twice daily	MD	Mean deviation
BMI	Body mass index	mg	Milligram
BP	Blood pressure	MHRA	Mental Health Risk Assessment
BUN	Blood Urea Nitrogen	MRI	Magnetic Resonance Imaging
CI	Confidence interval	PGB	Pregabalin
CLcr	Creatinine clearance	PHQ	Patient health Questionnaire
CNS	Central Nervous System	Placebo	Inert compound identical to investigational drug
CRF	Case Report Form	RBC	Red Blood Cell
CSA	Clinical Study Agreement	SAP	Statistical Analysis Plan
C-SSRS	Columbia-Suicide Severity Rating Scale	SBQ-R	Suicidal Behaviors Questionnaire-Revised
CT	Computerized Tomography	SITA	Swedish Interactive Threshold Algorithm
CTA	Clinical Trial Agreement	S-STS	Sheehan-Suicidality Tracking Scale
D	Diopters	ULN	Upper Limit of Normal
dB	Decibels	US	United States
ECG	Electrocardiogram	VFT	Visual Field Test
EDP	Exposure During Pregnancy	VNS	Vagus Nerve Stimulator
EEG	Electroencephalogram	WBC	White Blood Cell
EIU	Exposure in Utero		
ET	Early Termination in the study		
ETDRS	Early Treatment Diabetic Retinopathy Study		
EU	European Union		
GABA	Gamma-aminobutyric acid		
GCP	Good Clinical Practice		
HR	Heart rate		
IB	Investigator Brochure		
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use		

Appendix 2. Special Notes about Visual Field Testing

Even though the Humphrey Field Analyzer is programmed with highly refined testing and analysis methods, the technician continues to play a central role. Without proper management and instruction, the results of perimetric examinations are often of poor quality.

Only central reader trained, certified perimetrists will administer VFT in this study. Confirmation of perimetrist qualified to perform VFT will be documented.

Important Instructions for the perimetrist

The chair height and instrument height should be adjusted for subject comfort.

It is particularly important to tell the subject what to expect during the test. At the beginning of the test you should explain/show to your subject:

- The task;
- What the stimulus will look like, where it might appear;
- How long the test will last;
- When blinks are allowed;
- How to sit;
- How to pause the test;
- That more than half of the stimuli shown in a threshold test will be too dim to be seen and that the stimuli that are seen are likely to be barely visible.

The perimetrist must be available to monitor the entire test to ensure the subject remains in the proper position.

Intercede a test

During the test, the perimetrist may pause the procedure if he/she detects obvious artifact(s). The test may be resumed after a 5–10 minute break. Investigators/perimetrist can repeat/reschedule sessions for another time when subjects have poor compliance that interferes with visual field testing.

Timing of the test

It is recommended that all the visual field testing be performed in the morning (or when the subject is most alert), and it is recommended that the subject withholds the morning dose of the investigational product until the ophthalmic tests are completed to reduce any potential CNS effects - that may occur (eg, somnolence) with pregabalin which may interfere with

testing. If the subject has taken the morning study dose of medication, testing should be performed when the subject is least probably affected by any potential CNS events that may occur to ensure the subject is optimally alert during the test.

Common artifacts

Common false patterns may be caused by:

- Lack of previous perimetric experience;
- Droopy eye lid – place a surgical tape between eye lid and eye brow;
- Misaligned correction lenses;
- Subject anxiety – counsel subject prior to testing.

Role of Central Reader/Reading Center

It is the responsibility of central reader/reading center to ensure VFTs are collected properly and accurately. The central reader /reading center is responsible for:

Training

- All investigators and staff who will perform study procedures will receive extensive training. Refresher training may be offered periodically throughout the study as needed;
- Completion of training and approval of perimetrist will be documented;
- Investigator and staff will not perform the tests until they have been certified by central reader.

During the study, the center reader performs the following:

- Confirms VFT outcomes and decides if a repeat is necessary. This result will be communicated to the site within 72 hours of receiving test results;
- Review VFT conduct and quality control on a monthly basis. Communicate results with the sponsor. Implement improvement measurements as necessary;
- Tabulated (post-processed) data will be electronically transferred to Pfizer from the Central Reader for storage and data analysis as specified in Statistical Analysis Plan (SAP).

Appendix 3. Clinical Protocol Amendment 1

Current Amendment:

Amendment No.	Date	Country (ies)	Site(s)
1	17 October 2006	All	All

SUMMARY

Reason(s) for Amendment

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The "change from" section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

- The "change to" section represents the revised text, with the revisions shown in the "change from" section in normal text.

1. Summary and Section 3, Trial Design

Change From

A total of 284 subjects will participate in the study, 142 randomized to pregabalin, 142 to placebo. Approximately ~~10~~**15** centers will be selected that have the capability to perform the comprehensive visual field testing.

Change To

A total of 284 subjects will participate in the study, 142 randomized to pregabalin, 142 to placebo. Approximately 15 centers will be selected that have the capability to perform the comprehensive visual field testing.

2. Section 4.1, Inclusion Criteria

Change From

6. Be 18 to 65 years old ~~and weigh ≥ 50kg (110 lb) with BMI 18 - 32~~;

Change To

6. Be 18 to 65 years old;

3. Section 6.1, Week –1 (Screening)

Change From

At the Screening visit (~~one week~~ **up to 21 days** prior to Baseline), subjects will be eligible for the study after verification of the inclusion/exclusion criteria and the study has been explained to them. The following procedures will be completed at the screening visit:

Change To

At the Screening visit (up to 21 days prior to Baseline), subjects will be eligible for the study after verification of the inclusion/exclusion criteria and the study has been explained to them. The following procedures will be completed at the screening visit:

Appendix 4. Clinical Protocol Amendment 2

Current Amendment: 2

Amendment No.	Date	Country (ies)	Site(s)
2	12 August 2009		

Previous Amendments:

Amendment No.	Date	Country (ies)	Site(s)
1	17 October 2006	All	All

SUMMARY

Reason(s) for Amendment

The rational is “add to reflect current internal SOP”.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.
- The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section <Insert section number> , <Insert section title> , Page <Insert page number as appropriate>

