

TITLE: Efficacy and Safety of Pregabalin in Treatment of Neuropathic Pain in Patients with Idiopathic Small Fiber Neuropathy

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1. INTRODUCTION

1.1. Indication

The purpose of this study is to assess safety and efficacy of treatment with pregabalin in patients with idiopathic small fiber neuropathy proven by skin biopsy.

1.2. Background and Rationale

Pregabalin is an alpha-2-delta (a2d) ligand that has analgesic, anxiolytic, and anticonvulsant activity. It has demonstrated anti-nociceptive activity in animal models of neuropathic pain and in patients with painful diabetic neuropathy (DPN), post-herpetic neuralgia (PHN), and fibromyalgia. Pregabalin (Lyrica) is approved for the treatment of neuropathic pain in the European Union and Canada, and for the management of neuropathic pain associated with DPN and PHN in the United States and South Africa. Pregabalin has been shown to be an effective treatment for other indications, including generalized anxiety disorder, and central neuropathic pain associated with spinal cord injury.

Small fiber neuropathy is a sub-type of sensory neuropathies that predominantly affects the small unmyelinated fibers. Small fiber neuropathy has been defined as “peripheral neuropathy manifest by paresthesias with findings of small-fiber dysfunction on neurologic examination”[1]. Paresthesia is often painful in these patients and signs of involvement of large fibers are absent or minimal. Patients typically present with positive sensory symptoms, including tingling, burning, shooting pain, or aching. The pain is often worse at night and may interfere with sleep. Patients may also have negative symptoms, including numbness, feeling of tightness around the feet, and coldness. Symptoms are usually distal and length-dependent [2]. The exam findings often include a reduction in sensitivity to pain and temperature along with normal strength, proprioception, and tendon reflexes.

Diagnostic electrophysiologic studies are often performed in patients with suspected small fiber neuropathy to rule out the presence of large fiber neuropathy. The routine nerve conduction studies are often normal [3]. Skin biopsy with quantification of epidermal nerve fibers and sweat glands is an effective way to diagnose small fiber neuropathy[4]. Quantitation of epidermal nerve fibers has a positive predictive value of 75% and a negative predictive value of 90%, with a diagnostic efficiency of 88% for patients with sensory neuropathies[5]. The sensitivity (74–90%) and specificity (64–90%) of skin biopsy for diagnosis of small fiber neuropathy is high[6]. Therefore, consensus guidelines have recommended skin biopsy as preferred method to establish diagnosis of small fiber neuropathy[7]. IENFD is an unbiased pathological measure of c-fiber nociceptors that is increasingly used as an outcome measure in human clinical trials. These fibers express TRPV1 and therefore are important in pain perception and painless injuries. In cross sectional studies IENFD is reduced in many neuropathic populations including people with HIV infection, diabetes, Fabry disease and genetic amyloid. In some instances morphological changes of nerve fibers such as large swellings have been associated with subsequent nerve fiber loss. Decreases or loss of IENFD has been correlated with increases in heat pain and cold thresholds. IENFD correlates with unmyelinated nerve fiber counts derived from electron microscopy studies of sural nerve biopsies and led to an editorial in Neurology

that concluded that skin biopsies should replace sural nerve biopsies in patients with normal nerve conduction test results. Epidermal nerve fibers are affected early in the course of most peripheral neuropathies compared to large myelinated nerve fibers. This is postulated to represent the increased metabolic demands that small unmyelinated nerve fibers are under to maintain a membrane potential. Thus a reduction in IENFD is often the only objective evidence of neuropathy in patients with early HIV-associated sensory neuropathy or early diabetic neuropathy. IENFD also offers a confirmatory documentation that a patient with painful feet actually has a peripheral neuropathy and not another condition that could mimic neuropathy.

Skin biopsy has been instrumental in defining a population of patients with painful peripheral neuropathy and relatively normal examinations and no known etiology for their neuropathy. Such patients are often labeled as having idiopathic small fiber neuropathy and typically complain of numbness, burning pain, paresthesias, or allodynia in the feet, usually with cutaneous sensory loss but with an otherwise normal neurologic examination. Small fiber neuropathy remains idiopathic in large number of patients despite extensive laboratory testing, especially in adults over 60 years old[8]. Diabetes, impaired glucose tolerance test, alcohol, Sjogren syndrome, medications, toxins, HIV infection, amyloidosis, Tangier disease, and Fabry's disease are among identifiable causes of small fiber neuropathy. The incidence and prevalence of small fiber neuropathy is not well known. One study from Netherlands suggested an overall minimum incidence over of 11.73 cases/100,000/year and an overall minimum prevalence of 52.95 cases/100,000 [9].

Small fiber neuropathy has been shown to have a detrimental effect on quality of life and to be a major source of disability [10]. Bakkers et al reported that idiopathic small fiber neuropathy can be as disabling as neuropathy caused by diabetes mellitus or other forms of small fiber neuropathy with an identifiable cause. Patients with small fiber neuropathy have ongoing, sometimes excruciating pain and experience continuous difficulty dealing with the consequences of their illness, causing severe reduction in all aspects of quality of life. A study of 100 patients diagnosed with idiopathic small fiber neuropathy showed that these patients experience moderate to severe pain, which negatively impacts health status, function, and productivity, and leads to substantial direct and indirect costs [11].

Treatment of idiopathic small fiber neuropathy is mostly symptomatic. Unfortunately, there is no direct evidence for treating idiopathic small fiber neuropathy and most of the medications currently used are based on the assumption that evidence from small fiber neuropathy due to diabetes, HIV or other causes can be generalized to idiopathic cases [12]. However, studies in the past have shown that this generalization is not always successful, as we learned that some medications that are useful in diabetic induced small fiber neuropathy are not that effective for cases caused by HIV infection [13].

Pregabalin has been used for treatment of painful small fiber neuropathy caused by diabetes. Multiple studies have shown safety and efficacy of pregabalin in controlling pain in patients with diabetic neuropathy. However, very few of these studies have patients with skin biopsy proven small fiber neuropathy. In a study of 157 patients with neuropathic pain from various etiologies (diabetes, HIV, post-trauma, etc), Gilron et al used an enriched enrollment protocol [14, 15] to

study the effect of pregabalin on pain score and reported a modest but significant effect. Only 8 patients in their treatment group had idiopathic small fiber neuropathy and they did not use skin biopsy to confirm the diagnosis [16]. In a double-blinded randomized control trial of pregabalin in HIV-induced painful small fiber neuropathy, pregabalin was well tolerated but was not superior to placebo in pain control [17]. In a meta-analysis of 11 randomized controlled trial of pregabalin in treatment of neuropathic pain in elderly patients, the drug was shown to be effective and safe with dizziness, somnolence, peripheral edema, asthenia, dry mouth, weight gain, and infections being most common side effects [18]. However, they did not report the number of patients with idiopathic small fiber neuropathy.

Since idiopathic small fiber neuropathy is a relatively common and disabling disorder, there is a need to develop treatment strategies and identify medications that can ameliorate pain, improve function and quality of life. Currently, there is no evidence regarding best treatment options for idiopathic small fiber neuropathy. Additionally, most of the studies that have examined the efficacy of various treatment options including Pregabalin on neuropathic pain did not use an objective and quantitative measure of small fiber neuropathy such as skin biopsy to select their study subjects. This might create a dilutional effect on the efficacy measures since some of the included subjects might have pain that is not originated from a neuropathic process. Since pregabalin has been shown to be a cost effective treatment for some types of small fiber neuropathy such as diabetic neuropathy [19] and improves quality of life [20], it would be a valuable therapeutic option for idiopathic small fiber neuropathy if proven effective. However, there is no study directly examining the effect of pregabalin on idiopathic, skin biopsy proven small fiber neuropathy. Therefore, we aim to study the effect of pregabalin on pain control specifically in a group of patients with idiopathic small fiber neuropathy proven by skin biopsy in a partially enriched enrollment plan. This design would allow us to improve upon previous studies in several aspects. Using skin biopsy as inclusion criteria would prevent recruitment of patients that might have non-neuropathic pain and therefore confound the data. Using a partial enrichment plan would help us to exclude patients who are non-respondent to treatment and increase the power of study.

