

North Central Cancer Treatment Group

**The Use of Topical Baclofen, Amitriptyline HCl, and Ketamine (BAK) in a PLO Gel vs. Placebo for the Treatment of Chemotherapy Induced Peripheral Neuropathy: A Phase III Randomized Double-Blind Placebo Controlled Study**

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**Protocol Resources**

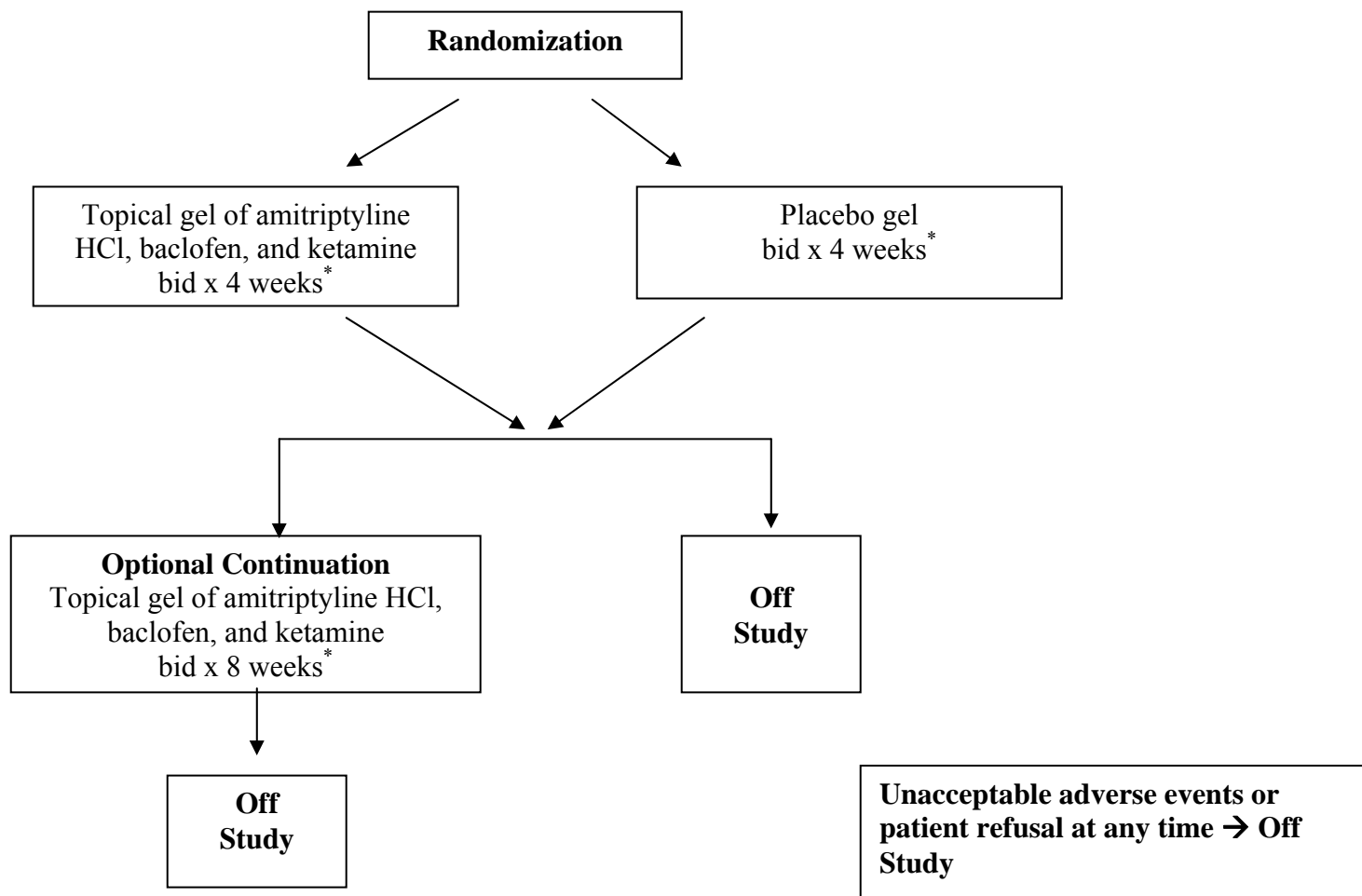
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**Schema**



If patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

\*Cycle Length = 7 days

<p>Generic name: Amitriptyline HCl            Brand name:            NCCTG abbreviation: AMTRIP            Availability: NCCTG Research Base Pharmacy</p>	<p>Generic name: Baclofen            Brand name:            NCCTG abbreviation:            Availability: NCCTG Research Base Pharmacy</p>	<p>Generic name: Ketamine            Brand name:            NCCTG abbreviation:            Availability: NCCTG Research Base Pharmacy</p>	<p>Generic name: Placebo            Brand name:            NCCTG abbreviation: PLACEB            Availability: NCCTG Research Base Pharmacy</p>
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## 1.0 Background

### 1.1 Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose limiting side effect of many chemotherapeutic agents including vincristine, paclitaxel, cisplatin, and oxaliplatin<sup>1-7</sup>. The incidence of CIPN can be variable, ranging from 0-70% of patients receiving chemotherapy, but commonly occurs in 30 to 40% of patients. A number of factors influence the incidence, including age, dose intensity, cumulative dose, duration of therapy, coadministration of other neurotoxic chemotherapy agents, and pre-existing conditions such as diabetes and alcohol abuse<sup>2-3,8-14</sup>. While symptoms may resolve completely in some cases, in some instances, the CIPN is only partly reversible and in the worst cases, it does not appear to be reversible at all<sup>13</sup>.

CIPN can be extremely painful and/or disabling, causing significant loss of functional abilities and quality of life<sup>15</sup> (QOL). Neurotoxic chemotherapeutic agents may cause structural damage to peripheral nerves resulting in aberrant somatosensory processing of the peripheral and/or central nervous system<sup>7</sup>. This resultant peripheral neuropathy can potentially affect both small fiber axons (temperature, pin prick) and large fiber sensory axons (vibration, proprioception)<sup>15</sup>. A common clinical course begins with paresthesias (tingling) and dysesthesias, commonly located in the toes and fingers that can be extremely painful. These symptoms then spread proximally to affect both lower and upper extremities in a characteristic “glove and stocking” distribution<sup>16</sup>. The pain associated with CIPN has not been adequately characterized nor quantified clinically. Compared to other neuropathies or neuropathic pain syndromes, there are many similarities to diabetic neuropathy with similar glove and stocking distribution and characteristics such as pain, paresthesias, and dysesthesias.

It is important to consider that the symptoms of CIPN can cause other dimensions of suffering and distress in patients, especially in the setting of malignant disease. It is well recognized that, in patients with cancer, pain may cause significant distress, altered mood, decreased functional abilities, and decreased health related quality of life<sup>17-21</sup>. Furthermore, there is considerable evidence that when pain is improved, many of these other associated challenges can also be improved<sup>21</sup>.

### 1.2 Current Management Strategies for Chemotherapy-Induced Peripheral Neuropathy

Unfortunately, CIPN is a difficult problem to manage. There are no effective therapies for prophylaxis and no standardized regimen for treating CIPN once it develops<sup>13</sup>. Prevention mainly consists of cumulative dose-reduction or lower dose intensities, especially in patients who are at higher risk to develop neurotoxic side effects. When patients develop peripheral neuropathy while actively receiving neurotoxic chemotherapy, the most common therapeutic strategy is to decrease or discontinue the chemotherapy in effort to minimize further neurotoxicity<sup>6</sup>. However, decreased chemotherapeutic dosing may potentially affect tumor responsiveness, prognosis, and overall survival.

There is limited information evaluating the use of pharmacologic agents in the management of CIPN. It is generally accepted that opioid analgesics are used clinically but there is insufficient available evidence about their efficacy. Adjunctive analgesics have been tried, but there is a distinct lack of randomized controlled trials to determine

their effectiveness in the setting of CIPN. Adjunctive analgesic agents can be defined as drugs that have primary indications other than providing analgesia, such as tricyclic antidepressants (TCAs), anti-convulsants, and others. There is evidence suggesting that TCAs can be effective agents in treating certain painful neuropathies, such as diabetic neuropathy and postherpetic neuralgia<sup>22-24</sup>. Tricyclic antidepressants have been widely studied in the treatment of postherpetic neuralgia and painful diabetic neuropathy and their efficacy established in these populations<sup>25-28</sup>. One of the few randomized controlled trials to evaluate pharmacologic treatment for CIPN (NCCTG study 93-92-52) evaluated nortriptyline, a commonly used TCA. However the results were disappointing in that nortriptyline did not appear to alleviate the symptoms of painful cisplatin-induced peripheral neuropathy<sup>29</sup>. In addition, tricyclic antidepressants can have many side effects including, but not limited to, sedation, postural hypotension, dizziness, dry mouth, and constipation<sup>26-27</sup>. These effects can be especially challenging for patients with symptoms related to the cancer or cancer treatment.