Change From

Change To

1. Section ABBREVIATIONS/DEFINITIONS

Change From

AED	Anti-Epileptic drug	lb	Pound
ALT	Alanine Aminotransferase	MD	Mean deviation
ANCO~~B~~**V**A	Analysis of **C**~~e~~ovariance	Mg	Milligram
AST	Aspartate Aminotransferase	MRI	Magnetic Resonance Imaging
BID	Twice daily	PGB	Pregabalin
BMI	Body mass index	Placebo	Inert compound identical to investigational drug
BP	Blood pressure	RBC	Red Blood Cell
BUN	**Blood Urea Nitrogen**	SAP	Statistical Analysis Plan
CI	Confidence interval	**SITA**	**Swedish Interactive Threshold Algorithm**
CLcr	**Creatinine clearance**	**S-STS**	**Sheehan-Suicidality Tracking Scale**
CNS	Central Nervous System	**ULN**	**Upper Limit of Normal**
CRF	Case Report Form	**VFT**	**Visual Field Test**
CT	Computerized Tomography	**VNS**	**Vagus Nerve Stimulator**
D	**Diopters**	**WBC**	**White Blood Cell**
dB	Decibels		
ECG	Electrocardiogram		
EEG	Electroencephalogram		
EIU	Exposure in Utero		
ET	**Early Termination in the study**		
ETDRS	Early Treatment Diabetic Retinopathy Study		
GABA	Gamma-aminobutyric acid		
GCP	Good Clinical Practice		
HR	Heart rate		
ICH	International **C**onference on **H**armonization of technical requirements for registration of pharmaceuticals for human use		
IEC	Independent Ethics Committee		
IOP	Intra **O**cular **P**ressure		
IRB	Institutional Review Board		
ITT	Intent-to-treat		
kg	Kilogram		

Change To

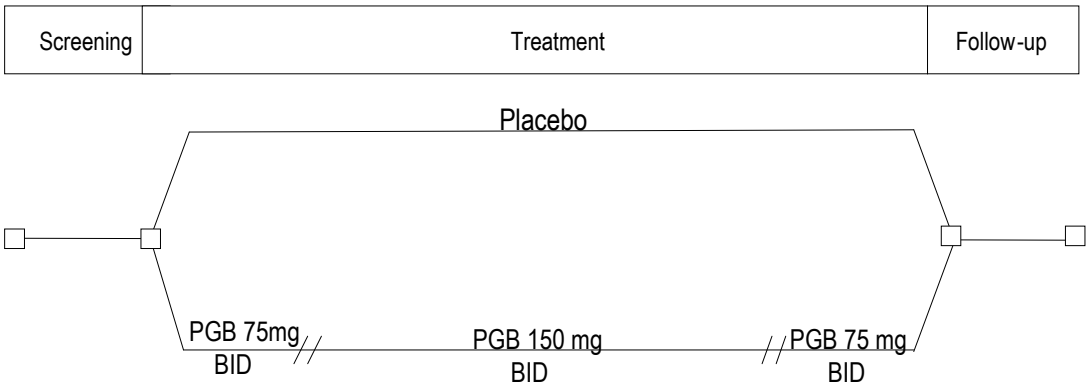
AED	Anti-Epileptic drug	lb	Pound
ALT	Alanine Aminotransferase	MD	Mean deviation
ANCOVA	Analysis of Covariance	Mg	Milligram
AST	Aspartate Aminotransferase	MRI	Magnetic Resonance Imaging
BID	Twice daily	PGB	Pregabalin
BMI	Body mass index	Placebo	Inert compound identical to investigational drug
BP	Blood pressure	RBC	Red Blood Cell
BUN	Blood Urea Nitrogen	SAP	Statistical Analysis Plan
CI	Confidence interval	SITA	Swedish Interactive Threshold Algorithm
CLcr	Creatinine clearance	S-STS	Sheehan-Suicidality Tracking Scale
CNS	Central Nervous System	ULN	Upper Limit of Normal
CRF	Case Report Form	VFT	Visual Field Test
CT	Computerized Tomography	VNS	Vagus Nerve Stimulator
D	Diopters	WBC	White Blood Cell
dB	Decibels		
ECG	Electrocardiogram		
EEG	Electroencephalogram		
EIU	Exposure in Utero		
ET	Early Termination in the study		
ETDRS	Early Treatment Diabetic Retinopathy Study		
GABA	Gamma-aminobutyric acid		
GCP	Good Clinical Practice		
HR	Heart rate		
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use		
IEC	Independent Ethics Committee		
IOP	Intra Ocular Pressure		
IRB	Institutional Review Board		
ITT	Intent-to-treat		
kg	Kilogram		

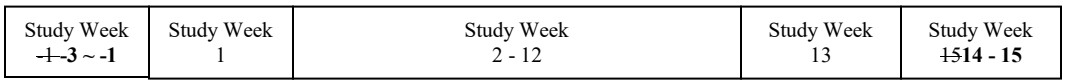
2. Section SUMMARY, Trial Design

Change From

This is a Phase IV, multicenter, randomized controlled trial to further characterize visual fields in subjects with partial epilepsy dosed for ~~with pregabalin or placebo. Pregabalin will be dosed at eoomg/day for 11 weeks after one week initiation with 150 mg/day, followed by one week tapering of 150 mg/day. Total treatment period will be 13 weeks.~~ **13** weeks**, including a 1 week up titration and 1 week down titration from the target dose of pregabalin 300mg/day versus placebo**. Comprehensive ophthalmologic testing will be done at pre-treatment baseline to exclude those with pre-existing eye disease.

A total of 284 subjects will participate in the study, 142 randomized to pregabalin **and** 142 to placebo. Approximately ~~15~~ **60** centers will be selected that have the capability to perform the comprehensive visual field testing.

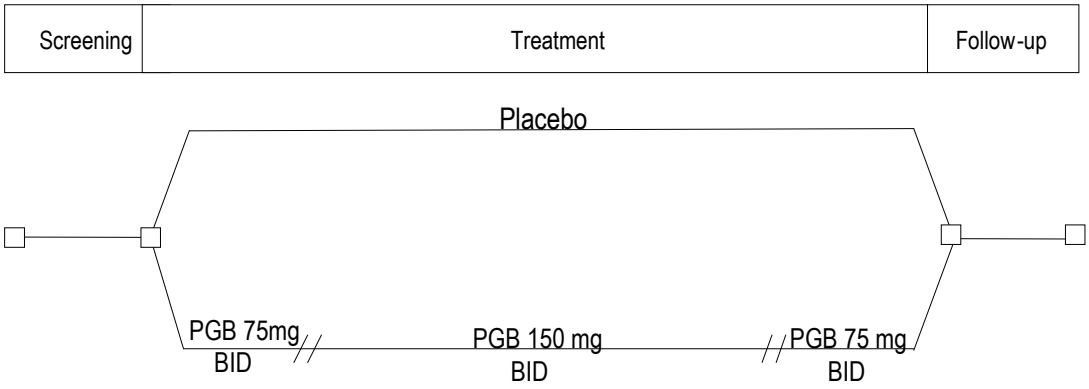




Change To

This is a Phase IV, multicenter, randomized controlled trial to further characterize visual fields in subjects with partial epilepsy dosed for 13 weeks, including a 1 week up titration and 1 week down titration from the target dose of pregabalin 300mg/day versus placebo. Comprehensive ophthalmologic testing will be done at pre-treatment baseline to exclude those with pre-existing eye disease.

A total of 284 subjects will participate in the study, 142 randomized to pregabalin and 142 to placebo. Approximately 60 centers will be selected that have the capability to perform the comprehensive visual field testing.