Enriched enrollment with randomized withdrawal design is recommended by The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), comprising experts in the design and evaluation of treatments for chronic pain, in efficacy studies (Dworkin, et al 2010). Patients exhibiting a response to treatment for neuropathic pain defined as a 30% or greater reduction in neuropathic pain from baseline (and mean NRS pain intensity ≤ 7) will be randomized in this study if they have met all inclusion and no exclusion criteria. The 30% pain reduction criteria is consistent with publications which characterize this as substantial improvement in pain (Dworkin et al, 2008; Farrar, et al 2001) and with evidence that enrichment based on this response criteria is consistent with good assay sensitivity in a neuropathic pain population (Hewitt 2011). Durability of effect (ie, time to efficacy failure) will be assessed in the randomized withdrawal phase of the study by using the time to efficacy failure definition of the first 3 days of at least 30% increase in pain intensity relative to final maintenance week of single blind treatment phase and mean 24 hour pain intensity level >4.0 (or discontinuation due to lack of efficacy).

The safety and tolerability of pregabalin has been examined several clinical studies. Pregabalin has been or is currently being investigated in over 102 clinical controlled and uncontrolled Phase 2/3 studies. These studies have been conducted in 3 different therapy areas: pain, epilepsy, and psychiatric indications (anxiety disorders and acute mania). In the controlled studies, doses of 50 to 600 mg/day of pregabalin administered in 2 or 3 divided doses per day were evaluated for efficacy and safety. The most common adverse events reported are dizziness (30%), somnolence (18%), headache (12%), and weight increase (10%).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective:

To evaluate the efficacy of pregabalin (150-600 mg/day, flexibly administered BID) compared with placebo for the treatment of pain associated with idiopathic distal symmetrical small fiber peripheral neuropathy.

Secondary Objectives:

1. To evaluate the efficacy of pregabalin compared with placebo on global assessment of treatment ;
2. To evaluate the efficacy of pregabalin compared with placebo on quality of life ;
3. To explore the relationship between proteomics and lipidomics profile and treatment response;
4. To explore the relationship between metabolite profile and treatment response;
5. To assess the safety and tolerability of pregabalin.

2.2. Endpoints

Primary Efficacy Endpoint

Mean endpoint 24-h average pain intensity based on pain intensity scores after 12 weeks maintenance treatment phase.

Secondary Measures and Efficacy Endpoints

1. Brief Pain Inventory (BPI-sf);
2. Daily Sleep Interference Rating Scale (SIRS);
3. Patient Global Impression of Change (PGIC);
4. EuroQoL 5-Dimensions (EQ-5D);
5. Small Fiber Neuropathy Symptom Inventory Questionnaire (SFN-SIQ);

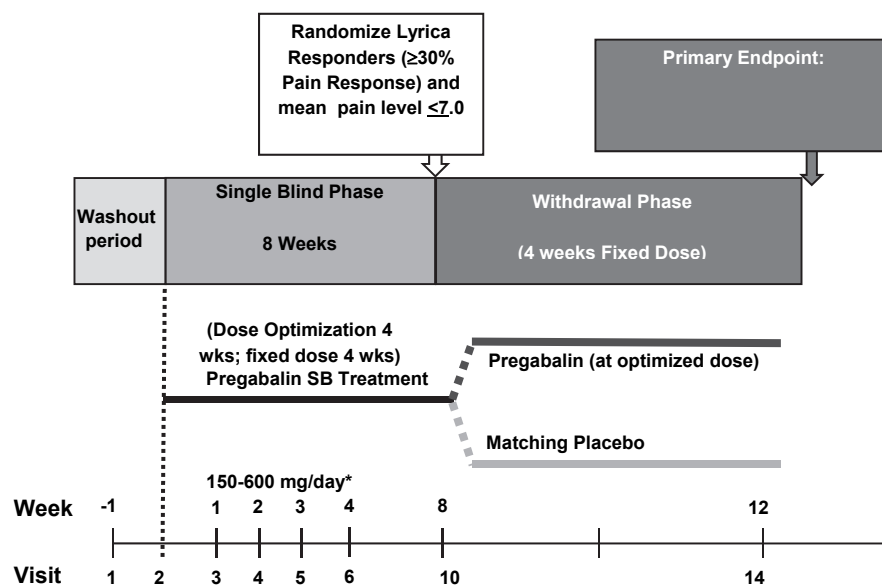
6. Proteomics, lipidomics and metabolite exploratory analysis for treatment response.

Safety and other Diagnostic Assessments

- Adverse events monitoring;
- Physical exam/Neurological exam;
- Vital signs;
- Suicidality Assessment (C-SSRS).

3. STUDY DESIGN

This enriched enrollment randomized withdrawal study comprises 4 phases: a screening and selection phase, a 2-4 weeks washout period from previous pain medication for enriched enrollment, an 8 week single-blind pregabalin treatment phase; and a 4 week randomized withdrawal phase. Patients who show any increase in their pain intensity score during the washout phase will be eligible for the single blind pregabalin treatment phase. Patients who respond to pregabalin, with at least 1 point improvement in neuropathic pain from baseline at the end of the single-blind pregabalin treatment phase and meeting all other study requirements are considered eligible for participation in the withdrawal phase. These eligible patients are randomly assigned (1:1) to continue pregabalin or to be switched to placebo for a comparison of pregabalin efficacy and safety. Patients who have a worsening of average pain relative to the last week of the single blind pregabalin treatment period by more than one point and average pain level ≥ 4 will be considered to have a loss of therapeutic response (LTR).



*Low creatinine clearance patients: 150-300 mg/day

4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study;
2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures and are able to read and participate in all study assessments;
3. Subjects with idiopathic predominate-small fiber neuropathic pain based on medical history, neurological examination, and punch biopsy results. Diagnosis of small fiber neuropathy is based on presence of at least 2 of the following symptoms, one of the following signs and abnormalities in skin biopsy consistent with small fiber neuropathy. Idiopathic small fiber neuropathy is defined as ruling out presence of diabetes, HIV infection and other conditions listed in exclusion criteria;

a. Symptoms:

- Burning pain in feet
- Numbness
- Tingling (pins and needles)
- Hypersensitive to touch, heat, or cold

b. Signs

- Allodynia (mechanical brush)
- Diminished perception of pain with pinprick
- Hyperalgesia to pin prick
- Diminished temperature sensation (cold or heat)

4. Subject must have chronic peripheral neuropathic pain consistent with predominately small fiber neuropathy. Pain history indicates that pain started in the feet or legs and has been present for more than 3 months;
5. A score >3 and <8 on Pain intensity scale for pain in prior week at first visit;
6. Show increase in pain intensity scores during the 2 weeks of wash off period;
7. Age older than 18 years;

