A Randomized, double-blind, Placebo controlled, Multi-center, Phase III Clinical Trial to evaluate the Efficacy of Lamotrigine in the Management of Chemotherapy Induced Peripheral Neuropathy

Study Chair:

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SYNOPSIS

Study Title

Lamotrigine, an anti-epileptic agent, has been reported as being effective in reducing symptoms of neuropathy associated with various etiologies. Based on such data, a multi-center , double-blind , placebo controlled, randomized trial will be conducted to evaluate the effect of lamotrigine on pain and other neuropathic symptoms due to chemotherapy induced peripheral neuropathy (CIPN).

Objectives

Primary objective:

Improvement of pain due to neuronal damage during chemotherapy using the Numerical Rating Scale (NRS) of pain.

Secondary objectives:

Improvement of other chemotherapy induced neuropathic symptoms using the TNS (Total Neuropathy Score) , improvement of overall quality of life using the EORTC QLQ-CIPN20.

Design, Outcomes, Interventions and Duration

The study will employ a randomized , double-blind, placebo controlled design. Eligible patients will be randomly treated with lamotrigine (target dose of 300 mg , based on published data) versus an identical appearing placebo. Patients will be started on a placebo or lamotrigine at dose of 25 mg at bed time for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks , then 100 mg twice daily for 2 weeks and then the dose will be escalated to 150 mg twice daily, at which time therapy will continue for 12 weeks. Dose escalation will be continued per this schedule to allow each patient to reach his/her tolerated dose. After a total of 22 weeks of therapy from the time of drug initiation patients will be tapered off this drug / placebo over a 4-week period. If a patient wishes to stop sooner for any reason before 22 weeks , he/she will be encouraged to taper the drug over a 4-week period rather than discontinuing therapy abruptly.

For eligible patients baseline NRS (primary outcome) , TNS and QLQ-CIPN20 (secondary outcomes) scores will be obtained . These primary and secondary outcomes, as well as adverse events, will be assessed weekly over a 22-week period.

At the end of the 22 weeks of therapy symptom severity and adverse events will be compared with the baseline in both the lamotrigine and placebo arms respectively.

Study duration for each patient will be 26 weeks (24 weeks of therapy with lamotrigine or placebo and additional 4 weeks of tapering off the drug / placebo) and for each center participating in the study 52 weeks (28 weeks for subject enrollment and 24 weeks for every patient).

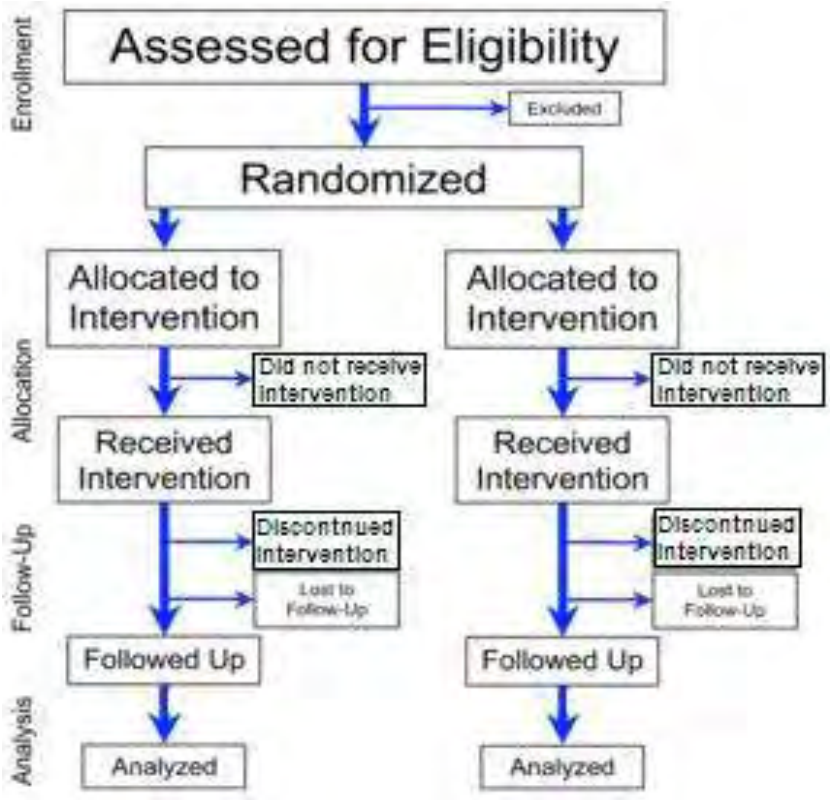
Sample size and population

Adult patients with symptomatic CIPN $\geq$ 1 month duration because of neurotoxic chemotherapy with taxanes, platinum compounds, vinca alkaloids, proteasome inhibitors or combination of them will be eligible. To be eligible , patients have to report having 'average' daily pain severe enough to have either 1) a rating of ≥ 4 in the NRS or 2) > 1 in the TNS . Serum creatinine $\leq 1{,}5$ times the upper limit of normal and an estimated life expectancy of ≥ 6 months will be required.

Patients will be stratified by type of neurotoxic chemotherapeutic agents (taxanes vs platinum compounds vs vinca alkaloids vs proteasome inhibitors vs combination of 2 or more of the previous agents) , age and whether the patient is enrolled during chemotherapy vs after completion of therapy.

The study will have 60 patients in each arm (a total of 120 patients) in order to provide 80% power.

The study's flowchart is depicted in the following diagram:



Picture 1. Study design

1. STUDY OBJECTIVES

1.1 Primary objective

The study's primary objective is to evaluate the efficacy of oral lamotrigine twice daily up to a maximum dose of 300 mg for 24 weeks in reducing the 'average' daily NRS pain score in patients suffering from CIPN.

1.2 Secondary objectives

The study's secondary objectives are the decline of the TNS score and the improvement of the patients' overall quality of life according to the QLQ-CIPN20 at the end of a 24-week period of therapy with oral lamotrigine .