Study Week - 1	Study Week 1	Study Week 2-12	Study Week 13	Study Week 15

Study Week -3 ~ -1	Study Week 1	Study Week 2 - 12	Study Week 13	Study Week 14 - 15

3. Section, Schedule of Activities

Change From

Schedule of Activities

Protocol Activity		~~Wk -1~~ (Screening)	~~Wk 0~~ (Baseline)	**Wk 0 ~~Rand~~Randomization**	Wk 1	Wk 6	Wk 12 **(**Or ~~Term~~**ET)**	Week 15 w-Up)
Visit Number[n]		**1**	**2**	**3[m]**	**4**	**5**	**6**	**7**
Informed Consent		X						
Inclusion/Exclusion Criteria		X	X	X				
History/Diagnosis/Demographics		X						
Physical Examination		X					X	
Concomitant Medication		X	X	X	X	X	X	X
Body Weight		X	X		X	X	X	X
Vital Signs (Sitting BP/HR)		X	X		X	X	X	
ECG (Singlet)		X						
EEG		X[a]						
CT or MRI		X[b]						
Clinical Laboratory	1) Hematology[c]	X					X	
	2) Chemistry[d]	X					X	

	3) Urinalysis[e]	X					X	
Urine Pregnancy Test[f]		X					X	
Urine Drug Screen		X						
Ophthalmic Examination	1) External Eye Exam	X					X	X[g]
	2) ETDRS Acuity	X	X			X	X	X[g]
	3) Intraocular Pressure	X						
	4) Dilated Funduscopic	X						
	5) VFT (24-2 SITA)	X[h, l]	X[h, l]			X[h]	X[h]	X[g,h]
Patient assessment of seizure frequency							X	
Sheehan-Suicidality Tracking Scale		X	X	X	X	X	X	X
Patient Health Questionnaire–8 (PHQ-8)		**X**						
Adverse Events Report		X----------						----------X
Study Medication Dispensing				X [i,j,~~k~~]	X[k]	X[k]	X[j]	

[a] Subjects who have not had a test within 2 years. See inclusion criteria #1
[b] Subjects who have not had a test within 3 years. See inclusion criteria #4
[c] Hemoglobin, hematocrit, RBC count, WBC count, platelet count
[d] Electrolytes (Na, K, Ca, Cl, bicarbonate), creatinine, BUN, glucose, AST, ALT, alkaline phosphatases, bilirubin, CK, uric acid, albumin, total protein
[e] Specific gravity, PH, Glucose (qual), Protein (qual), Blood (qual), Ketones**, Nitrite** and Microscopy if urine dipstick is positive for blood or protein
[f] Childbearing potential female subjects only
[g] Subjects who have had visual findings on Week 12 and subsequently confirmed
[h] A repeat may be necessary upon the confirmation from central reader
[i] Recommend subject to take first dose ~~on~~ **in** the evening
[j] Titration/tapering dose
[k] Treatment dose
[l] Conduct 2 tests
[m] Usually occur between the 3rd – 7th day after Baseline (Visit 2) when the verification of VFT is available
n Screening procedures can be completed within 21 days prior to Baseline; Study Visit 4 – 7 have a +/- 3 days window.

Change To

Schedule of Activities

Protocol Activity		**Screening**	**Baseline**	**Wk 0 Randomization**	**Wk 1**	**Wk 6**	**Wk 12** (Or ET)	**Week 15** (Follow-Up)
Visit Number[n]		1	2	3[m]	4	5	6	7
Informed Consent		X						
Inclusion/Exclusion Criteria		X	X	X				
History/Diagnosis/Demographics		X						
Physical Examination		X					X	
Concomitant Medication		X	X	X	X	X	X	X
Body Weight		X	X		X	X	X	X
Vital Signs (Sitting BP/HR)		X	X		X	X	X	
ECG (Singlet)		X						
EEG		X[a]						
CT or MRI		X[b]						
Clinical Laboratory	1) Hematology[c]	X					X	
	2) Chemistry[d]	X					X	
	3) Urinalysis[e]	X					X	
Urine Pregnancy Test[f]		X					X	
Urine Drug Screen		X						
Ophthalmic Examination	1) External Eye Exam	X					X	X[g]
	2) ETDRS Acuity	X	X			X	X	X[g]
	3) Intraocular Pressure	X						
	4) Dilated Funduscopic	X						
	5) VFT (24-2 SITA)	X[h, l]	X[h, l]			X[h]	X[h]	X[g,h]
Patient assessment of seizure frequency							X	
Sheehan-Suicidality Tracking Scale		X	X	X	X	X	X	X
Patient Health Questionnaire–8 (PHQ-8)		X						
Adverse Events Report		X----------						----------X
Study Medication Dispensing				X[i,j]	X[k]	X[k]	X[j]	

[a] Subjects who have not had a test within 2 years. See inclusion criteria 1.
[b] Subjects who have not had a test within 3 years. See inclusion criteria 4.
[c] Hemoglobin, hematocrit, RBC count, WBC count, platelet count.
[d] Electrolytes (Na, K, Ca, Cl, bicarbonate), creatinine, BUN, glucose, AST, ALT, alkaline phosphatases, bilirubin, CK, uric acid, albumin, total protein.
[e] Specific gravity, PH, Glucose (qual), Protein (qual), Blood (qual), Ketones, Nitrite and Microscopy if urine dipstick is positive for blood or protein.
[f] Childbearing potential female subjects only.
[g] Subjects who have had visual findings on Week 12 and subsequently confirmed.
[h] A repeat may be necessary upon the confirmation from central reader.
[i] Recommend subject to take first dose in the evening.
[j] Titration/tapering dose.
[k] Treatment dose.
[l] Conduct 2 tests.
[m] Usually occur between the 3rd – 7th day after Baseline (Visit 2) when the verification of VFT is available.
[n] Screening procedures can be completed within 21 days prior to Baseline; Study Visit 4 – 7 have a +/- 3 days window.

4. Section 1. INTRODUCTION, 1.1. Background, 1st and 3rd paragraphs

Change From

Pregabalin (Lyrica®) has been approved in over ~~50~~ **110** countries to date for varying neuropathic pain indications and for adjunctive treatment of patients with partial seizures **and for generalized anxiety disorder**. Lyrica **is** ~~was~~ approved in the United States ~~in December 2004~~ for management of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia~~, and in June 2005~~ for the adjunctive treatment of **adult** patients with partial **onset** seizures**, and for management of fibromyalgia.**[1]. Lyrica **is**~~was~~ approved in ~~the~~ European Union countries ~~in July 2004~~ for the treatment of peripheral neuropathic pain**,** ~~and as~~ adjunctive treatment of partial seizures with or without secondary generalization, and ~~in March 2006~~ for the treatment of generalized anxiety disorder. [2]

Formal visual field testing was conducted in over 2400 patients treated with pregabalin for neuropathic pain, chronic pain syndromes, intractable epilepsy, or generalized anxiety disorder in randomized controlled clinical trials of up to 3 months in duration and in over 3600 patients in open-label trials of up to 4 years in duration. Ophthalmologic assessments were included in the program due to concerns expressed at the time on emerging reports of visual field disturbances with the anticonvulsant vigabatrin, a gamma-aminobutyric acid (GABA)-transaminase inhibitor.~~[3-9]~~**–[11]** The mechanism of the visual field defects with vigabatrin is unknown but was considered as possibly related to its GABA mechanism. As a structural derivative of GABA, regulatory agencies considered similarity of pregabalin to vigabatrin as possible. Subsequently, it became clearer that the mechanism of action of pregabalin was not related to GABA-transaminase inhibition or to a GABA related mechanism. While the mechanism of action of pregabalin is not completely understood, results in animal models indicate that binding to the alpha-2-delta subunit of voltage-gated calcium channels may be involved in the activity of pregabalin.