4.2. Exclusion Criteria

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

1. Subjects with large-fiber predominant neuropathy defined as sural SNAP amplitude less than 6 μ v or Peroneal CMPA recorded at EDB of less than 1 mV;
2. Subjects with peripheral neuropathic pain secondary to specific etiologies including HIV infection, trigeminal neuralgia (TGN), carpal tunnel syndrome (CTS), toxic neuropathy (e.g. chemotherapy exposure), paraneoplastic neuropathy, monogamopathy, inflammatory neuropathy, celiac disease, systemic lupus, peripheral vascular disease, connective tissue disorders, hepatitis C, Fabry disease, and diabetes;
3. Subjects with uncontrolled thyroid or B12 disorders (subjects with a history of thyroid or B12 disorders currently taking replacement therapy with normal screening values are allowed);
4. Subjects with pain due to Complex Regional Pain Syndrome (CRPS, Type I or Type II);
5. Subjects with skin conditions in the affected area that in the judgment of the investigator could interfere with evaluation of neuropathic pain condition;
6. Pain that is not present in both feet/legs (ie, pain is not bilateral);
7. Patients with only negative symptoms defined as numbness without clear evidence of spontaneous pain either constant or episodic;
8. Subjects with pain that is not present every day (chronic) or where pain description does not have a classic stocking distribution per the clinical assessment with clinician (pain may vary in severity during the day);
9. Subjects with other pain that may confound assessment or self-evaluation of the peripheral neuropathic pain such as back pain, radicular pain, and fibromyalgia;

10. Subjects who have failed pregabalin treatment due to lack of efficacy with an adequate course of therapy (doses greater than 150 mg/day for at least 4 week), have hypersensitivity or intolerance to pregabalin or gabapentin, or participated in a pregabalin clinical trial at any time. Subjects that have failed to respond to more than 3 drug treatment trials of adequate dose/duration;
11. Any subject considered at risk of suicide or self-harm based on investigator judgment and/or the details of a risk assessment;
12. Use of prohibited medications in the absence of appropriate washout periods;
13. Subjects with any clinically unstable cardiovascular (including a myocardial infarction in the 3 months prior to Visit 1), hematological, autoimmune, endocrine, renal, hepatic (including chronic hepatitis B, hepatitis B within the past 3 months or ALT or AST > 3X ULN), respiratory, or gastrointestinal disease; epilepsy, symptomatic peripheral vascular disease including intermittent claudication, pernicious anemia, untreated hypothyroidism, venous insufficiency, spinal stenosis, or HIV infection;
14. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with compliance or the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study;
15. Subjects who have had a diagnosis of malignancy other than basal cell carcinoma or carcinoma in situ of the cervix within the past 5 years;
16. Subjects with creatinine clearance (CLcr) ≤ 60 mL/min (estimated prior to Visit 2 from serum creatinine obtained at Visit 1, body weight, age, and gender using the Cockcroft and Gault equation;; Subjects who have an estimated CLcr ≤ 60 mL/min by this screening method may have their CLcr measured, at the investigator's discretion, with a 24-hour urine collection performed at the central laboratory. If this 24-hour urine CLcr is >60 mL/min, the subject may be eligible. Subjects on dialysis are not eligible;
17. Subjects with a current diagnosis (DSM-IV-TR) of current major depression, history of bipolar diagnosis, or any diagnosis of a psychotic disorder;
18. History of known analgesic or illicit drug abuse within 12 months of first visit;
19. Patients that meet the DSM-IV criteria for alcohol abuse or dependence in the last two years;

20. Subjects with pending Worker's Compensation, Worker's Compensation, civil litigation or disability claims pertinent to the subject's based upon trauma; current involvement in out-of-court settlements for claims pertinent to subject's trauma;
21. Participation in other interventional studies within 28 days before the current study begins and/or during study participation;
22. Pregnant females; breastfeeding females.

4.3. Randomization Criteria

A list of allowed and disallowed concomitant pain medication is provided in sections 5.3.7 and 5.3.8. If patients is on any of the disallowed pain medications, this medication will be discontinued during the washout phase with an appropriate taper schedule based on the clinician judgment. Subjects must meet the following criteria after the washout period to be randomized for single-blind pregabalin treatment phase:

1. Subjects must have worsening in neuropathic pain from baseline to the end of washout phase.
2. Subjects must have an average pain score ≤ 8 in the final week of washout phase.

Subjects must meet the following criteria after the single-blind pregabalin treatment phase to be randomized for withdrawal phase:

1. Subjects must have response to treatment defined as at least one point decrease in pain intensity score at the end of the single-blind pregabalin treatment phase.

4.4. Life Style Guidelines

Subjects should not initiate or alter an exercise regimen during the study, as this could influence efficacy results based on the pain scale scores.

Subjects should not modify stable medication regimens, and should not have surgery or interventional medical procedures for the duration of the study.

Female patients at child bearing age must be informed that pregabalin is a category C medication for pregnancy which means that a risk cannot be ruled out and therefore use of an effective birth control method is recommended.

5. STUDY TREATMENTS

During the screening phase, the medication history of the subjects who are eligible for the study based on meeting the inclusion and exclusion criteria will be reviewed. The current pain medications of the subjects will be categorized into allowed and disallowed medications (see sections 5.3.7 and 5.3.8 for a complete list of these medications). If patient is on any of the

disallowed neuropathic pain medication such as gabapentin, these medications will be discontinued during the washout phase. A written instruction will be provided to the patient on how to discontinue the medication during the washout phase. Patient will complete a daily pain diary during this phase. Patient can continue to take the allowed pain medications but no change in dose or frequency is permitted. At the end of the washout period which is at least 14 days and might be longer based on the type of medication being discontinued, patient will be evaluated for eligibility for the study again based on randomization criteria mentioned in section 4.3.

All patients entering the study will be treated with single-blind pregabalin at doses of 150-600 mg/day for 8 weeks. The first 4 weeks of the single-blind phase comprise the dose optimization phase, and the next 4 weeks the single blind maintenance phase.

During the initial week of the single-blind pregabalin treatment phase, all patients will be treated with pregabalin 150 mg/day, and dose is to be increased based on response and tolerability until the end of Week 4. If the patient is unable to tolerate the higher dose, the dose should be reduced by one dose level per investigator discretion. This dose reduction may occur outside of the scheduled visit. Patients unable to tolerate a dose of 150 mg/day pregabalin during the Single-Blind phase will discontinue from the study (no taper necessary). After the end of the 4th week of the Single-Blind phase, no further dose escalation is permitted. During the next 4 weeks of the Single-Blind phase, fixed dose pregabalin treatment at the optimized dose within the range of 150 to 600 mg/day administered BID will be provided. One additional dose reduction may occur if needed during the last 4 weeks of the single blind period. Patients unable to tolerate the fixed dose of study medication will be discontinued from the study.

Patients meeting all eligibility criteria for withdrawal phase will be randomized in a 1:1 fashion to continue the fixed dose of pregabalin treatment as they were taking in the Single-Blind phase or placebo. Patients will continue in the withdrawal portion of the study for 4 weeks.

Patients who discontinue from the study during or at the end of the single-blind pregabalin treatment phase will complete a taper. Patients who had been receiving pregabalin 450 or 600 mg/day will receive pregabalin 300 mg/day for 4 days and 150 for 3 days. Patients receiving pregabalin 150 or 300 mg/day will receive 150 mg/day for 4 days and 50 mg for 3 days. Patients who have not taken study medication for the past 24 hours or more are not required to receive the taper medication.

At the end of the single-blind pregabalin treatment phase, patients will be randomized to receive either pregabalin at the optimized dose (150-600 mg/day pregabalin), as determined during the treatment phase, or matching placebo. No further dose adjustments will be allowed.

Patients randomized to pregabalin will continue at the optimized pregabalin dose

Patients randomized to placebo who were receiving pregabalin 450-600 mg/day will be tapered to placebo to mask any changes in adverse events. The taper will consist of pregabalin 300 mg/day for 4 days and 150 mg/day for 3 days. Subsequently these patients will receive placebo. Placebo treatment will continue until end of withdrawal period.

Patients randomized to placebo who were receiving 150-300 mg/day pregabalin will receive 150 mg/day for 4 days and 50 mg/day for 3 days during the first week of the withdrawal phase, then which will continue through the end of withdrawal phase.