2. BACKGROUND

2.1 Rationale

Adult patients with symptomatic CIPN ≥ 1 month duration, because of neurotoxic chemotherapy (ie, taxanes [paclitaxel and docetaxel] , platinum compounds [carboplatin, cisplatin, and oxaliplatin],vinca alkaloids [vincristine and vinblastine] and proteasome inhibitors (bortezomid)will be eligible.Patients who will be currently receiving chemotherapy, as well as those who will have completed therapy at the time of study entry, will be eligible. To be eligible, patients have to report having 'average' daily pain severe enough to have either 1) a rating of 4 using the Numerical Rating Scale (NRS: 0 = no pain and 10 = worst pain possible), or 2) >1 using the TNS score. Serum creatinine 1.5 times the upper limit of normal and an estimated life expectancy of 6 months will be required. Patients will be ineligible if they have preexisting symptomatic neuropathy because of other causes (eg, radiation or malignant plexopathy, lumbar or cervical radiculopathy, vitamin B12 deficiency or diabetes), or if they are pregnant or lactating. Patients using the following agents at baseline will be ineligible: antidepressants, opioids, adjuvant analgesic agents (eg, anticonvulsants, clonazepam, or mexelitine), topical analgesics, and amifostine (although therapy with any of these agents can be initiated after study entry, if necessary). The use of NSAIDs will be permitted. Lamotrigine is an antiepileptic agent that is reported to inhibit the function of neuronal sodium channels in a concentration-dependent and voltage-dependent manner, decreasing the release of excitatory neurotransmitters, especially glutamate and aspartate. Lamotrigine has been suggested as potentially useful agent for treating pain in neuropathic syndromes,based on the observation that increased activity of sodium channels appears to be the basis for hyperalgesia (eg, as suggested by the benefit of sodium channel inhibitors such as lidocaine on raising the pain threshold).

In normal volunteers lamotrigine has been demonstrated to raise the threshold to cold-induced pain compared with placebo.At the time this study is designed,data are available to suggest a role for lamotrigine in the therapy of pain from a variety of etiologies, including painful diabetic neuropathy, central poststroke pain, human immunodeficiency virus (HIV)-associated neuropathy and trigeminal neuralgia. In addition to these data, local anecdotal experience of using lamotrigine to treat patients with CIPN suggested that some patients appeared to benefit with such therapy, with a reduction in pain and other symptoms (such as numbness and tingling). Based on these preliminary data, a phase 3 randomized placebo-controlled study can be conducted to evaluate the efficacy of lamotrigine in treating pain and other neuropathic symptoms resulting from chemotherapy exposure.

Currently available therapy options for CIPN (eg, opioids or nonsteroidal antiinflammatory drugs [NSAIDs]) are suboptimal because they are only minimally effective in relieving symptoms (pain and discomfort) of CIPN and/or result in significant adverse events.Tricyclic antidepressants and antiepileptics (eg, gabapentin) are often utilized in clinical practice to treat CIPN; however, clinical trials evaluating the benefits of such therapies for therapy or

prophylaxis of CIPN do not support such use. Beside bone marrow suppression and renal toxicity the neurotoxic side-effects of the most common chemotherapeutic agents are very often the reason for stopping the anti-tumour therapy or changing the dose regimen, leading to compromised treatment and therefore reduction of the survival rate.

2.2 Supporting Data

CIPN

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting toxicity of several chemotherapeutics used in the treatment of all the most common malignancies. There are several defined mechanisms of nerve damage that take place along different areas of the peripheral and the central nervous system.[1] It is the most common neurologic complication of cancer treatment, particularly with the use of platinum-derived agents, taxanes, vinca alkaloids and proteasome inhibitors which are first-line agents in the treatment of solid tumors[2]. Chemotherapy regimens that utilize combination therapy may potentiate the sequela of neuropathy through agents that produce nerve damage via different mechanisms of action. Initial presentation begins with decreased vibration sense in the toes and loss of the ankle jerk reflex. Further, neuropathy may present as sensory deficits, loss of motor function and pain due to damage that occurs at multiple locations along the peripheral and central nervous system.It is estimated that up to 90% (60-90 %) of all cancer patients treated with chemotherapy will be affected by chemotherapy-induced peripheral neuropathy[3], [4] By example, the development of neuropathy is the most common reason for altering a platinum-based chemotherapy regimen, either by decreasing dose and frequency or by selecting a different therapeutic agent[5]. Depending on the chemotherapy regimen, chemotherapy-induced painful peripheral neuropathy may self-resolve in weeks or persist for years[6-8].Studies on the pathophysiology of chemotherapy induced peripheral neuropathy suggest anatomical and/or functional changes of intraepidermal nerve fibers, primary sensory neurons, CNS neurons,and involvement of glial and immune cells.

Commonly used CIPN-inducing chemotherapy agents are shown in the following table:

Table 1. Commonly used CIPN-inducing chemotherapy agents [10]

Classification	Agent	Type of nerve damage
Platinum-based compounds	Cisplatin Carboplatin Oxaliplatin	Sensory
Vinca alkaloids	Vincristine Vindesine Vinblastine Vinorelbine	Sensory and Motor
Taxanes	Paclitaxel Docetaxel	Sensory and Motor
Proteasome inhibitors	Bortezomid	Sensory

Basic science research has demonstrated chemotherapy-induced nerve damage both at the level of the peripheral and the central nervous system.Penetration of chemotherapeutic agents into the central nervous system is relatively poor, whereas high levels have been found to accumulate within the dorsal root ganglia (DRG) and peripheral nerves[11].
Activation of innate immunity in the DRG as a consequence of chemotherapy treatment appears to be a key early event in the initiation of CIPN[1],[12],[13].The DRG of peripheral nerves are susceptible to disruption at many points, including sodium, calcium, and potassium ion channels,glutamate-activated N-methyl-D-aspartate (NMDA) receptors, and mitochondria.The expression of numerous ion channels in DRG neurons are altered following chemotherapy treatment[14]. Activation of ion channels triggers changes in intracellular calcium that leads to the release of free radicals that subsequently induce neuropathic pain.Mitochondrial damage also increases permeability to and release of intracellular calcium, which causes activation of protein kinase C,phosphorylation of transient receptor potential vanilloid (TRPV), activation of capases and calpains, and the release of nitric oxide and free radicals.The end result is cytotoxic to axons and neuronal cell bodies[15].The alpha-2-delta-1 subunits of calcium channels of the DRG and dorsal horn are upregulated by paclitaxel and vincristine. Increased cytosolic calcium is present due to the release from extracellular and intracellular stores of mitochondria[16-18]. Paclitaxel, vincristine and oxaliplatin increase the Na+ current in the DRG which accounts for the paresthesias and fasciculations associated with neuropathy[19-21].There is decreased expression of mechano-gated and temperature-sensitive potassium channels (TREK 1, TRAAK types) in the presence of oxaliplatin and increased expression of pro-excitatory channels such as the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels[22].
At the mitochondrial level, paclitaxel, vincristine, cisplatin, and bortezomib cause swelling and vasculization within the peripheral nerve axon, which increases permeability to and leakage of intracellular calcium. This in turn activates a caspase-mediated apoptotic pathway, leading to neuronal cell death[23-25]. By increasing cytosolic calcium,oxaliplatin, paclitaxel, vincristine, and bortezomib also increase free radicals in DRG cells[26-28].