Change To

Pregabalin (Lyrica®) has been approved in over 110 countries to date for varying neuropathic pain indications and for adjunctive treatment of patients with partial seizures and for generalized anxiety disorder. Lyrica is approved in the United States for management of neuropathic pain associated with diabetic peripheral neuropathy or postherpetic neuralgia, for the adjunctive treatment of adult patients with partial onset seizures, and for management of fibromyalgia.[1] Lyrica is approved in European Union countries for the treatment of peripheral neuropathic pain, adjunctive treatment of partial seizures with or without secondary generalization, and for the treatment of generalized anxiety disorder. [2]

Formal visual field testing was conducted in over 2400 patients treated with pregabalin for neuropathic pain, chronic pain syndromes, intractable epilepsy, or generalized anxiety disorder in randomized controlled clinical trials of up to 3 months in duration and in over 3600 patients in open-label trials of up to 4 years in duration. Ophthalmologic assessments were included in the program due to concerns expressed at the time on emerging reports of visual field disturbances with the anticonvulsant vigabatrin, a gamma-aminobutyric acid (GABA)-transaminase inhibitor.[3-11] The mechanism of the visual field defects with vigabatrin is unknown but was considered as possibly related to its GABA mechanism. As a structural derivative of GABA, regulatory agencies considered similarity of pregabalin to vigabatrin as possible. Subsequently, it became clearer that the mechanism of action of pregabalin was not related to GABA-transaminase inhibition or to a GABA related mechanism. While the mechanism of action of pregabalin is not completely understood, results in animal models indicate that binding to the alpha-2-delta subunit of voltage-gated calcium channels may be involved in the activity of pregabalin.

5. Section 2. TRIAL OBJECTIVES AND ENDPOINTS, Title

Change From

2. TRIAL OBJECTIVES **AND ENDPOINTS**

Change To

2. **TRIAL OBJECTIVES AND ENDPOINTS**

6. Section 2. TRIAL OBJECTIVES AND ENDPOINTS, 2.1. Objective, title and section

Change From

2.1 Objective

To ~~monitor~~ **evaluate** visual fields in subjects with partial epilepsy receiving **12 weeks treatment of** pregabalin **compared to** ~~or~~ placebo ~~for 12 weeks under highly controlled conditions~~.

Change To

2.1 Objective

To evaluate visual fields in subjects with partial epilepsy receiving 12 weeks treatment of pregabalin compared to placebo.

7. Section 2. TRIAL OBJECTIVES AND ENDPOINTS, 2.2. Endpoints, Title and section

Addition

2.2 Endpoints

Primary endpoint:

The proportion of subjects with a decrease in the threshold value from baseline to week 12 for any five points (in either eye) at the p<.05 level repeated in the same five points on subsequent computerized automated perimetry testing (Humphrey 24-2 SITA standard).

Secondary endpoints:

Change in mean deviation score from baseline to week 12 from the Humphrey threshold test.

Change in visual acuity from Baseline to Week 12 expressed by number identified in ETDRS visual acuity assessment.

8. Section 3. TRIAL DESIGN, 2nd paragraph

Change From

A central reader will assure the quality of all visual field test results with pre-specified criteria. Any field failing this quality assurance either due to poor subject compliance or due to failure to follow testing protocol will be repeated within one week. A total of 284 subjects will participate in the study, 142 randomized to pregabalin, 142 to placebo. Approximately ~~15~~ **60** centers will be selected that have the capability to perform the comprehensive testing.

Change To

A central reader will assure the quality of all visual field test results with pre-specified criteria. Any field failing this quality assurance either due to poor subject compliance or due to failure to follow testing protocol will be repeated within one week. A total of 284 subjects will participate in the study, 142 randomized to pregabalin, 142 to placebo. Approximately 60 centers will be selected that have the capability to perform the comprehensive testing.

9. Section 4. SUBJECT SELECTION, 4.1. Inclusion Criteria, 1st number

Change From

1. Diagnosis of epilepsy with partial seizures (as defined in the International League Against Epilepsy Classification of Seizures). Diagnosis must be established by subject's medical history (eg, seizures), family history, and the results of electroencephalogram testing done within 2 years prior to baseline (if none available, must be taken during **Screening)**~~baseline~~). Results must be consistent with the diagnosis of focal-onset epilepsy;

Change To

1. Diagnosis of epilepsy with partial seizures (as defined in the International League Against Epilepsy Classification of Seizures). Diagnosis must be established by subject's medical history (eg, seizures), family history, and the results of electroencephalogram testing done within 2 years prior to baseline (if none available, must be taken during Screening). Results must be consistent with the diagnosis of focal-onset epilepsy;

10. **Section 4. SUBJECT SELECTION, 4.2. Exclusion Criteria, 6th, 12th and 18th numbers**

Change From

6. Refractive error in either eye exceeding +/-5 D (sphere) or +/-2.5 D (cylinder);

12. ~~Prior or current pregabalin treatment~~**Subject with a history of intolerability to pregabalin, or with a history of insufficient response (based on investigator's clinical judgment) to pregabalin in the treatment of partial seizure, or subjects with current pregabalin treatment**;

18. Have a significant psychiatric disorder**,** ~~, or~~ recurrent episodes of severe depression (any pharmacologic treatment or hospitalization for the illness within 1 year prior to Screening)**, or subjects with serious suicidal risk per criteria described in the section 7.5.1 of the protocol**. Subjects with mild, chronic depression without recent hospitalization who are being maintained on a stable dose of a single antidepressant are acceptable;

Change To

6. Refractive error in either eye exceeding +/-5 D (sphere) or +/-2.5 D (cylinder);

12. Subject with a history of intolerability to pregabalin, or with a history of insufficient response (based on investigator's clinical judgment) to pregabalin in the treatment of partial seizure, or subjects with current pregabalin treatment;

18. Have a significant psychiatric disorder, recurrent episodes of severe depression (any pharmacologic treatment or hospitalization for the illness within 1 year prior to Screening), or subjects with serious suicidal risk per criteria described in the section 7.5.1 of the protocol. Subjects with mild, chronic depression without recent hospitalization who are being maintained on a stable dose of a single antidepressant are acceptable;

11. Section 5. TRIAL TREATMENTS, 5.1. Prohibited/Allowable Medications or Precautions

Change From

Apart from the background antiepileptics, a~~A~~dministration of **p**~~CNS-active compounds~~**sychotropic compounds** is prohibited during the trial, with the exception of a single antidepressant. Concurrent treatment with other investigational agents or devices is not allowed during the study. The prior or current use of vigabatrin is prohibited in this trial.