At any time during the study (single-blind pregabalin treatment or withdrawal), if the patient cannot tolerate a dose of 150 mg/day pregabalin (or matching placebo in withdrawal phase) the patient will discontinue from the study, with no taper necessary. Patients experiencing inadequate pain relief should be assessed to determine whether the pain level is tolerable to complete the study or will need to be withdrawn due to lack of efficacy. Subjects requiring dosing adjustment during the withdrawal phase will be discontinued.

5.1. Allocation to Treatment

Subjects will be assigned a single subject identification number (SSID). This number will be retained throughout the study. A separate randomization number will be assigned by the experimental pharmacy at randomization and will be recorded on the case report form.

Following the treatment phase, qualified patients will be randomized in a 1:1 ratio to receive either pregabalin at the optimized dose or placebo.

5.2. Breaking the Blind

The study drug and placebo will be identical in appearance in order to preserve the study blinding. The investigator will be aware of the subject's treatment during the study but will not share this information with the subject. Blinding should only be broken for serious, unexpected, and related adverse events, and only for the subject in question, or when required by local regulatory authorities. Subjects whose randomization codes are broken in this way will be withdrawn from the study. The investigator must record the reason for breaking the blind in the subject's source documents.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

Study medication will be supplied as blinded capsules of pregabalin and matching placebo. The pregabalin capsules are composed of pregabalin, lactose monohydrate, cornstarch, and talc encapsulated in opaque hard gelatin capsule shells composed of gelatin and titanium dioxide. The placebo capsules will contain lactose monohydrate, microcrystalline cellulose, sucrose octaacetate, and magnesium stearate.

STUDY DRUG	
Generic name:	Pregabalin
Trade name:	Lyrica
Dosage form:	Capsules
Strength:	75 mg, 150 mg, 225 mg, 300 mg
Manufacturer:	Pfizer PPD, Freiburg, Germany
Supplier:	Pfizer Global Research Development
Ingredients:	Active: Pregabalin Inactive: Lactose monohydrate, corn starch, talc, gelatin, titanium dioxide, black iron oxide
Description:	Grey/Grey #0 capsules
PLACEBO	
Dosage form:	Capsules
Manufacturer:	Pfizer PPD, Freiburg, Germany
Supplier:	Pfizer Global Research Development
Ingredients:	Lactose monohydrate, microcrystalline cellulose, sucrose octaacetate, magnesium stearate, gelatin, titanium dioxide, black iron oxide
Description:	Grey/Grey #0 capsules identical in appearance to Pregabalin

The active trial medication and the placebo will be of identical appearance, and packaged in identical bottles.

5.3.2. Preparation and Dispensing

Pfizer will provide the pharmacy at investigative site with sufficient amounts of study medication. Study medication will be supplied in non-subject-specific bottles. Dispensing of study medication will be documented in the CRF and/or other study drug records including date of receipt and amounts dispensed to and returned by the study subjects. The investigator is responsible for assuring the retrieval of all full, partially full and empty medication bottles from subjects.

The pharmacy will administer/dispense the trial medication only to subjects included in this study following the procedures set out in the protocol. The investigator must maintain accurate and adequate records regarding shipments and dispensing of study medication.

5.3.3. Administration

Throughout the study, patients will be blinded to the treatment they are receiving. After the washout period, patients who meet eligibility criteria will be randomized to receive pregabalin or matching placebo for the remainder of the study phase. Once a subject has been randomized, the subject will be blinded to the treatment assignment.

During the single-blind pregabalin treatment and withdrawal phase patients will take 1 capsule twice daily. The study medication will be administered orally, BID, with or without food. Sufficient study medication will be provided to cover visit windows.

Subjects should be instructed on use of the study medication. When patients are dispensed multiple bottles of study medication, instruct the patient carefully regarding which bottle to use

and to take study medication from only one bottle at a time. Dose adjustments may be made by telephone.

Subjects should return medication bottles and any unused tablet(s) in each bottle to the site. Any dosing errors must be fully documented in source documentation and (if applicable) in the case report form. Dosing errors that may impact subject safety will be discussed by the investigator and sponsor.

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).

5.3.4. Compliance

Investigational product compliance will be assessed at each follow up clinic visit following. Any deviations in compliance should be recorded and an explanation provided. Study drug compliance is assessed using dosing compliance calculation:

$\% \text{ Compliance} = \text{number of tablets taken} / \text{number of tablets expected to have taken} \times 100.$

The subject is non-compliant with dosing if the percentage compliance according to the above formula is less than 80% or greater than 120% study drug compliance.

If the subject has not been compliant with the dosing/administration regimen at a given visit, the subject's participation in the study should be re-evaluated. If the subject's compliance is outside this range, this will be recorded as a protocol deviation.

Compliance with daily pain and sleep diary completion will be assessed. Subjects must complete at least 4 daily pain and sleep diaries over each consecutive 7-day period in the study. The completion of fewer than 8 daily pain and sleep diaries over the course of 14 days will be recorded as a protocol deviation. If the subject has not been compliant with diary completion, the subject's participation in the study should be re-evaluated.

5.3.5. Drug Storage

Dispensing of study medication will be documented in study drug records including date of receipt and amounts dispensed to and returned by study subjects. All bottles (including empty bottles) must be returned to the investigator by the subject.

The investigator must ensure that authorized personnel correctly receive deliveries of investigational product from the sponsor and that all receipts are recorded in writing.

Clinical drug supplies must be stored at 25°C, with excursions permitted from 15°C to 30°C, under secure (locked) conditions. The investigator, or an approved representative, e.g. pharmacist, will ensure that all investigational products are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements.

5.3.6 Concomitant Medication(s)

Medication taken within 30 days before the first dose of study medication (V1) and all medications taken after the first dose during the study will be documented in the subject's medical record form and on the case report forms (CRF). Drug history for medications used to treat neuropathy over the prior 5 years will also be collected. All concomitant medications and non-pharmacological treatments must be recorded with respect to type, dosage, duration of use and reason for use. In this study, subjects may remain on existing permitted pain medications provided that the dose and frequency of dosing does not change during the study period and that the subject has been on a stable dose for at least 30 days prior to Screening.

Permitted medications for pain management include -the-counter medications such as aspirin, acetaminophen, and NSAIDS such as ibuprofen if used by the patient for a condition other than neuropathic pain. Herbal and homeopathic remedies should not be initiated during the study; however, subjects who have taken a stable dose of these products for at least 30 days prior to the screening visit will be allowed to continue their regimen. The sponsor should be consulted on a case by case basis in determining whether or not specific medications are permitted.

Medications with activity at Alpha-2-delta binding site or sodium channels e.g. gabapentin, lamotrigine, carbamazepine, oxcarbazepine, mexiletine, amitriptyline, topical analgesics e.g. lidocaine patches, and oral/injectable corticosteroids are prohibited until the end of the study period and require a washout period prior to the Screening visit, and capsaicin patches for 90 days prior to screening. Drugs with possible efficacy for neuropathic pain including opioids or other mu agonists including tramadol and tapentadol, SNRI's (eg, duloxetine) are disallowed. Patients should also be excluded that use marijuana either illicitly or prescribed.

5.3.7. Allowed Medications

The following medications are permitted as described below. Medications listed must be taken for the indications specified, must be stable for the periods indicated prior to the first visit, and may not exceed the doses specified for subjects to be eligible for study participation. Subjects who do not meet these criteria are excluded from participation in the study.