Neuronal apoptosis is also initiated by the activation of calcium-dependent proteases, calpains and caspases in DRG cells in the presence of paclitaxel, vincristine, and oxaliplatin[29,30].
The transient receptor potential vanilloids (TRPVs) act as transducers of thermal and chemical stimuli in pain-sensing neurons. Cisplatin,oxaliplatin, and paclitaxel upregulate TRPV1 and transient receptor potential (TRP) ion channels of the subgroups TRPA1 (transient receptor potential cation channel, subfamily A, member 1), TRPM8 (transient receptor potential cation channel, subfamily M (menthol), member8 and TRPV4 in the DRG neurons causing nociceptor hyperexcitability[31-33]. Substance P and calcitonin gene-related peptide (CGRP) are neurotransmitters that relay pain signals and these are increased inDRG neurons by paclitaxel and cisplatin[34,35]. Vincristine increases the 5-hydroxytryptamine 2A receptors of 5-hydroxytryptamine on the DRG neurons and dorsal horn of the spinal cord thereby sensitizing spinal dorsal horn neurons and peripheral nociceptive fibers[36,37].
The platinum-based chemotherapy agents (oxaliplatin, cisplatin,carboplatin) bind to DNA strands thereby inducing apoptotic cell death, particularly within the cell bodies of the DRG. Oxaliplatin leads to chronic neuropathy by damaging DNA and by altering the function

of voltage-gated sodium channels in the peripheral nerves[38,39]. Of the platinumagents, carboplatin is the least likely to produce significant neuropathy. Cisplatin has been found to accumulate in the DRG and peripheral nerves[11,40,41].Paclitaxel activates macrophages and microglia in the DRG, peripheral nerves and spinal cord. In addition it has been found to stabilize microtubules and decrease epidermal nerve fiber density. With large cumulative doses, paclitaxel can also affect motor nerves[42,43].

Assessment and grading of CIPN[44,45]:

Quantitative assessments of CIPN, such as nerve conduction velocity, vibration perception threshold and electromyography, have been applied in the clinical setting. However, some of these methods are invasive and uncomfortable for patients, others may lack diagnostic value and are costly in terms of time and resources.Of the many existing neuropathic pain scales, only a few actually assess the location of the pain, which is an important neurological clue. Other important diagnostic clues include the frequency of the pain, whether it is spontaneous or induced, the character of the pain in terms of the patient's actual reported symptoms and interference with the activities of daily living.

The National Cancer Institute Common Toxicity Criteria Evaluation (NCI-CTC) evaluation performed by experienced examiners has been shown to overestimate the occurrence of motor neuropathy, possibly due to the presence of confounding factors (e.g. fatigue, depression, cachexia), which is difficult to exclude without a formal neurological examination.In one prospective multi-centre study, 155 patients were treated with Cisplatin/Carboplatin or Paclitaxel/Docetaxel, and the neuropathy was examined using the NCI-CTC scale and the *Total Neuropathy Score (TNS).* The TNS was found to be able to detect and estimate the severity and the type of CIPN more accurately than the NCI-CTC score, and it has made it possible to identify misdiagnosed motor neuropathies. However, some limitations have been recognized. For instance, pain is not detected by the scale, although it can represent a severe feature in CIPN patients and this evaluation should be added in the clinical work up of these patients. Moreover, the presence of sensory or motor impairment in both arms and legs or only in legs does not imply a different score, as it depends only on the distal-to-proximal extension of the impairment . The full, reduced (TNSr), modified (mTNS) and clinical (TNSc) versions do not adequately assess CIPN-related pain severity . Some limited data favour the TNS's psychometric properties but further revision and testing of the tool are recommended.

Cavaletti *et al*. showed the reliability and effectiveness of the simplified TNSc for accurately grading and reporting CIPN in comparison with oncological grading scales; Although, the work may have been premature, the progress of TNS is chosen to be the secondary objective in the present study, while pain score will be separately measured with the NRS score as the primary outcome[44].

Treatment of CIPN

There is no effective CIPN prevention strategy, while treatment of established chronic CIPN is limited.Classes of medications utilized include anticonvulsants,antidepressants, opioids, non-opioid analgesics, and topicals.Anti-epileptic drugs (AEDs) are commonly utilized for non-epileptic conditions, including pain syndromes and neuropathic pain.

Lamotrigine [46-48]

Lamotrigine is a novel anti-epileptic agent with at least two anti-nociceptive properties: It stabilizes the neural membrane through blocking the activation of voltage-sensitive sodium channels , and inhibits the presynaptic release of glutamate. Lamotrigine is absorbed rapidly and completely from the gastrointestinal tract. It is approximately 55% bound to plasma proteins. The drug is extensively metabolized by conjugation with glucuronic acid. Lamotrigine elimination half-time is 25-30 hours.

Adverse reactions

The drug's adverse reactions are described in the following table:

Table 2 : Lamotrigine's adverse reactions

Body System	Frequent (≥ 1 %)	Infrequent (1%-0,1%)	Rare (< 0,1%)
Body as a whole	Ø	Allergic reaction, chills, and malaise	Ø
Cardiovascular	Ø	Flushing,hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation	Ø
Dermatological	Ø	Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, urticaria	Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma,multiforme erythema, petechial rash, pustular rash, Stevens-Johnson syndrome, vesiculobullous rash
Digestive	Ø	Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration	Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis,

			hemorrhagic colitis, hepatitis,melena, stomach ulcer, stomatitis, and tongue edema
Endocrine	Ø	Ø	Goiter and hypothyroidism
Hematologic and Lymphatic	Ø	Ecchymosis and leukopenia	Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia and thrombocytopenia
Musculoskeletal	Ø	Arthritis, leg cramps, myasthenia, twitching	Bursitis, muscle atrophy, pathological fracture, tendinous contracture
Nervous	Confusion, paresthesia	Akathisia,apathy, aphasia,CNS depression, depersonalization, dysarthria, dyskinesia, euphoria,hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, sleep disorder, stupor, suicidal ideation	Choreoathetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, faintness, grand mal convulsions, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, muscle spasm, neuralgia, neurosis, paralysis, peripheral neuritis
Respiratory	Ø	Yawn	Hiccup, hyperventilation
Urogenital	Ø	Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, urinary incontinence	Acute kidney failure, anorgasmia, breast abscess, breast neoplasm, creatinine increase, cystitis,dysuria, epididymitis, female lactation, kidney

			failure, kidney pain, nocturia, urinary retention, urinary urgency
Special senses	Amblyopia	Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion,tinnitus	Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, visual field defect
Metabolic and Nutritional Disorders	Ø	Aspartate transaminase increased.	Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema,gamma glutamyl transpeptidase increase

Dose escalation and therapy discontinuation[46,48]:

The use of lamotrigine has been limited by the risk of potentially life-threatening dermatological reactions, principally SJS and TEN. Risk factors for these reactions include rapid titration, concurrent VPA administration, prior history of anticonvulsant-associated rash, female sex and age less than 13 years. Since the introduction of a gradual titration schedule in 1994, the rate of severe rashes with lamotrigine has declined from 1% to 0.1–0.01%. Although the incidence was reduced ten-fold after small dose introduction and slow dose escalation, the incidence of the severe skin reaction (SJS, TEN and hypersensitivity syndrome) induced by lamotrigine is still possible. Therefore in the present study, a careful dose escalation as described above will be applied.