Change To

Apart from the background antiepileptics, administration of psychotropic compounds is prohibited during the trial, with the exception of a single antidepressant. Concurrent treatment with other investigational agents or devices is not allowed during the study. The prior or current use of vigabatrin is prohibited in this trial.

12. Section 5. TRIAL TREATMENTS, 5.2. Allocation to Treatment

Change From

Following the ~~1-week~~ **B**~~b~~aseline **visit** and after confirmation of the validity of the VFTs from the central reader, subjects will be randomized to receive either pregabalin or placebo. Subjects will be randomly assigned to treatment regimens in a 1:1 ratio according to a computer-generated random code. Each subject will receive the lowest randomization number available at the site.

Change To

Following the Baseline visit and after confirmation of the validity of the VFTs from the central reader, subjects will be randomized to receive either pregabalin or placebo. Subjects will be randomly assigned to treatment regimens in a 1:1 ratio according to a computer-generated random code. Each subject will receive the lowest randomization number available at the site.

13. Section 6. TRIAL PROCEDURES, 6.1. Screening, Title and 15th, 16th bullets and 3rd number

Change From

6.1. ~~Week -1 (~~Screening~~)~~

- **Sheehan-Suicidality Tracking Scale (S-STS) Appendix 2**;
- **Patient Health Questionnaire – 8 (PHQ – 8) Appendix 3;**

3. Intraocular pressure **by calibrated Goldmann, Perkins, or Tonopen® tonometry as long as one is used consistently throughout the study.**

Change To

6.1. Screening

- Sheehan-Suicidality Tracking Scale (S-STS) Appendix 2;
- Patient Health Questionnaire – 8 (PHQ – 8) Appendix 3;

3. Intraocular pressure by calibrated Goldmann, Perkins, or Tonopen® tonometry as long as one is used consistently throughout the study.

14. Section 6. TRIAL PROCEDURES, 6.2.1. Baseline, Title and last bullet

Change From

6.2.1.~~Week 0 (~~Baseline~~)~~

- **Sheehan-Suicidality Tracking Scale (S-STS) Appendix 2**;

Change To

6.2.1. Baseline

- Sheehan-Suicidality Tracking Scale (S-STS) Appendix 2;

15. Section 6. TRIAL PROCEDURES, 6.2.2, Randomization Visit, 1st paragraph and 5th bullet

Change From

At this visit, subjects will be randomized after verification that they continue to meet the inclusion/exclusion criteria. This visit occurs after the central reader confirms the validity of the VFTs**, ie usually between 3 and 7 days after the Baseline visit.**

- **Sheehan-Suicidality Tracking Scale (S-STS) Appendix 2**;

Change To

At this visit, subjects will be randomized after verification that they continue to meet the inclusion/exclusion criteria. This visit occurs after the central reader confirms the validity of the VFTs, ie usually between 3 and 7 days after the Baseline visit.

- Sheehan-Suicidality Tracking Scale (S-STS) Appendix 2;

16. Section 6. TRIAL PROCEDURES, 6.2.3. Week 1 Visit, last bullet

Addition

- **Sheehan -Suicidality Tracking Scale (S-STS) Appendix 2**;

17. Section 6. TRIAL PROCEDURES, 6.2.4. Procedures during the Study Drug Treatment Period (Weeks 6 and 12)

Change From

Subjects will have the following assessments performed at 6 and 12 weeks following randomization (or at **Early Termination**~~endpoint~~ if subject does not complete 12 weeks of study).

Change To

Subjects will have the following assessments performed at 6 and 12 weeks following randomization (or at Early Termination if subject does not complete 12 weeks of study).

18. Section 6. TRIAL PROCEDURES, 6.2.4.1. The Following Will be Performed at Weeks 6 and 12 Visits, 8th bullet

Addition

- **Sheehan-Suicidality Tracking Scale, Appendix 2**;

19. Section 6. TRIAL PROCEDURES, 6.2.4.2. The Following Additional Assessments Will be Performed on Week 12 Only, 6th bullet and last paragraph

Change From

- **Patient assessment of seizure frequency.**

~~If the subject withdraws early, all Week 12 activities are to be conducted.~~

Change To

- Patient assessment of seizure frequency

Section 6. TRIAL PROCEDURES, 6.3. Follow-up Visit, Title and 4th bullet

Change From

6.3. Follow-up Visit **(Week 15 Visit)** ~~Week 15 (Follow-up) Visit~~

- **Sheehan Suicidality Tracking Scale, Appendix 2.**

Change To

6.3. Follow-up Visit (Week 15 Visit)

- Sheehan Suicidality Tracking Scale, Appendix 2.

20. Section 6. TRIAL PROCEDURES, 6.4. Subject Withdrawal, last bullet

Addition

- **Sheehan Suicidality Tracking Scale, Appendix 2.**

21. Section 7. ASSESSMENTS, 7.1.1. External Eye Examinations, 2nd paragraph

Change From

The external eye examination will be conducted at the ~~Week 1 (~~Screening **(Visit 1)** ~~)~~ and Week 12 **(Visit 6) v~~v~~**isits, and at the Week 15 (Follow-up**, Visit 7**) visits if deemed necessary.

Change To

The external eye examination will be conducted at the Screening (Visit 1) and Week 12 (Visit 6) visits, and at the Week 15 (Follow-up, Visit 7) visits if deemed necessary.

22. Section 7. ASSESSMENTS, 7.1.2. Direct and Indirect Funduscopy, 1st and 2nd paragraphs

Change From

At ~~Baseline~~**Screening visit**, direct and indirect funduscopy will be used to look at retinal morphology (dilated eyes). Indirect funduscopy will be performed using a biomicroscope (slit lamp) and a Volk 90 diopter lens allowing evaluation of **maculae and optic nerve. A 20 or 28 diopter lens can be used to evaluate the** the peripheral fundus and providing an overall view of the pigment epithelium. Direct funduscopy may be performed using a manual ophthalmoscope and will examine the macular ocular disc vessels, looking especially for edema and alterations of the macular reflex. Results will be collected on the case report form (CRF).

Funduscopy will be conducted at ~~Week 1 (~~Screening~~)~~ visit.

Change To

At Screening visit, direct and indirect funduscopy will be used to look at retinal morphology (dilated eyes). Indirect funduscopy will be performed using a biomicroscope (slit lamp) and a Volk 90 diopter lens allowing evaluation of maculae and optic nerve. A 20 or 28 diopter lens can be used to evaluate the the peripheral fundus and providing an overall view of the pigment epithelium. Direct funduscopy may be performed using a manual ophthalmoscope and will examine the macular ocular disc vessels, looking especially for edema and alterations of the macular reflex. Results will be collected on the case report form (CRF).