Class of Medication	Examples (not a comprehensive list)	Minimum Period on Medication Prior to V1
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Analgesics	Acetaminophen	Maximum dose of acetaminophen or any acetaminophen-containing products should not exceed 3 grams/day
	NSAIDS, COX-2 inhibitors	Patients using NSAIDS at the start of the trial for conditions other than neuropathic pain may continue but should not change the pattern of use during the trial. NSAIDS may be initiated for acute conditions during the trial unrelated to neuropathic pain if clearly clinically necessary for the care of the patient.
	Aspirin	For myocardial infarction and stroke prophylaxis
Antidepressants	Antidepressants other than TCAs and SNRIs	Stable for one month prior to V1; therapy may not be initiated during the study. A maximum of one antidepressant may be used.
Benzodiazepines	Lorazepam	Subjects must be on a stable regimen within the last month (only bedtime dose; prescription for sleep only). Therapy may not be initiated during the Single-Blind or Double-Blind Phase. Long Life benzodiazepines(Diazepam) are not allowed.

GABA _A partial agonists	Zolpidem Eszopiclone	Subjects must be on a stable regimen within the last month. Therapy may not be initiated during the Single-Blind or Double-Blind Phase.
Antihistamines		For allergy nonsedating antihistamines should be

5.3.8. Disallowed Medications

Certain concomitant medications must be discontinued during the washout. These include but are not limited to those described below.

Class of Medication	Examples (not a comprehensive list)	Washout Period
PRN Local/topical agents for relief of PNeP	Lidoderm patch or other local anesthetics, steroids, capsaicin, topical opioid analgesics	At least 7 days prior to V1 or 5 half-lives.
Injections for relief of pain	Local anesthetics and steroids	At least 1 month prior to V1, and no injections over course of study
Oral or injectable medications for diabetes	Metformin,, Rosiglitazone, Exenatide (Byetta), Liraglutide	N/A
Antidepressants	TCA's, amitriptyline, SNRI's	>7 days
anticonvulsants	Gabapentin, carbamazepine, lamotrigine	> 7 days
Antidepressants used for pain control	SNRI's (eg, duloxetine), TCAs (eg, amitriptyline)	
Oral/IV Corticosteroids (topical corticosteroids are allowed)	dexamethasone, hydrocortisone, methylprednisolone,	≥7 days

5.3.9. Non Pharmacologic Treatment

Non Pharmacologic treatments, including but not limited to, TENS unit, acupuncture, acupressure, therapeutic massage, are disallowed during the entire study.

5.3.10. Rescue Therapy

Subjects may remain on their stable allowed pain medications as specified in Section 0 Acetaminophen doses of up to 3 g/day are allowed as rescue medication, and must be documented in the CRF.

6. STUDY PROCEDURES

6.1. Screening/Visit1

This is the clinic visit during which a new patient is diagnosed with idiopathic small fiber neuropathy or a patient who has been diagnosed with idiopathic small fiber neuropathy from peripheral neuropathy registry has presented for follow up and is informed about the study.

Informed consent procedures must be completed prior to initiating any study procedures during this visit. Visit 1 must occur between 14 days and 30 days prior to Visit 2, based on the amount of time required for screening procedures or washout period. The duration between Visits 1 and 2 will typically be approximately 14-30 days. A minimum 14 days is required to allow the washout phase.

The following procedures are to be performed at Visit 1. These procedures are not required to occur on the same day, but all results must be available by Visit 2.

- Informed consent
- Medical history, concomitant medications, prior treatments for neuropathy, any non-drug treatments, and adverse events will be reviewed.
- Weekly pain intensity score (1-week recall period) is completed by the patient
- Physical exam and neurological examination are performed, including height, weight heart rate and blood pressure
- SFN-SIQ
- BPI-sf
- EQ-5D
- Laboratory assessments are performed
- Columbia Suicidality Severity Rating Scale(C-SSRS) baseline and PHQ-8 are completed and reviewed
- Skin Biopsy if not performed previously

If the patient continues to meet entry criteria for the study following the completion of these procedures, the following will be completed:

- The patient will be instructed to complete a pain and sleep diary daily. A sample diary is to be completed and IVRS procedures reviewed with the patient to ensure comprehension.
- Blood draw to collect sample for proteomics and lipidomics.
- The patient will be instructed how to discontinue the current disallowed pain medication and will be scheduled to come to the clinic for Visit 2.

6.2. Treatment Phase

6.2.1. Visit 2 – Clinic Visit

- Review concomitant treatments, adverse events, and any non-drug treatments.
- Review laboratory results and Visit 1 assessments for eligibility.
- Review daily pain and sleep diaries for compliance and eligibility.
- Perform the following assessments: BPI-SF, SFN-SIQ and EQ-5D
- Review the study entry criteria to determine if the patient meets all inclusion and exclusion criteria (Section 4). Patients not meeting eligibility criteria should not complete the other assessments listed for this visit and will not continue in the trial.

For patients meeting study entry criteria, the following procedures will be performed:

- The patient will be reminded to continue completing daily pain and sleep IVRS diaries each evening.
- Study medication will be dispensed. Blinding must be maintained with the patient. If a supply is being dispensed to last through the next clinic visit (Visit 6/Week 4), instruct the patient regarding which bottle to use, and to take one capsule in the morning and once daily in the evening from a single bottle. The patient will be instructed to begin dosing the following morning.
- Schedule a telephone Visit for Day 7.

6.2.2. Visit 3 (Day 7) – Phone Visit

If the subject is tolerating the study medication, this visit may be completed by phone. At the investigator's discretion (eg, to further assess an adverse event), this visit may instead be conducted in the clinic.

The following will be completed at this visit:

Review adverse events, the daily pain and sleep diary, concomitant medications, and non-drug treatments. Remind the patient to continue completing diaries until the next scheduled visit.

Confirm that the patient is taking one study medication capsule twice daily from the correct bottle. Determine and discuss the pregabalin dose level to be administered and provide instructions for dose administration. This dose level should be taken at the next scheduled dose. Blinding must be maintained with the patient.

Schedule a phone visit for Visit 4 (Day 14).

6.2.3. Visit 4 (Day 14) – Phone Visit

If the subject is tolerating the study medication, this visit may be completed by phone. At the investigator's discretion (eg, to further assess an adverse event), this visit may instead be conducted in the clinic.

The following will be completed at this visit:

Review adverse events, the daily pain and sleep diary, the dosing diary, concomitant medications, and non-drug treatments. Confirm that the patient is taking one study medication capsule twice daily from the correct bottle. Remind the patient to continue completing diaries until the next scheduled visit.

Determine and discuss the pregabalin dose level to be administered and provide instructions for dose administration. This dose level should be taken at the next scheduled dose. Blinding must be maintained with the patient.

Schedule a Phone visit for Visit 5 (Day 28).

6.2.4. Visit 5 (Day 28) – Phone Visit

If the subject is tolerating the study medication, this visit may be completed by phone. At the investigator's discretion (eg, to further assess an adverse event), this visit may instead be conducted in the clinic.

The following will be completed at this visit:

Review adverse events, the daily pain and sleep diary, the dosing diary, concomitant medications, and non-drug treatments. Confirm that the patient is taking one study medication capsule twice daily from the correct bottle. Remind the patient to continue completing diaries until the next scheduled visit.

Determine and discuss the pregabalin dose level to be administered and provide instructions for dose administration. This dose level should be taken at the next scheduled dose. Blinding must be maintained with the patient.

Schedule a clinic visit for Visit 6 (Day 56). Remind the patient to bring the study medication (used and unused packages) with them to the clinic visit.

6.2.5. Visit 6 (Day 56) – Clinic Visit

Review adverse events, the daily pain and sleep diary, the dosing diary, concomitant medications, and non-drug treatments. Remind the patient to continue completing diaries until the next scheduled visit.

The C-SSRS will be completed by the patient and reviewed to determine if a risk assessment is required.

Perform the following assessments: NPSI, SFN-SIQ, BPI-SF, and EQ-5D

Determine from the IVRS system whether the patient meets the pain improvement criterion to be randomized into the withdrawal Phase of the study. If the patient meets response criteria, the patient continues in the study and is to be randomized at this visit. Blinding is to be maintained.