If a decision is made to discontinue therapy with lamotrigine, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal.

Drug interactions:

The apparent clearance of lamotrigine is affected by the coadministration of certain medications. The net effects of drug interactions with lamotrigine are summarized in table 3.

Table 3 : Drug Interactions with lamotrigine

Drug	Drug Plasma Concentration With Adjunctive lamotrigine	Lamotrigine Plasma Concentration With Adjunctive Drugs
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel)	↔	↓
Bupropion	Not assessed	↔

Carbamazepine (CBZ)	↔	↓
CBZ epoxide	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔
Oxcarbazepine	↔	↔
10-monohydroxyoxcarbazepine metabolite	↔	
Phenobarbital/primidone	↔	↓
Phenytoin (PHT)	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔	↔
Valproate	↓	↑
Valproate + PHT and/or CBZ	Not assessed	↔
Zonisamide	Not assessed	↔

Pregnancy and lactating:

There are no adequate and well-controlled studies in pregnant women suggesting any teratogenic effects of lamotrigine. Preliminary data indicate that lamotrigine passes into human milk. Because the effects onthe infant exposed to lamotrigine by this route are unknown, breastfeeding while taking lamotrigine is not recommended.

Review of literature[48,49]:

Oral lamotrigine 200mg daily is a well-tolerated and moderately effective treatment for central post-stroke pain and central pain. Trigeminal neuralgia is a chronic pain syndrome of still unestablished origin. Drug therapy initially helps a great majority of patients. Lamotrigine appears to be the most effective. Meta-analysis suggested combination carbamazepine with lamotrigine or baclofen is the second-line treatment when monotherapy fails, but the evidence is weak. Neuropathic pain and paroxysmal symptoms are common in Multiple Sclerosis (MS) patients, although no double-blind clinical trial has been conducted to support the use of anti-epileptic medications in MS. The principal neuropathic pain syndromes common in MS are trigeminal neuralgia and dysesthetic pain syndrome. Treatment is based on anti-epileptic medications acting on voltage-dependent sodium channels, such as carbamazepine and lamotrigine, or on tricyclic antidepressant. Lamotrigine is also used in preventing the cluster headache and in treating SUNCT(Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing)syndrome when used in high doses for a prolonged period of time, painful glossopharyngeal nerve, phantom limb pain and stump hypersensitivity, post-herpetic neuralgia and causalgia. It was well-tolerated nad effective in HIV- associated neuropathic pain in patients

receiving neurotoxic antiretroviral therapy and has demonstrated efficacy in relieving the pain associated with diabetic neuropathy. Finally , lamotrigine therapy is described in treatment of individuals or smaller groups of subjects such as the treatment of migraine-related vertigo, neuralgia after nerve section, spinal cord injury pain, postoperative analgesia and intractable sciatica.

Studies regarding lamotrigine in treatment of neuropathic pain are summarized in the following table:

Table 4: Lamotrigine in treatment of painful neuropathy[49].

Study (author, year)	Neuropathic pain	Conclusion- Effect of lamotrigine
Eisenberg et al, 1998	Diabetic neuropathy	Potentially effective
McCleane, 1999	Neuropathic pain	no effect
McCleane, 2000	Neuropathic pain	may be effective
Eisenberg et al, 2001	Diabetic neuropathy	effective
Vu, 2004	Neuropathic pain	first-line or adj. Therapy
Backonja and Serra, 2004	Neuropathic pain	first-line therapy
Singleton et al, 2005	Diabetic neuropathy	first-line therapy
Vinik et al, 2007	Diabetic neuropathy	effective
Coderre et al, 2007	Neuropathic pain	may reduce hyperalgesia
Chong and Hester, 2007	Diabetic neuropathy	effective

3. STUDY DESIGN

The present study is an open, double-blind , two – parallel groups (drug and placebo)randomized phase III clinical study to portray the efficacy of lamotrigine in reducing the NRS score and TNS score in patients who suffer from CIPN with a duration ≥ 1 month.The study duration for a single patient is 24 weeks and for the study center 52 weeks.

Serial number

At the time of the study enrollment, the patients will receive a unique coded identification number (serial number) by the investigator. This coded number will be formed by the number of the center in which the patient is recruited and the serial number the patient was assigned during the recruitment , eg 01, 02 , 03 etc. This unique serial number can not be reassigned to another patient once it has been assigned to a specific subject. If the patient does not finally participate in the study for any reason, the serial number will be recorded in the Patient Selection Record File along with the non-Participation reasons.

Randomization methods

A randomization list will be formed by or under the surveillance of the appointed statistician by a certified system which automatically randomly assigns patients to the two

treatment groups in a 1:1 ratio. The randomization program will be retested and secured after approval. T he patients' assignment to either of the two groups will be conducted by the appointed statistician and his/her team. The personnel who will be in contact with the patients and will perform all the study-related exams will have no access to the randomization program.

During the initial visit , the patients' randomization will be carried out according to the randomization number on the study's drug. The randomization number will be recorded in the patient's Case Report Form (CRF) and assigns him/her in one of the two study arms. The randomization numbers are consecutively assigned to the patients (no stratification is performed per center).

The randomization process will be conducted as following:A list of all numbers (patient 1 to patient 120) in ascending order will be created. Before the study initiation, a routine for random transpositions will be applied so that the list's elements are randomly transpositioned. The first half numbers will be assigned to lamotrigine and the second half will be assigned to placebo. All the selected patients will receive lamotrigine or placebo without the center's interferrence following the list's consecutive assignment. For example , the first patient will receive the drug respective to number 1 of the list, the second patient will receive the respective to number 2 of the list of drugs, etc.

Study drug and regimen design

The study drugs are lamotrigine (trade name " LAMICTAL ") tablets and placebo tablets. "LAMICTAL " has a specific and unique tablet form which is described below:

- 25 mg, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25"
- 100 mg, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100"
- 150 mg, cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150"
- 200 mg, blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200"

The drug will be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protected from light.In this study tablets up to 300 mg daily , divided in two single doses, will be used. This means that the tablets used will be the ones of 25 mg , 100 mg and 150 mg. The therapy schema as described earlier in this protocol includes a 2-week period in the escalation phase when the patient must receive 100 mg daily. At that time, they will be advised to receive two of the 25 mg tablets twice daily. The tablets will be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) in a dry place and protected from light . Each tablet will contain the labeled amount of lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100 mg tablet only); ferric oxide, yellow (150 mg tablet only); and FD&C Blue No. 2 Lake (200 mg tablet only).