Funduscopy will be conducted at Screening visit.

23. Section 7. ASSESSMENTS, 7.1.3. Visual Acuity, 4th paragraph

Change From

Visual acuity will be measured at ~~Week 1 (~~Screening **(Visit 1))**~~)~~, ~~Week 0 (~~Baseline **(Visit 2))**~~)~~, Week 6 **(Visit 5)** , **and** Week 12**(Visit 6) visits** ~~visits~~, and **at** Week 15 (Follow-up**, Visit 7**) visit~~s~~ if deemed necessary.

Change To

Visual acuity will be measured at Screening (Visit 1), Baseline (Visit 2), Week 6 (Visit 5), and Week 12 (Visit 6) visits, and at Week 15 (Follow-up, Visit 7) visit if deemed necessary.

24. **Section 7. ASSESSMENTS, 7.1.4. Visual Field Test, 1st- 3rd and last paragraphs**

Change From

All investigators will receive extensive training at the investigator's meeting and periodically throughout the study to improve the reliability of measurements by monitoring subject compliance and recognizing artifact in visual field examination. Investigators can repeat/reschedule sessions when subjects have poor compliance **or any difficulties** which interfere**s** with visual field testing.

Prior to performing the computerized automated perimetry (Humphrey 24-2 SITA), pupil size will be measured and recorded and must be 3 mm or greater for VFT, otherwise the pupil must be dilated. Visual fields will be measured using the Humphrey 24-2 SITA and analyzed using STATPAC according to the guidelines. A detailed guideline is provided in the Appendix **1** of this document. Because visual field results are strongly affected by experience, visual field tests will be repeated on two occasions at Screening and at Baseline visits.

All automated perimetry results (in **computer** disc form) will be read by a central reader within ~~three~~ **seven** days of the examination. If the central reader assesses the visual field exam to be of poor quality, the exam will be repeated within one week. The repeat test will be performed only on the eye whose test was considered to give a poor result.

VFT will be conducted at the ~~Week -1 (~~Screening**(Visit 1))**~~,~~ ~~Week 0 (~~Baseline**(Visit 2))**~~,~~ Week 6**(Visit 5)**, and Week 12**(Visit 6) v**~~v~~isits as well as at the Week 15 (follow-up**, Visit 7)**) visit if deemed necessary.

Change To

All investigators will receive extensive training at the investigator's meeting and periodically throughout the study to improve the reliability of measurements by monitoring subject compliance and recognizing artifact in visual field examination. Investigators can repeat/reschedule sessions when subjects have poor compliance or any difficulties which interferes with visual field testing.

Prior to performing the computerized automated perimetry (Humphrey 24-2 SITA), pupil size will be measured and recorded and must be 3 mm or greater for VFT, otherwise the pupil must be dilated. Visual fields will be measured using the Humphrey 24-2 SITA and analyzed using STATPAC according to the guidelines. A detailed guideline is provided in the Appendix 1 of this document. Because visual field results are strongly affected by experience, visual field tests will be repeated on two occasions at Screening and at Baseline visits.

All automated perimetry results (in computer disc form) will be read by a central reader within seven days of the examination. If the central reader assesses the visual field exam to be of poor quality, the exam will be repeated within one week. The repeat test will be performed only on the eye whose test was considered to give a poor result.

VFT will be conducted at the Screening (Visit 1), Baseline(Visit 2), Week 6 (Visit 5), and Week 12 (Visit 6) visits as well as at the Week 15 (follow-up, Visit 7) visit if deemed necessary.

25. **Section 7. ASSESSMENTS, 7.2. Clinical Laboratory Tests, 7.3. Vital Sign, Body Weight and Physical Examination, 7.4. Electrocardiogram (ECG, 7.5. Suicidality Assessment, 7.5.1. Sheehan-Suicidality Tracking Scale (S-STS), 7.5.2 Patient Health Questionnaire-8 (PHQ), 7.5.3. Suicidality Assessments, and 7.6. Patient Assessment of Seizure Frequency**

Additions

7.2. Clinical Laboratory Tests

Laboratory

The following safety laboratory tests will be performed at the Screening (Visit 1) and Week 12 (Visit 6).

Safety Laboratory

Hematology	Chemistry	Urinalysis	Other
Hemoglobin **Hematocrit** **RBC Count** **Platelet Count** **WBC Count**	**Creatinine** **BUN** **Glucose** **Ca^{++}** **Na^{+}, K^{+}, Cl^{-}** **Total CO_2 (Bicarbonate)** **AST, ALT** **Total Bilirubin** **Alkaline phosphatase** **Uric acid** **Albumin** **Total protein** **Creatine phosphokinase**	**PH** **Color** **Clarity** **Specific gravity** **Glucose (qual)** **Protein (qual)** **Blood (qual)** **Ketones** **Nitrates** **Microscopy[b]**	**Urine Pregnancy test[a]** **Urine drug testing[c] (amphetamines, antidepressants, barbiturates, benzodiazepines, canabinoids, cocaine, methadone, methaqualone, opiates, phenothiazines, propoxyphene and alcohol)**

[a] **Childbearing potential females only**
[b] **Only if urine dipstick is positive for blood or protein**
[c] **Only at Screening**

Results of the urine drug tests at screening (V1) must be negative for the subject to receive trial medication on Day 1.

- **Safety laboratory tests from Screening must have no clinically significant findings, as judged by the investigator, in order for a subject to receive trial medication on Day 1.**
    - **CLcr will be estimated from creatinine at screening to determine eligibility using the equations that follow.[12]**

$$\text{Male } CL_{cr} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}$$

$$\text{Female } CL_{cr} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine}}\right] \times 0.85$$

In order to use SI units for creatinine (µmol/L), use the following formulas:

$$\text{Male } CL_{cr} \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{\text{Serum Creatinine}} \quad \text{x} \quad 1.23$$

$$\underset{CL_{cr}}{\text{Female}} \text{ (mL/min)} = \left[\frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{\text{Serum Creatinine}}\right] \times 1.23 \quad \times 0.85$$

7.3. Vital Sign, Body Weight and Physical Examination

Vital signs (sitting heart rate and blood pressure) will be obtained at Screening (Visit 1), Baseline (Visit 2), Week 1 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6) and Early Termination (ET). BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. The same arm (preferably the dominant arm) will be used throughout the trial. BP and heart rate will be measured after at least 5 minutes in sitting position. When done manually, heart rate will be measured in the brachial/radial artery for at least 30 seconds. The use of automated devices for measuring BP and heart rate are also acceptable.

Body weight will be collected at Screening (Visit 1), Baseline (Visit 2), Week 1 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6), Week 15 (Visit 7) and Early Termination (ET). Any negative changes from the screening examination will be recorded as adverse events.