6.2.5.1. Discontinuation

- Patients discontinuing from the study will complete a taper. Dispense a bottle of taper medication to the patient and schedule a Follow-Up phone visit.

6.2.5.2. Randomization

- If the patient meets response criteria, the patient should not be informed that randomization will occur or that a treatment change may occur at this visit. The following procedures are to be performed for patients
- Randomize the patient. Dispense study medication and provide instructions for dose administration. Instruct the patient as to study medication instructions, and to continue to take one capsule twice times daily as directed. Remind the patient to bring the study medication (used and unused packages) with them to the next clinic visit.
- Remind the patient to continue completing diaries until the next scheduled visit.
- Schedule a clinic visit for Visit 7 (Week 14).

6.2.6. Visits 7 (at Weeks 14) – Clinic Visits

- Review adverse events, the daily pain and sleep diary, the dosing diary, concomitant medications, and non-drug treatments. Confirm that the patient is taking one study medication capsule twice daily. Remind the patient to continue completing diaries daily.
- The C-SSRS will be completed by the patient and reviewed to determine if a risk assessment is required.
- Perform the following assessments: SFN-SIQ questionnaire, BPI-SF, and EQ-5D
- Dispense a bottle of taper medication to the patient and provide instructions for dose administration.
- Schedule a follow-Up phone visit.

6.3. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. 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 subjects to return all unused investigational product(s), request the subjects to return for a final visit, if applicable and follow-up with the subject regarding any unresolved adverse events.

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

7. ASSESSMENTS

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

7.1. Intra-epidermal Nerve Fiber (IENF) Biopsy

Skin biopsies will be obtained during the screening period. One 3-mm punch skin biopsy will be obtained from the distal-leg, approximately 10 cm proximal to the malleolus. And one biopsy from the proximal thigh (10 cm distal to the greater trochanter in the mid-axillary line. The biopsy sites will be prepped with alcohol and a subcutaneous wheal of 2% lidocaine with epinephrine will be subcutaneously injected using an insulin syringe for the purpose of anesthesia. Biopsies will be obtained at a depth of ~2 mm using disposable skin punches (Acuderm, Fort Lauderdale, FL). The tissue will be placed immediately into 2-3 ml of fixative for approximately 12-24 hours and then transferred to cryoprotectant solution. Samples will then be shipped overnight to the Johns Hopkins Cutaneous Nerve Laboratory.

Hemostasis at the biopsy site may be accomplished by local pressure. In very rare instances, Gelfoam can be applied to the biopsy site in order to stop any bleeding. A sterile adhesive Band-Aid is placed over the biopsy site. The bandage should be replaced daily until a scab forms. An antibacterial cream, such as Neosporin should only be used if the subject has successfully used them before without any local irritation. It is normal for the biopsy site to develop mild erythema along the border of the incision though this typically does not extend more than 1-2mm. The biopsy site should never express puss. Infections are rare (about 1:500), and should be evaluated and treated on an individual basis.

7.2. Efficacy Assessments

7.2.1. Daily IVRS Diary

The daily diary, comprising the daily pain NRS and the SIRS is to be completed daily by IVRS, every evening, from Visit 1 until study completion.

The daily diary assessments obtained via IVRS during the 7 days between Visit 1 and Visit 2 will be used to determine subject eligibility into the trial. A minimum of 4 days of daily diaries between Visits 1 and 2 must be completed for a subject to be considered compliant.

7.2.1.1. Primary Efficacy Parameter: Daily Pain

The Daily Pain scores will be assessed on an 11-point numerical rating scale (NRS-Pain) ranging from 0 (no pain) to 10 (worst possible pain). Subjects are to describe their pain during the past 24 hours by choosing the appropriate number between 0 and 10. A rating of 1-3 is considered mild pain; 4-6, moderate pain; and 7-10, severe pain. The NRS-Pain is included in the subject electronic diary and self-assessment will be completed twice daily upon awakening and in the evening. Subjects will complete an NRS Pain assessment for 2 questions: Average pain and Current pain, for each day. Average pain and Current pain will be asked in the evening, and Current pain will also be asked in the morning upon awakening. Subjects should be trained to use the electronic diary during Visit 2 to confirm subjects are comfortable with the electronic diary and are familiar with the protocol anchors. The site should document in source notes that the subject was able to rate themselves with the electronic diary successfully in the clinic and agrees to complete all diary ratings at the

times specified prior to being randomized. The NRS-Pain will be completed by daily diary (twice per day) starting at Visit 2 until the completion of the study.

Daily IVRS diaries will be completed by the subject from the evening of Visit 1/Screening through Visit 10 /Termination.

At Screening only, subjects will be asked to rate their “pain during the past week” on a similar 11 point scale. This will be completed on paper for screening only.

7.2.1.2. Secondary Efficacy Assessment: Sleep Interference Rating Scale (SIRS)

The Daily Sleep Interference Rating Scale (SIRS) consists of an 11-point NRS ranging from 0 (“pain does not interfere with sleep”) to 10 (“pain completely interferes with sleep” [unable to sleep due to pain]). Subjects describe how pain has interfered with their sleep during the past 24 hours:

Select the number that best describes how your neuropathic pain has interfered with your sleep during the past 24 hours on a scale from 0 to 10 where 0 represents ‘does not interfere with sleep’ and 10 represents ‘completely interferes which means you are unable to sleep due to pain.

Daily IVRS diaries will be completed by the subject from the evening of Visit 1/Screening through Termination.

7.3. Other Assessments

7.3.1. Small Fiber Neuropathy – Symptom Inventory Questionnaire (SFN-SIQ)

The SFN-SIQ has been developed specifically for evaluation of autonomic symptoms in SFN patients. It includes 13 questions that address the following aspects: presence of palpitations,

flushes, constipation or diarrhea, urination problems (incontinence or hesitation), changes in sweating pattern, restless legs, orthostatic dizziness, dry eyes or mouth, oversensitivity and intolerance to sheets on legs and burning feet. Responses are graded as “never”, “sometimes”, “often” or “always”.

7.3.2. Brief Pain Inventory-Short Form (BPI-sf)

The Brief Pain Inventory-Short Form (BPI-sf) is a self-administered questionnaire developed to assess pain severity and pain interference with functional activities during a 24 hour period prior to evaluation. Four questions assess pain severity on an 11-point scale ranging from “no pain” (0) to “pain as bad as you can imagine” (10): worst pain in the past 24 hours, least pain in the past 24 hours, average pain in the past 24 hours and current pain (“right now”). Seven items assess pain interference with functional activities: general activity, mood, walking ability, normal work (includes both work outside the home and housework), relations with other people, sleep and enjoyment of life. These items are also measured on an 11-point scale, ranging from “does not interfere” (0) to “completely interferes” (10). The Brief Pain Inventory-Short Form will be completed by the subject at all scheduled face to face visits.

7.3.3. Sleep Score from the Daily Sleep Diary (NRS-Sleep)

Pain-related sleep interference will be assessed on an 11-point numerical rating scale

(NRS Sleep) ranging from 0 (did not interfere with sleep) to 10 (completely interfered [unable to sleep due to pain]). Subjects are to describe how their pain has interfered with their sleep during the past 24 hours by choosing the appropriate number between 0 and 10. The NRS-Sleep is included in the subject electronic diary and self-assessment will be performed daily upon awakening from baseline to the end of the study.

7.3.4. Patient Global Impression of Change (PGIC)

The PGIC is a subject rated global measure that provides a clinically relevant and easy to interpret account of a patient’s perception of the clinical importance of their improvement or worsening during their involvement in a clinical study. Subjects rate their overall improvement on a 7-point scale where scores range from 1 (very much improved) to 7 (very much worse).