Blindness control

This study is a double-blind study. Because of the very unique form of the tablet , which is described above in the " Study drug " section in order to preserve the investigator's blindness , an identical placebo tablet has been manufactured by the pharmaceutical company and will be preserved separately at the sponsor's site and finally the drug administered is unknown to the investigator and their designated personnel.

Summary of the study procedures

Patients meeting the inclusion criteria, which will be checked during a screening period, will participate in the study after signing the informed consent form (initial visit, visit 1). At this initiation visit , the subjects will be asked to complete the QLQ-CIPN20 questionnaire as well as estimate their pain severity using the NRS score. A baseline TNS score will also be obtained by the expert neurologist of the study, as well as a thorough physical examination , ECG and blood test analysis. In this visit the patients will be randomized in the two arms (lamotrigine and placebo) and will be given extended advice on the drug use. They will be strongly advised to take the tablet at the same time once daily (at bed time) for 2 weeks , then twice daily at a standard time with a 12 hour space between the two doses (e.g. at 9:00 and at 21:00) and also be reminded that there will be a 2-week period when they must take two tablets at every scheduled time of the day. They will also be asked to fill the quality of life questionnaire at the end of every single week of therapy. In order to make sure they have done so , the investigator or his/her staff will make a phone call at the end of every week to check on the patients and remind them of the questionnaire. During this phone call they will be asked by the investigator to rate their pain severity and so a NRS score will be obtained.

At the end of every 2-week period , if no adverse reactions or events have taken place in the mean time, the patients will visit the study center, where they will be physically examined and undergo ECG , blood tested, submit the filled questionnaires and also the new NRS and TNS scores will be obtained.

In conclusion the number of scheduled visits is 10:

- Visit 1 : Initial visit
- Visit 2 : End of 2nd week of therapy (initial dose 25 mg at bed time)
- Visit 3 : End of 4th week of therapy (escalated dose 25 mg twice daily)
- Visit 4 : End of 6th week of therapy (escalated dose 50 mg twice daily)
- Visit 5 : End of 8th week of therapy (escalated dose 100 mg twice daily)
- Visit 6 : End of 10th week of therapy (escalated dose 150 mg twice daily)
- Visit 7 : End of 14th week of therapy (maximum dose)
- Visit 8 : End of 18th week of therapy

- Visit 9 : End of 20th week of therapy (end of the 12-week period of maximum dose - start of drug- tapering off and exact advise of the tapering off process .)
- Visit 10 : End of 24th week (End of the tapering off period)

In case any patient reaches their maximum tolerated dose earlier (e.g. 200 mg daily), they will start the 12-week period of steady dose earlier (at the respective time) and pay less visits to the investigation center.

4. SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion criteria

DISEASE CHARACTERISTICS:

- Diagnosis of cancer
- Received, or are currently receiving, neurotoxic chemotherapy, including any of the following:
  - Taxanes (e.g., paclitaxel or docetaxel)
  - Platinum-based compounds (e.g., carboplatin, cisplatin, or oxaliplatin)
  - Vinca alkaloids (e.g., vincristine or vinblastine)
  - Proteasome inhibitors (e.g. bortezomid)
- Experiencing pain or symptoms of peripheral neuropathy for at least 1 month attributed to chemotherapy
  - Average daily pain rating of at least 4 out of 10 NRS
  - Peripheral neuropathy at least grade 1 using TNS neuropathy rating

PATIENT CHARACTERISTICS:

Age

- 18 and over

Life expectancy

- At least 6 months

Hepatic

- Bilirubin < 2 times upper limit of normal (ULN)

Renal

- Creatinine ≤ 1.5 times ULN

Other

- Fertile patients must use effective contraception
- Able to complete questionnaires

PRIOR CONCURRENT THERAPY:

Chemotherapy

- See Disease Characteristics
- More than 7 days since prior methotrexate or other dihydrofolate inhibitors

Other

- More than 7 days since prior, and no concurrent use of any of the following:
  - Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, or desipramine)
  - Concurrent selective serotonin reuptake inhibitors allowed
  - Monoamine oxidase inhibitors
  - Opioid analgesics
  - Anticonvulsants (e.g., gabapentin, topiramate, valproic acid, or clonazepam)
  - Adjuvant analgesics (e.g., mexiletine)
  - Prior nonsteroidal anti-inflammatory drugs allowed
  - Topical analgesics (e.g., lidocaine gel or patch) to the affected area
  - Amifostine
- More than 30 days since prior investigational agents for pain control
- No other concurrent investigational agents for pain control

4.2 Exclusion Criteria

- Pregnant or nursing
- Positive pregnancy test
- Prior allergic reaction or intolerance to lamotrigine
- Extreme difficulty swallowing pills
- Other identified causes of painful paresthesia preceding chemotherapy, including any of the following:
  - Radiation or malignant plexopathy
  - Lumbar or cervical radiculopathy

Pre-existing peripheral neuropathy of another etiology, such as any of the following:

- Cyanocobalamin deficiency
- AIDS
- Diabetes
- Heavy metal poisoning amyloidosis
- Syphilis
- Hyperthyroidism or hypothyroidism
- Inherited neuropathy
- Significant psychiatric illness (e.g., mania, psychosis, or schizophrenia) that would preclude study participation

4.3 Withdrawal criteria

Since participation in the clinical trial is completely voluntary the patients can withdraw from the study at any given time they wish to do so,without having any personal or medical cost, as it is clearly described in the informed consent form.

In the same way , the investigator can remove any patient from the study under various circumstances (e.g. violation of inclusion criteria, patient safety, etc) and the exact reasons of patient withdrawal must be extensively reported in the patient report form and also analyzed in the final report.

The primary objective's statistical analysis is based on the per protocol population,therefore the participating must be carefully chosen , so that the withdrawal percentage does not exceed 10 %.

4.4 Study enrollment procedures

For the patient selection, medical history will be thoroughly examined by the investigator. During the patient selection phase, patients with specific co-existing diseases will be detected after thorough study of the medical history and personal data, physical examination and laboratory testing and will be excluded from the study.

5. STUDY INTERVENTIONS

5.1 Interventions , Administration and Duration

The study drug is Lamotrigine given orally in tablets of 25 , 100 and 150 mg , which is compared to identical placebo, given by the same route and at the same dosage. Patients will be started on a placebo or lamotrigine at dose of 25 mg at bed time for 2 weeks, then 25 mg twice daily for 2 weeks, then 50 mg twice daily for 2 weeks , then 100 mg twice daily for 2 weeks and then the dose will be escalated to 150 mg twice daily, at which time therapy will continue for 12 weeks. Dose escalation will be continued per this schedule to allow each patient to reach his/her tolerated dose. After a total of 20 weeks of therapy from the time of drug initiation patients will be tapered off this drug / placebo over a 4-week period. If a patient wishes to stop sooner for any reason before 20 weeks , he/she will be encouraged to taper the drug over a 4-week period rather than discontinuing therapy abruptly.