To reduce measurement variability of body weight, subjects should be weighed on the same scale at each visit that body weight is assessed; should not carry extraneous items such as purses, blackberries, and cell phones onto the scale; should remove their coats and shoes before being weighed, and should empty their pockets of any heavy items.

A physical exam will be performed at Screening (V1) and Week 12 (Visit 6). Items included will be:

- **General appearance – including height (at Screening only);**
- **Skin – Examination for the presence of rash;**
- **HEENT – Examination of extraocular movements, pupillary response, determination of nystagmus, and visual field examination by confrontation;**
- **Lungs and Cardiovascular – Auscultation of lung fields, determination of BP, cardiac rhythm and rate auscultation for the presence of murmurs, gallops, or rubs;**
- **Neurologic – Including mental status, station and gait, cranial nerves, motor and sensory function, reflexes, and coordination;**
- **Abdominal – Palpation and auscultation performed.**

Additional physical assessment will be made as necessary to evaluate symptoms or adverse experiences at the discretion of the investigator.

7.4. Electrocardiogram (ECG)

A 12-lead ECG (singlet) will be performed at Screening (Visit 1). ECG should be performed after the subject has rested quietly for at least 10 minutes in a supine position. ECG tracing will be evaluated by the investigator in a real time for the safety monitoring of the subjects. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

7.5. Suicidality Assessment

7.5.1. Sheehan-Suicidality Tracking Scale (S-STS)

The Sheehan-Suicidality Tracking Scale (S-STS, see Appendix 3) is an 8-item prospective rating scale that tracks treatment-emergent suicidal ideation and behaviors.[12] This scale was adapted from the Suicidality Module of the Mini International Neuropsychiatric Interview (MINI) Structured Diagnostic Interview for DSM-IV. Items 1a, 2-6, 7a, and 8 are scored on a 5-point Likert scale (ranging from 0= not at all to 4=extremely). Items 1, 1b, and 7 require yes or no responses. This scale can be administered either by a clinician or patient through self-report. In this study, the scale will be completed by the patient (self-report). The Baseline-Lifetime Assessment will be completed at Screening and the "Since Last Visit" version will be completed at Baseline(Visit 2) , Randomization(Visit 3), Week 1 (Visit 4), Week 6 (Visit 5), Week 12 (Visit 6), Week 15 (Visit 7) and ET.

7.5.2. Patient Health Questionnaire-8 (PHQ), Appendix 3.

The PHQ-8 (See Appendix 3) is a self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-9 is the depression module, which scores each of the 9 DSM-IV criteria as 0 (not at all) to 3 (nearly every day).[15] The PHQ-8, a validated subset of the PHQ-9, which comprises the first 8 items of the measure, will be completed by subjects at Screening (Visit 1).

7.5.3. Suicidality Assessments

During Screening

A risk assessment should be done by a qualified mental health professional (MHP: a psychiatrist or licensed PhD level clinical psychologist) to assess whether it is safe for the subject to participate in the trial if at least one of the following three conditions are met:

- **Subject's responses on the S-STS items 1a, 1b, 3 and 4, 5, 6, or 8 is positive (score ≥ 1);**

or

- **Subject's Total PHQ- 8 score ≥15;**

or

- **Presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.**

A written copy of the risk assessment should be included in the subject's clinical record (source documentation).

During the Clinical Trial:

At the Baseline and post-baseline visits, if there are any positive response on the S-STS (since last visit version) items 1a, 1b, 3, 4, 5, 6, or 8, 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 trial. Subjects who have a positive response on S-STS items 1a, 1b, 3 and 4, 5, 6, or 8 on more than one occasion during a trial must have their potential suicidality managed appropriately by the PI together with a qualified MHP (or the PI alone if the PI is a qualified MHP). In addition, the PI should consult with the Pfizer medical monitor to determine whether the subject can continue the trial.

7.6. Patient Assessment of Seizure Frequency

Global change of seizure frequency will be rated as increased, no change or decreased by patient at Visit 6 (Week 12) or Early Termination (ET).

26. **Section 8. ADVERSE EVENT REPORTING, 8.1. Adverse Events, 2nd paragraph, last sentence**

Addition

The pregabalin Core Data Sheet (CDS) is the Single Safety Reference Document for this study and will be used in determining expected versus unexpected adverse events.

27. Section 8. ADVERSE EVENT REPORTING, 8.2. Reporting Period, 2nd paragraph

Change From

- Adverse events (serious and non-serious) should be recorded on the CRF beginning with the ~~Week -1~~ Screening Visit through the last subject visit.

Change To

- Adverse events (serious and non-serious) should be recorded on the CRF beginning with the Screening Visit through the last subject visit.

28. Section 8. ADVERSE EVENT REPORTING, 8.6. Hospitalization, 1st paragraph

Change From

Adverse events reported from clinical trials associated with hospitalization or ~~prolongation of hospitalization are~~**prolongation of hospitalization is** 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).

Change To

Adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization is 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).

29. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.4.5. Other Safety Measurements

Change From

Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication, **and Sheehan Sucidality Tracking Scale (S-STS),** Appendix 2 will be summarized by treatment group, but not analyzed inferentially.

Change To

Other safety parameters, including adverse events, physical examination results, vital signs, body weight, clinical laboratory results, and subject assessment of seizure frequency as compared to before taking study medication, and Sheehan Sucidality Tracking Scale (S-STS) Appendix 2, will be summarized by treatment group, but not analyzed inferentially.

30. Section 12. ETHICS, 12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Addition

12.4. Reporting of safety issues and serious breaches of the protocol or ICH GCP

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

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

31. Section 13. DEFINITION OF END OF TRIAL, 13.1. End of Trial in all Participating Countries, 13.2. End of Trial in a Member State of European Union

Additions

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in all Participating Countries

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

13.2. End of Trial in a Member State of European Union

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.

32. Section 15. PUBLICATION OF TRIAL RESULTS, 15.1. Communication of Results by Pfizer, 15.2. Publications by Investigators

Additions

15.1 Communication of results by Pfizer:

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer posts the results of studies that fall into either of the following categories:

- **Studies that Pfizer registered on www.clinicaltrials.gov, (ClinicalTrials.gov) regardless of the reason for registration; OR**
- **All other studies for which the results have scientific or medical importance as determined by Pfizer.**
- **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 already approved in any country and for studies that do not involve a Pfizer product, Pfizer posts results within one year after study completion, defined as 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 one year after the first regulatory approval of the product;**

- **For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year after such discontinuation.**

Pfizer's posting on ClinicalStudyResults.org includes the following elements:

- **Protocol title, study phase, and indication;**

- **A link to approved product labeling, if applicable;**

- **The synopsis of study results;**

- **Citations of known study publications;**

- **Legal disclaimer.**

The study results synopsis posted on ClinicalStudyResults.org (called the PhRMA website synopsis) uses the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis. Study results will be posted to ClinicalStudyResults.org within one year of last subject last visit. For all studies subject to the FDA Amendments Act Title VIII and the state of Maine disclosure legislation, Pfizer also posts data in the basic results database on clinicaltrials.gov within 1 year of the primary outcome completion date.