The PGIC is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) as a measure of “participant rating of global improvement and satisfaction with treatment.” It is one of six core outcomes measures recommended for use in clinical trials of chronic pain treatment efficacy and effectiveness. The PGIC will be completed by the subject at Visits 5 and 6. Completion instructions for subjects will indicate that global improvement refers to the condition under study.

7.3.5. EuroQol-5D (EQ-5D)

The EQ-5D is a brief health status measure used in clinical and health economic appraisals (The EuroQol Group, 1990). The EQ-5D comprises of 5 items that assess the level of difficulty (none, some, severe) subjects report in 5 health status domains: mobility, self-care, usual

activities, pain/discomfort and anxiety/depression. The EQ-5D also includes a visual analogue scale that rates the patient's current perception of overall health status that is scored from 0 (worst imaginable health state) to 100 (best imaginable health state). It takes approximately 2-5 minutes to complete.

7.3.6. Proteomics, Lipidomics and Metabolomics analysis

Proteomics and Lipidomics are large scale study of proteins and lipids in biological systems. These techniques are being extensively used to determine biomarkers of the disease, as well predictors of the response to treatment. Metabolomics is the scientific study of chemical processes involving metabolites. Specifically, metabolomics is the systematic study of the unique chemical fingerprints that specific cellular processes leave behind by studying their small-molecule metabolite profiles. The metabolome represents the collection of all metabolites in a biological cell, tissue, organ or organism, which are the end products of cellular processes. Thus, while proteomic analyses do not tell the whole story of what might be happening in a cell, metabolic profiling can give an instantaneous snapshot of the physiology of that cell. By using these methods, we hope to find biomarkers of idiopathic small fiber neuropathy, as well as predictors of response to treatment.

7.4. Safety Assessments

7.4.1. Laboratory Assessments

- Samples for laboratory testing will be analyzed by laboratory.
- Tests required at Visit 1 are:
- Hematology: hemoglobin, hematocrit, WBC count including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count, platelet count.
- Chemistry: amylase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase, blood urea nitrogen, creatinine, electrolytes (sodium, potassium, chloride, calcium), glucose, total protein, total bilirubin, uric acid,
- Fasting plasma glucose and HbA1C
- A standard 3-mm dermatologic punch biopsy for intraepidermal small fiber nerve assessment if not done previously
- Thyroid-stimulating hormone (TSH) with reflex T4 done if TSH abnormal,
- B12/Folate.
- HIV Elisa (confirm with Western Blot if positive)
- Hep C Ab
- SED rate (ESR)
- RPR or similar test for syphilis

- CLcr will be estimated from creatinine at baseline using the Cockcroft and Gault equation:

$$CLcr = \frac{[(140 - \text{age (years)}) \times \text{weight (kg)}]}{[72 \times \text{Serum creatinine (mg/dl)}]} \quad (\times 0.85 \text{ for female patients})$$

SI Units:

$$CLcr = \frac{[1.23 \times [(140 - \text{age (years)}) \times \text{weight (kg)}]]}{\text{Serum creatinine } (\mu\text{moles/l})} \quad (\times 0.85 \text{ for female patients})$$

- Monitoring for Hy's Law (Drug-Induced Hepatotoxicity)

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

7.4.2. Physical and Neurological Examination

Physical examinations at Screening/Visit 1 and every clinic visit afterwards will include the following:

- General appearance (including height at baseline).
- Skin (examination for the presence of rash).
- HEENT (examination of head, eyes, ears, nose, and throat).
- Chest (auscultation of lung fields).
- Cardiovascular (auscultation of heart sounds [S₁ and S₂] and for the presence of murmurs, gallops, or rubs).
- Gastrointestinal (abdominal rigidity and tenderness).
- Edema assessment (severity of any peripheral edema, presence of generalized/abdominal edema or facial/periorbital edema).

Additional physical assessments may be performed as necessary to evaluate subjects. Any clinically significant negative changes from the entry examination should be recorded as an adverse event.

7.4.3. Neurological Examination

Neurological exam (including examination of mental status, motor function, sensory function, coordination) will be conducted at Screening (Visit 1) and end of study or in the event of early termination ET.

As part of the neurological exam a specific neuropathic pain assessment is to be conducted to assess eligibility for the study.

Patients will be assessed for the following:

- Mental status exam for short term memory, alertness, orientation, ability to do simple calculations and serial 7's, demonstrates comprehension of the concept of a numerical rating scale for pain severity.
 - Burning, stabbing or tingling sensation/pain in the feet
 - Numbness
 - Increased or decreased temperature sensation
 - Self-report of hypersensitivity to touch, heat, or cold
 - Pin prick perception in feet and legs
 - Increased or decreased sharp sensation (eg, pinprick testing);
 - Position sense for big toe
 - Vibratory sensation with 128 Hz tuning for at large toe;
 - Reflexes: patellar, biceps, and Achilles
 - Motor strength for toe dorsiflexion, and any evidence of muscle wasting in legs or arms
- Screening only: Complete and submit a copy of the neuropathic pain eligibility worksheets. The neuropathic pain eligibility worksheet should be kept in the subject's source documentation.
 - For quality assurance purposes, Pfizer, or its designated representative, may review and validate subject eligibility based on the Screening neurological examination and neuropathic pain assessment, painDETECT, skin biopsy results, and worksheets. Subjects may be deemed eligible or ineligible based upon this review.
 - painDETECT: painDETECT is a questionnaire that was developed to detect neuropathic components of pain. Exploratory analyses of efficacy results will be conducted based on painDetect scores at Screening (Visit 1). The painDETECT will also assist the clinician in confirming that the patient has a symptom profile that is consistent with small fiber neuropathy though no specific score is required for inclusion.

7.4.4. Vital Signs

Vital signs (sitting heart rate and blood pressure, weight; height at Screening only) will be obtained at Screening visit and every clinic visit afterwards.

7.5. Suicidality Assessment

7.5.1. 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). The PHQ-8, a validated subset of the PHQ-9 (the first 8 items of the PHQ-9) will be completed by subjects at Screening (Visit 1).

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

This semi-structured interview was originally developed to evaluate the link between antidepressants and suicidal behavior and ideation in youth, adverse events from pediatric clinical trials. C-SSRS is utilized in current study to provide a summary measure of suicidal risks.

7.5.2.1. Risk Assessment During Screening

The Investigator will review the results of the C-SSRS (baseline), and medical history. The following criteria would indicate a potential suicide risk:

- The subject may have had suicidal ideation associated with actual intent and/or plan in the past year based on C-SSRS assessment.

Note: in an event a suicidal ideation is identified in baseline C-SSRS, the Investigator should inquire the timeframe of the event and determine whether it occurred during the past year.

- Any previous lifetime history of suicide behaviors based on C-SSRS assessment.
- Investigator's judgment that a risk assessment is required.

If any of these criteria are met the subject is considered not eligible to participate in the trial.

Beginning with Visit 2, if there are any positive responses on C-SSRS (since last visit), a risk assessment should be done by a qualified mental health provider. Suicidal risk should be managed appropriately by the Investigator together with a qualified MHP. In addition, the Investigator should consult with the Pfizer medical monitor to determine whether the subject can continue the trial.

A suicidal narrative should be constructed for subjects who have undergone any post-baseline risk assessment, using information from the C-SSRS and should be kept as a source document.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

8.2. Reporting Period

For serious adverse events, the 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. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

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

8.3. Definition of an Adverse Event

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

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

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

- Drug overdose;

- Drug withdrawal;
- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Exposure during pregnancy;
- Exposure during breast feeding.