5.2 Handling of study interventions

The sponsor of the clinical study will be responsible for the supply of both the drug and the placebo. The products will be sent to each center by the sponsor/manufacturer, packed according to the randomization program and labeled according to the current law and the GMP compliance. Caution will be taken for the right storage of the drugs. In a room with a room temperature of 20-30 º C and a humidity of 50-60 % , while temperature and humidity will be monitored daily. The investigational products will be available only for the current study under the responsibility of the prime investigator, who has to ensure that they will not be used outside the current study and in any undesirable ways. The investigator will be checked and has to certify the use of each drug and keep detailed records in the Case Report Form. A detailed file of distribution has to be written and updated by the investigator. Full and empty bottles of the administered drug will be returned to the monitor of the CRO at the end of the study.

5.3 Concomitant interventions

Any concomitant therapy before or during the clinical study will be recorded in the Case Report Form. The investigator , by checking the inclusion criteria will decide whether the patient can enter or go on with the study. The concomitant therapy has to be standard and not changed during the study. There are several drugs that cannot be concurrently administered and if a need comes up for any of them to be administered to the patient, then he'she will have to report it immediately to the investigator and leave the study.

5.4 Adherence Assessment

Since the patients will receive the medication at home , they will be asked to bring the bottle with the remaining tablets at every visit (every 2 weeks) , when the number of the remaining tablets will be counted and recorded at the Case Report Form. At the end of the therapy the patients will be asked to return the bottle to the investigator. In addition at the weekly scheduled phone call the patients will be reminded of the therapy regimen (colour of pill, daily dosis).

6. CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of evaluations

Visit 1 : Baseline NRS, TNS , QLQ-CIPN20, ECG Blood test analysis for: Hb, Ht, Cr , TBIL, Glucose ,B12 ,Vitamin K,cGTP(female patients) , TSH,FT3, FT4, HbA1C, HIV test and PCR for the detection of Treponema Pallidum, physical examination

Visit 2-9 : NRS, TNS , QLQ-CIPN20, ECG, Blood test analysis for: Hb, Ht, Cr , TBIL, Glucose , B12 ,Vitamin K, cGTP (female patients), TSH, FT3, FT4, HbA1C, physical examination

Visit 10 : NRS , TNS , QLQ-CIPN20, ECG, Hb, Ht, Cr , TBIL, Glucose , B12 , Vitamin K,cGTP (female patients), TSH, FT3, FT4, HbA1C, physical examination.

6.2 Timing of evaluations

The TNS score will be obtained at the patients' visits to the investigation center, while NRS will be evaluated weekly by telephone and QLQ-CIPN20 will be answered weekly by the patients and handed to the investigator at the patients' visits, when they will also submit in writing the NRS score, so it can be compaired with the values given per phone. In case of great differences in the values, the patients will be asked to try to remember whether the pain was intense or not and if they are not able to recall that either a mean value will be noted as the correct one.

6.3 Special Instructions and Definitions of Evaluations

In the present clinical study three different evaluation tests will be used:

1. **Numerical Rating Scale (NRS)** for the evaluation of pain intensity.

The patient is asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours.

The average of the 3 ratings will be used to represent the patient's level of pain over the previous 24 hours.

Patient Instructions (adopted from (McCaffery, Beebe et al. 1989):

"Please indicate the intensity of current, best, and worst pain levels over the past 24 hours on a scale of 0 (no pain) to 10 (worst pain imaginable)"

2. **Total Neuropathy Score (TNS)** for the quantitative assessment of peripheral neuropathic symptoms and signs

	Total Neuropathy Score				
Parameter	0	1	2	3	4
Sensory symptoms	None	Symptoms limited to finger and toes	Symptoms extend to ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbow or functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/ assistance	Paralysis
Autonomic symptoms, n°	0	1	2	3	4 or 5
Pin sensitivity	Normal	Reduced in fingers and toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensitivity	Normal	Reduced in fingers and toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild (MRC:4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Parálisis (MRC 0-1)
Deep tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
Vibration sensation (QST vibration % ULN)	Normal to 125%ULN	126%-150% ULN	151%-200% ULN	201%-300% ULN	> 300%ULN
Sensory Nerve SNAP; %LLN	Normal/ reduced to < 5%LLN	76%-95% of LLN	51%-75% of LLN	26%-50% of LLN	0%-25% of LLN
Peroneal nerve CMAP; %LLN	Normal/ reduced to < 5%LLN	76%-95% of LLN	51%-75% of LLN	26%-50% of LLN	0-25% of LLN

3. Quality of Life Questionnaire - CIPN20

The QLQ-CIPN20 contains 20 items assessing sensory (9 items), motor (8 items), and autonomic symptoms (3 items). Using a 4-point Likert scale (1 = "not at all," 2 = "a little," 3 = "quite a bit," and 4 = "very much"), individuals indicate the degree to which they have experienced sensory, motor, and autonomic symptoms during the past week. Sensory raw scale scores range from 1 to 36, motor raw scale scores range from 1 to 32, and autonomic raw scale scores range from 1 to 12 for men and 1–8 for women (erectile function item is excluded). All scale scores are linearly converted to a 0–100 scale, with higher scores indicating more symptom burden.

QLQ CIPN20 items:

1. Did you have tingling fingers or hands?[a]
2. Did you have tingling toes or feet?[a]
3. Did you have numbness in your fingers or hands?[a]
4. Did you have numbness in your toes or feet?[a]
5. Did you have shooting or burning pain in your fingers or hands?[a]
6. Did you have shooting or burning pain in your toes or feet?[a]
7. Did you have cramps in your hands?[b]
8. Did you have cramps in your feet?[b]
9. Did you have problems standing or walking because of difficulty feeling the ground under your feet?[a]
10. Did you have difficulty distinguishing between hot and cold water?[a]
11. Did you have a problem holding a pen, which made writing difficult?[b]
12. Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?[b]
13. Did you have difficulty opening a jar or bottle because of weakness in your hands?[b]
14. Did you have difficulty walking because your feet dropped downwards?[b]
15. Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?[b]
16. Were you dizzy when standing up from a sitting or lying position?[c]
17. Did you have blurred vision?[c]
18. Did you have difficulty hearing?[a]

Please answer the following question only if you drive a car

19. Did you have difficulty using the pedals?

Please answer the following question only if you are a man

20. Did you have difficulty getting or maintaining an erection?[c]

[a]Sensory scale items

[b]Motor scale items
[c]Autonomic scale items

7. MANAGEMENT OF ADVERSE EXPERIENCES

The definition adverse experiences consists of two separate terms. Adverse Events and Adverse Reactions.