Pfizer posts citations only for publications that are accessible in recognized (searchable) publication databases. Single-centre results publications for a multi-centre study are generally not posted because they may not accurately reflect the results of the study.

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.

33. Section 16. REFERENCES, numbers 1, 2, 13, 14

Additions, then references renumbered

1. **Lyrica USPI, Pfizer Inc, April 2009**
2. Lyrica SPC, Pfizer Inc, http://emc.medicines.org.uk/medicine/14651/SPC/Lyrica+Capsules/
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
14. Kroenke, K, Spitzer, R.LThe PHQ-9. A new depression diagnostic and severity measure. Psychiatric Annals .2002; 32 (9): 1-7.

34. Section APPENDICES, Appendix 2, Sheehan-Suicidality Tracking Scale (S-STS), and Appendix 3, Patient Health Questionnaire (PHQ-8)

Additions

Appendix 2 Sheehan-Suicidality Tracking Scale (S-STS)

STB001

SHEEHAN - SUICIDALITY TRACKING SCALE (LIFETIME ASSESSMENT): (Page 2 of 2)

INSTRUCTIONS: CHOOSE ONLY ONE ANSWER FOR EACH QUESTION.

PLEASE ENSURE THAT ALL DIMENSIONS OF THE QUESTION ARE TAKEN INTO ACCOUNT IN CHOOSING THE APPROPRIATE RESPONSE (FOR EXAMPLE, TIME FRAME, FREQUENCY AND SEVERITY).
THE RESPONSE "NOT AT ALL" TO ANY QUESTION MEANS "NONE" AND MEANS THE THOUGHT OR BEHAVIOR "DID NOT OCCUR AT ALL".

1. Did you ever suffer an accident? (this includes taking too much of your medication accidentally). ☐ (0) No ☐ (1) Yes

IF NO, SKIP TO QUESTION 2.
IF YES, GO TO QUESTION 1a:

	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
1a. to what extent did you plan or intend to hurt yourself in that accident (either passively or actively)?	☐	☐	☐	☐	☐

IF THE ANSWER TO QUESTION 1a IS 0 (=Not at all), SKIP TO QUESTION 2.
IF IT IS SCORED ≥ 1, GO TO QUESTION 1b:

1b. Did you intend to die as a result of this accident? ☐ (0) No ☐ (1) Yes

How seriously did you ever:	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
2. think that you would be better off dead or wish you were dead?	☐	☐	☐	☐	☐
3. want to harm yourself or to hurt or to injure yourself?	☐	☐	☐	☐	☐
4. think about suicide?	☐	☐	☐	☐	☐
5. plan for a suicide?	☐	☐	☐	☐	☐
6. take active steps to prepare for a suicide attempt in which you expected or intended to die?	☐	☐	☐	☐	☐

7. Did you ever injure yourself on purpose? ☐ (0) No ☐ (1) Yes

IF NO, SKIP TO QUESTION 8.
IF YES, GO TO QUESTION 7a:

How seriously did you:	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
7a. deliberately injure yourself without intending to kill yourself?	☐	☐	☐	☐	☐
8. attempt suicide?	☐	☐	☐	☐	☐

srsaoz

SHEEHAN - SUICIDALITY TRACKING SCALE (SINCE LAST VISIT): (Page 2 of 2)

INSTRUCTIONS: CHOOSE ONLY ONE ANSWER FOR EACH QUESTION.

PLEASE ENSURE THAT ALL DIMENSIONS OF THE QUESTION ARE TAKEN INTO ACCOUNT IN CHOOSING THE APPROPRIATE RESPONSE (FOR EXAMPLE, TIME FRAME, FREQUENCY AND SEVERITY).
THE RESPONSE "NOT AT ALL" TO ANY QUESTION MEANS "NONE" AND MEANS THE THOUGHT OR BEHAVIOR "DID NOT OCCUR AT ALL".

1. Since your last visit did you suffer an accident? (this includes taking too much of your medication accidentally). ☐ (0) No ☐ (1) Yes

IF NO, SKIP TO QUESTION 2.
IF YES, GO TO QUESTION 1a:

	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
1a. to what extent did you plan or intend to hurt yourself in that accident (either passively or actively)?	☐	☐	☐	☐	☐

IF THE ANSWER TO QUESTION 1a IS 0 (=Not at all), SKIP TO QUESTION 2.
IF IT IS SCORED ≥ 1, GO TO QUESTION 1b:

1b. Did you intend to die as a result of this accident? ☐ (0) No ☐ (1) Yes

Since your last study visit, how seriously did you:	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
2. think that you would be better off dead or wish you were dead?	☐	☐	☐	☐	☐
3. want to harm yourself or to hurt or to injure yourself?	☐	☐	☐	☐	☐
4. think about suicide?	☐	☐	☐	☐	☐
5. plan for a suicide?	☐	☐	☐	☐	☐
6. take active steps to prepare for a suicide attempt in which you expected or intended to die?	☐	☐	☐	☐	☐

7. Since your last study visit, did you injure yourself on purpose? ☐ (0) No ☐ (1) Yes

IF NO, SKIP TO QUESTION 8.
IF YES, GO TO QUESTION 7a:

Since your last study visit, how seriously did you:	Not at all (0)	A little (1)	Moderately (2)	Very (3)	Extremely (4)
7a. deliberately injure yourself without intending to kill yourself?	☐	☐	☐	☐	☐
8. attempt suicide?	☐	☐	☐	☐	☐

Appendix 3. Patient Health Questionnaire (PHQ-8)

PHQ10CE

PATIENT HEALTH QUESTIONNAIRE (PHQ-8): (Page 2 of 2)

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all (0)	Several days (1)	More than half the days (2)	Nearly every day (3)
1. Little interest or pleasure in doing things?	☐	☐	☐	☐
2. Feeling down, depressed, or hopeless?	☐	☐	☐	☐
3. Trouble falling or staying asleep, or sleeping too much?	☐	☐	☐	☐
4. Feeling tired or having little energy?	☐	☐	☐	☐
5. Poor appetite or overeating?	☐	☐	☐	☐
6. Feeling bad about yourself--or that you are a failure or have let yourself or your family down?	☐	☐	☐	☐
7. Trouble concentrating on things, such as reading the newspaper or watching television?	☐	☐	☐	☐
8. Moving or speaking so slowly that other people could have noticed? Or the opposite--being so fidgety or restless that you have been moving around a lot more than usual?	☐	☐	☐	☐

If you are experiencing any of the problems on this form, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people?

Not difficult at all (1)	Somewhat difficult (2)	Very difficult (3)	Extremely difficult (4)
☐	☐	☐	☐

PHQ-8 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at kkroenke@regenstrief.org. Use of the PHQ-8 may only be made in accordance with the Terms of Use available of http://www.pfizer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.