8.4. Abnormal Test Findings

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

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

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

8.5. Serious Adverse Events

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

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

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

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

8.5.1. Potential Cases of Drug-Induced Liver Injury

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

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

- A. *Subjects with AST or ALT baseline values within the normal range* who subsequently present with AST or ALT ≥ 3 times the upper limit of normal concurrent with a total bilirubin ≥ 2 times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the upper limit of normal or not available.
- B. *Subjects with pre-existing AST or ALT baseline values above the normal range* who subsequently present with AST or ALT ≥ 2 times the baseline values and ≥ 3 times the upper limit of normal, or ≥ 8 times the upper limit of normal (whichever is smaller) concurrent with a total bilirubin of ≥ 2 times the upper limit of normal and increased by one upper limit of normal over baseline or > 3 times the upper limit of normal (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times the upper limit of normal or not available.

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 and for oncology studies, the possibility of hepatic neoplasia (primary or secondary) should be considered). In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), international normalized ratio (INR) and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting criteria A or B, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

8.6. Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to

an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

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

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

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

8.7. Severity Assessment

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

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

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

8.8. Causality Assessment

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

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

8.9. Withdrawal Due to Adverse Events

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

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

8.10. Eliciting Adverse Event Information

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

8.11. Reporting Requirements

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

8.11.1. Serious Adverse Event Reporting Requirements

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

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

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

8.11.2. Non-Serious Adverse Event Reporting Requirements

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

8.11.3. Sponsor Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

The study is designed to provide 90% power to detect a difference of at least 1.1 (a clinically meaningful difference) in the pain severity score from baseline between pregabalin-treated

subjects and placebo at an alpha level of 0.05, a tolerance for type II error set at beta 0.10, and a common SD of 2. This requires 20 patients in each group for a total of 40 patients.

9.1.1. Analysis of Primary Endpoint

- To evaluate efficacy, we will compare the endpoint mean pain score for the Lyrica group compared to the placebo group using an analysis of covariance (ANCOVA) model with treatment and center as main effects and the baseline PI score as a covariate.
- A BOCF and a modified or hybrid approach (mBOCF) will be used to account for missing data at last treatment Week. As a sensitivity we will look at the LOCF, MMRM and the missing imputation (suggested the National Academy of Sciences report).

9.1.2. Analysis of Secondary Endpoints

Secondary analyses included examination of the PGIC and sleep interference rate will be compared between treatment groups using a Cochran-Mantel-Haenszel test.

9.2. Safety Analysis

Safety data will be presented separately for both single-blind and double-blind phases of the study. Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The study site may be subject to review by the Institutional Review Board (IRB). It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

11.2. Record Retention

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

12. ETHICS

12.1. Institutional Review Board (IRB)

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

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

12.2. Ethical Conduct of the Study

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

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

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

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

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

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

13. DEFINITION OF END OF TRIAL

End of Trial is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the protocol.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB, drug safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 2 weeks. All study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Results will be publicly disclose through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov).

For all publications relating to the Study, investigator 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.

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APPENDIX 1. SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments for detailed information on each procedure and assessment required for compliance with the protocol.

Study Phase:	Baseline (V1 to V2)	Single-Blind Treatment Phase (8 weeks)					Randomized Withdrawal Phase (4 weeks)
Clinic Visit No.:	V1 ^{a,e}	V2 ^{a,c}	V3	V4	V5	V6	V7
Visit:	Screening	Enrollment	Wk 1	Wk2	Wk 4	Wk 8	Wk 12
Study Day:	-30 to -14	0	7	14	28	56	84
Visit Type:	Clinic	Clinic	Phone	Phone	Phone	Clinic	Clinic
Visit Window:	N/A	7 - 21 days	±2 days	±2 days	±2 days	±3 days	±3 days
Observation/Procedure							
Informed consent ^b	X						
Inclusion/Exclusion	X	X					
Medical History	X						
Physical exam/Neurological exam	X						X
Vital Signs ^e	X	X					X
Clinical labs	X						
Retained blood sample for proteomics, etc.	X						
IENF biopsy	X						
PainDETECT	X						
PHQ-8	X						
Suicidality Assessment (C-SSRS)	X	X				X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant/Rescue medications ^f	X	X	X	X	X	X	X
Study medication dispensing		X				X	X
NPSI		X				X	X

Study Phase:	Baseline	Single-Blind Treatment Phase					Randomized Withdrawal
	(V1 to V2)	(8 weeks)					Phase (4 weeks)
SFN-SIQ		X				X	X
Numeric Rating Scale for Pain (NRS-Pain - 1 week recall)	X						
IVRS Daily Diary, (Pain NRS and SIRS)	X	X	X	X	X	X	X
Brief Pain Inventory - short form (BPI-sf)	X	X				X	X
EuroQOL 5-Dimensions (EQ-5D)		X				X	X
Patient Global Impression of Change (PGIC)						X	X

- a Visit 1 may occur between 30 days and 14 days prior to Visit 2, based on the amount of time required for screening procedures such as punch biopsy or washout period for previous pain medications. The screening visit may also be split into two visits. A 14-day minimum baseline between Visit 1 and Visit 2 is required to establish baseline pain level. The maximum 30-day screening period does not include prior completion of the informed consent.
- b Informed consent must be completed prior to performing any other study procedures, including any medication changes made to participate in the study. Any such medication changes must be considered for medical appropriateness to protect patient well-being.
- c V2 is the Single-blind Baseline visit (enrollment).
- d V6 is the final visit of the single-blind phase and also the randomization visit for subjects who are eligible to continue in the withdrawal phase.
- e Includes weight, blood pressure, and pulse at all clinic visits, and height at Visit 1 only.
- f Rescue medications may NOT be taken within the 2 hours prior to daily diary completion

APPENDIX 2. Dose Assessment and Adjustment

Visit	Days	Response/Assessment	Action	Bottle
V2	0-7	--	Start 150 mg/day pregabalin/placebo (75 mg BID):	Bottle A
V3	7-14	Subject tolerates 150 mg/day well	Increase dose to 300 mg/day pregabalin/placebo (150 mg BID)	Bottle B
		In investigator's judgement, dose should not be increased based tolerability (ie, subject has pregabalin associated adverse events that clinically preclude dose increase	Remain at 150 mg/day pregabalin/placebo	Continue with Bottle A
V4	14-28	Subject tolerates 300 mg/day well	If at 300 mg/day pregabalin/placebo, increase dose to 450 mg/day.	If at Bottle B, proceed to Bottle C
		Subject tolerates 150 mg/day	If still at 150 mg/day pregabalin/placebo, increase dose to 300 mg/day.	If at Bottle A, proceed to Bottle B
		In investigator's judgement, dose should not be increased based tolerability (ie, subject has pregabalin associated adverse events that clinically precludes dose increase	Remain at current dose pregabalin/placebo.	Maintain current bottle and dosing
		Not acceptable tolerability while receiving 300 mg/day	Reduce to 150 mg/day pregabalin/placebo.	Return to Bottle A
V5	28	Acceptable tolerability	Remain at current dose level; no further changes.	Maintain current bottle and dosing
		Not acceptable while receiving current dose	Reduce dose 1 level	
V6		Acceptable tolerability	Remain at current dose level; no further changes	Maintain current bottle and dosing
		Not acceptable while receiving current dose	Reduce dose 1 level	

APPENDIX 3. Study Medication Taper Schedule

Pregabalin Dose	Taper Day 1 (mg/day)	Taper Day 2 (mg/day)	Taper Day 3 (mg/day)	Taper Day 4 (mg/day)	Taper Day 5 (mg/day)	Taper Day 6 (mg/day)	Taper Day 7 (mg/day)
150 mg	150	150	150	150	50	50	50
300 mg	150	150	150	150	50	50	50
450 mg	300	300	300	300	150	150	150
600 mg	300	300	300	300	150	150	150