An adverse event (AE) can be any unintended , unpleasant reaction (including abnormal laboratory findings), symptom, diagnosis, major clinical deviations from baseline, vital signs , clinical deterioration of any concurrent diseases recorded at the time of study initiation or any new clinical manifestation coincidental with the initiation of the investigational product. Pathological clinical signs observed or measured during the study will be defined as Adverse Events, only if:

- It causes clinical signs or symptoms or
- needs therapy or
- urges the interruption of therapy

Adverse events related to the underlying disease will not be considered as serious but will recorded at the CRF. In any case the causality should be defined and the sponsor must be informed.

Adverse events reported by the patient or the investigator will be recorded individually at the CRF : the specific event, whether it occurred prior to the study initiation or not, the exact date it happened, the severity, the duration ,the intensity, its relevance to the study drug, specific measures taken and its outcome. Patients showing adverse events at the time of the final visit will be followed up for 30 days and the events will be documented. Serious adverse events will be followed up until they are resolved. All this information will be reported to the sponsor.

Adverse events are considered serious (SAE) if (regardless the dose of the drug) :

- It leads to death
- It is life threatening
- It causes permanent or significant disability / incompetence
- it causes congenital abnormality
- it leads to hospital admittance or prolongation of hospital stay

An Adverse Reaction (ADR) is any unpleasant and unexpected reaction to the investigational

product related to the administered dose , whose intensity does not comply with the investigator's brochure or the insert package information.

The drug's relevance to the ADR must be defined by a medically authorized person as follows:

Relevant: The ADR follows the drug administration and cannot be logically attributed to any other cause.

Irrelevant: The ADR possibly derives from the patient's condition or other concurrent therapy.

The ADRs are classified regarding their severity as:

- Mild: Does not affect daily activities
- Moderate: Affects the usual daily activities
- Serious: Inability to perform daily activities

All adverse experiences will be documented by the investigator in the CRF whether or not they are attributed to the drug. A description of the adverse experience , date of start and recession, severity, clinical relevance to the drug and applied measures must be reported. A follow up must be upheld, if necessary. ADRs must be followed up until recession or stabilization. If they lead to patient withdrawal there must be followed up until a satisfactory solution is given. Whether or not the patient decides to withdraw from the study due to an adverse reaction , he/she should be provided with the proper medical care until their improvement or stabilization.

In case of SAE , the investigator must immediately communicate with the sponsor either by phone or per fax within 24 hours of the event. The sponsor will check the report and ask of any additional information. The sponsor will immediately submit security reports to the regulatory authorities and will inform the investigators about the regulatory reports. The investigators must file security reports according to the Investigation Review Board (IRB) / National Ethics Committee within specific time defined by the local regulatory authorities. The documentation of the immediate security report admission and reception must be preserved in the investigation center.

Any case of pregnancy during the study or within 30 days after completion of therapy should be reported to the sponsor as a SAE. The expected time of birth, pregnancy termination, information about the neonate, etc must be included. The investigator is obliged to documenting both the mother's and fetus' medical condition.

8. CRITERIA FOR INTERVENTION DISCONTINUATION

The sponsor can at any time disrupt the study if he/she has information about issues concerning **quality**, **effectiveness**, **safety** of the drugs being studied, or any other information that could affect the correct conduction of the study. The sponsor has the right to send a written termination announcement, quoting the reasons of the termination.

If the investigator intents to withdraw his participation in the study he/she is obliged to inform the sponsor and refer to the reasons leading to his withdrawal.

9. STATISTICAL CONSIDERATIONS

9.1 General design issues

The statistical analysis will be coordinated by the assigned bio-statistician. A statistical analysis plan will be written which will include every single detail. Before securing the database, every questionable case , that has difficulties in being assessed clearly will be thoroughly examined by the database operator, the assigned bio-statistician and the study administrator.

The study will employ a randomized , double-blind, parallel group (drug vs placebo) design to determine the efficacy of lamotrigine in treatment of CIPN. The NRS score will be used to measure the primary outcome, which is the efficacy of lamotrigine on CIPN-related pain relief. The TNS score which is considered according to literature valid and reliable and a highly valid and reliable questionnaire , specific for assessment CIPN patients' quality of life will be used to measure the secondary outcomes.

No p-value correction has to be applied , since there is only one primary end point.

The subjects will be stratified by gender , chemotherapy agent receiving/-ed and by whether they are currently receiving chemotherapy or they have completed their cancer treatment.

The subjects that undergo no ADRs will be followed for 3 months after study completion.

9.2 Outcome

In the present study , one primary and two secondary outcomes will be measured. The primary outcome is the mean difference between the baseline NRS score and the NRS score at the end of the study. The secondary outcomes are the mean difference between the baseline and the final TNS score as well as the mean difference between the QLQ-CIPN20 scores in the beginning and at the end of the study.

9.3 Sample size and accrual

In order to estimate the sample size for the study, the power approach for two-independent groups will be used.

In calculating the sample size for the clinical trial , the following parameters are defined:
The difference ($\mu 1$) in average mean NRS score in the placebo arm, according to literature is 0.5 and the SD= 0.57.
A decrease in average mean NRS score to 0.3 ($\mu 2$) in the lamotrigine arm is considered as clinical significant, so $\Delta = \mu 1 - \mu 2 = 0.2$.

The p-value is set at 0.05 and the power at 80%. After the adjustment of an extra 10% that could withdraw from the study the sample size is estimated to be 120 patients (60 subjects in each arm) .

The patient randomization will be stratified. There is no sample size goal for each

stratum. The patients will be assigned to strata according to the strata characteristics.

9.4 Data monitoring

The study duration is 52 weeks. Interim monitoring visits are scheduled once a month after the first patient's study initiation. There will be one interim analysis once half of the patients participating in the study complete their 12 - week period of treatment with their maximum tolerated dose.

In case, after the 28-week period given to patient recruitment, during the monitor's visit one or more of the following is noted , the study will be discontinued:

- Slow Accrual (less than 2 patients recruited weekly)
- High Losses to follow-up (more than 30% missing data)
- Poor quality control (inappropriate or unmonitored study drug storage conditions,poor service of the medical equipment used in the study, e.g. electromyographs, poor storage conditions for the blood samples, inadequate follow up by telephone due to failure or omission, misfilled or misfiled questionnaires > 30%)
- More than 2 reports of SAEs
- Inadequate update of CRFs
- Major protocol violations

No separate monitoring considerations for each stratum are demanded.

9.5 Data analysis

The primary analysis will be conducted according to per protocol analysis. In addition , in order to compensate for the missing data an ITT (intention-to-treat) analysis will be also conducted.

The primary objective is the mean difference in NRS score between baseline and final visit. A co-variation analysis (ANCOVA) having the treatment set as a factor and the baseline NRS score as a co-variate. The difference between means and the 95% CI will be calculated. The null hypothesis is that lamotrigine and placebo are equal in reducing the mean NRS score. The secondary objectives will be also measured using ANCOVA, where TNS and QLQ-CIPN20 baseline scores will be respectively set as co-variates.

The analysis of the above data will be done per stratum. There will be three strata in our analysis: gender , chemotherapy agent and whether chemotherapy is active or has ended either due to completion or to discontinuation.

The demographic patient data at study initiation ,as well as the baseline Creatinine and TBIL values, will be compared using the parametric independent t-test or the non-parametric Mann-Whitney U- test for numerical values and the chi-square test or Fisher's exact test for categorical values.

An adverse reaction occurrence comparison will be conducted applying a chi-square test.

10. DATA COLLECTION AND SITE MONITORING

10.1 Records to be kept

Documents related to the clinical study must be kept with the investigator's resposibility until the completion of the study.

With the completion of the clinical study records will be classified and stored in the general archive according to the standards of correct clinical practice.

10.2 Role of Data Management

Relevant information will be documented with either a blue or a black pen on the CRF. The CRFs must be filled out in a legible way in order to facilitate the statistical analysis. By the end of the study every information on the CRF will be evaluated for the elaboration of the final report.

If corrections have to be made, false information must be erased with a single line so that they remain legible and corrected data must be documented, signed and dated. The CRF must contain the instructions mentioned above.

10.3 Quality Assurance

The progress of the clinical trial will be under constant supervision.Supervisors will be appointed by the sponsor. Frequent communication must be agreed between supervisors and investigators.

The supervisor will be responsible for the compliance to the protocol and the integrity, coherence and reliability of the data and must therefore have access to the patients medical history and files. The investigator must accept to cooperate
with the supervisor in order to detect and solve any problems.

11. HUMAN SUBJECTS

11.1 Ethics and Informed Consent

The clinical trial must be conducted according to the international norms, local legal commitments, the declaration of Helsinki and the instructions for correct clinical practice (ICH GCP).

A copy of the above mentioned files will be given to the investigators.

The instructions for correct clinical practice are an international ethical and scientific quality pattern about the design, conduction, documentation and report of clinical studies involving human subjects.

The conformity to this pattern is a declaration in public that rights, safety and prosperity of the individuals participating in clinical trials is protected according the declaration of Helsinki, and that medical data are credible.

The investigator agrees by signing to conform to the instructions and methods of this particular protocol,the directives of the declaration of Helsinki, and local legal commitments. The investigator as well as his/her team are obliged to submit to these rules.

The clinical trial will start only after the consent of the national ethics committee about drugs is acquired.

With the exception of emergencies, changes or deviations from the protocol are not allowed without the approval of the ethics committee and/or the drug organization. The committee is to be informed about any changes and must approve any deviation that could raise the patients' risk and /or could effect negative the patients' rights or the reliability of the study. This is not possible for changes made to reduce patients' suffering and danger, or changes concerning administrative matters.

Every patient is to be informed about the characteristics of the clinical trial by verbal and written means (through an information flyer) and the ICF that will contain information about:

- the rights of the individuals participating in the clinical trial
- the goal of the study
- issues concerning the methods used
- therapies that are to be studied
- potential risks and dangers
- possible unwanted reactions
- access to confidential files
- financial compensation and insurance contract

- investigators

After the patient is fully informed about all aspects and restrictions of the protocol of the clinical trial he/she must sign the informed consent document with the investigator before being enrolled in the study. With this signature the individual declares that he/she participates voluntarily and his intention to fulfill the protocol of the clinical trial and the investigator's instructions.

The patient must keep this signed Informed Consent document and information sheet during the clinical trial as well as the investigator's contact data.

The investigator must also keep the signed Informed Consent in his/her files.

11.2 Subject Confidentiality

The investigators must guarantee the anonymity of the individuals participating in the clinical trial. Neither in the CRF nor in any other file is it allowed for the patients to be recognizable by their names but only by an identity code. The investigator has to keep the file with the matching of codes and names. These files will not be handed over to the sponsor and are to kept under strict confidentiality by the main investigator.

Confidential data must be accessible only to the staff participating in the clinical trial, to the supervisors appointed by the sponsor and the competent authorities, as well as the ethics committee responsible for the particular study.

Access to the data will also be permitted to the statistic analyst who will be responsible for preserving the anonymity of the individuals.

Medical files as well as every study-related document are to be kept by the investigator and must be locked up for the agreed period of time.

11.3 Study Modification

In case of new information necessary for the correct conductance of the clinical trial that should lead to any deviation of the protocol the sponsor is to inform the responsible authorities as well as every investigator participating in the study.

The head of the investigation is responsible to inform the IRB/IEC and if necessary modifying the information for participants.

12. PUBLICATION OF RESEARCH FINDINGS

The results of the clinical trial will be discussed and reviewed by the investigators and the sponsors for the upcoming publication.

The results are not to be discussed with any other person until an agreement is signed by the sponsor concerning a lecture or the publication of an article.

As an exception, the investigators will be allowed to include the title of the clinical trial in their curriculum vitae.

13. LIST OF ABBREVIATIONS AND MEDICAL TERMS

ADR	Adverse Drug Reaction
AE	Adverse Experience
AED	Anti-Epileptic Drug
CBZ	CarBamaZepin
CGTP	Chorionic GonadoTroPin
CIPN	Chemothrapy Induced Peripheral Neuropathy
CNS	Central Nervous System
Cr	Creatinine
CRF	Case Report Form
DRG	Dorsal Root Ganglia
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
Ht	Hematocrit
IC	Informed Consent
ICH-GCP	International Conference of Harmonization – Good Clinical Practice
IRB	Institutional Review Board
ITT	Intention To Treat
MS	Multiple Sclerosis
NCI-CTC	National Cancer Institute – Common Toxixity Criteria
NMDA	N-Methyl-D-Aspartate
NRS	Numerical Rating Scale
NSAIDs	Non Steroid Anti-Inflammatory Drugs
PHT	Phenytoin

QLQ	Quality of Life Questionnaire
SAE	Serious Adverse Event
SJS	Steven-Johnson Syndrom
SUNCT	Short-lasting Unilateral Neuralgiform headache with Conjunctional injection and Tearing
TBIL	Total BILirubin
TEN	Toxic Epidermal Necrolysis
TNS	Total Neuropathy Score
TRPV	Transient Receptor Potential Vanilloid
TSH	Thyroid Stimulating Hormone

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