There has also been evidence that anti-convulsants, such as gabapentin and lamotrigine may be useful in the treatment of certain painful neuropathies such as diabetic neuropathy and postherpetic neuralgia<sup>25-27, 30-33</sup>. However, both gabapentin and lamotrigine have been evaluated by NCCTG in placebo-controlled randomized double-blinded clinical trials and both were found to be ineffective for the treatment of CIPN<sup>34-35</sup>.

The potential benefits of other pharmacologic agents, such as amifostine and glutamine, have been speculated<sup>36-37</sup>. Again, randomized controlled trials evaluating their efficacy are not available at this time. However, amifostine was found to be ineffective in reducing neurotoxicity related to paclitaxel in a pilot trial and the authors of this trial did not recommend further study of this agent<sup>38</sup>. To date, there are no randomized controlled trials evaluating the use of any of these agents in the management of chemotherapy-induced peripheral neuropathy.

Well-designed, randomized controlled trials to identify effective pharmacologic agents and strategies capable of improving the symptoms of CIPN are desperately needed to improve the care of the many patients suffering from this debilitating and challenging problem. Effective pharmacologic agents used for the treatment of other painful neuropathies, including diabetic neuropathy, should be evaluated in the setting of CIPN.

### 1.3 The physiology of analgesia in neuropathic pain

- 1.31 There are several physiologic mechanisms by which neuropathic pain can be altered. One of these mechanisms involves the depletion of substance P, a neurotransmitter affecting small diameter sensory afferent nerves. By depleting substance P, activation of these nerves can be quieted. Other physiologic pathways include modulation of voltage-gated sodium channels, inhibition of NMDA, alpha 2-adrenoreceptor agonist activity, adenosine A<sub>1</sub> receptor agonists (or adenosine kinase inhibitors), and GABA (in particular GABA<sub>B</sub>) agonists. Agents exhibiting one or more of these mechanisms of action are available and can be used either orally or topically.
- 1.32 Neuropathic pain is complex, with several physiologic pathways being active. The philosophy of expert compounding pharmacists in treating this type of pain is to ameliorate the pain by intervening in several different pathways. Experts in

the physiology of neuropathic pain point to the importance of the NMDA receptor, which has been identified in the periphery on unmyelinated axons at the dermal-epidermal junction. Hence, NMDA centered physiology plays an essential role in neuropathic pain and GABA agonists are an essential partner in this physiology. The chain of physiologic events is as follows, explained simply. Glutamate (from noxious sensory input) activates NMDA receptors. The ultimate response is an opening of the calcium channel and an influx of calcium into the intracellular space. However, in order for the calcium influx to occur, intracellular sodium reduces GABA inhibitory systems. GABA agonists inhibit pain signals. GABA<sub>b</sub> is part of the G-protein coupled complex that is associated with the NMDA receptor modulation of sensory input. Therefore, baclofen, which is a GABA<sub>b</sub> agonist, when used with NMDA antagonists, (ketamine) can more effectively turn OFF the glutamine activated calcium influx than by using either baclofen or ketamine alone. Some authors have referred to baclofen as having presynaptic depressant action at NMDA and non-NMDA receptors<sup>39</sup>.

- 1.33 One of the limitations of several of the systemic agents for pain is their side effect profiles. Many of these agents have a dose response curve and higher doses are accompanied by dose limiting toxicities (such as drowsiness, mental confusion, and interactions with other medications). Topical use of these agents has therefore been considered as an option. By applying medications to the skin in the affected area of pain, the pharmacologic action might occur at local peripheral sensory nerves, thereby avoiding systemic effects. In addition, local effects are almost immediate, within 15 - 30 minutes<sup>41,59</sup>. Topical administration should be differentiated from transdermal administration. Topical use is aimed to result in only local effects at the site of application whereas transdermal applications are designed to provide a means of systemic absorption of a drug to cause systemic pharmacologic activity. Formulations of capsaicin (cream) and lidocaine (patch) are currently available for topical use to treat neuropathic pain in humans. Preclinical studies provide evidence that topical peripheral applications of many other agents such as opioids, alpha<sub>2</sub>-adrenergic agonists, cholinergic receptor agonists, local anesthetics, and antidepressants also may be beneficial in neuropathic pain. Some clinical reports also provide support for topical application of such agents<sup>40</sup>.

#### 1.4 Topical analgesics for peripheral neuropathy

##### 1.41 Amitriptyline and Ketamine

Ketamine is an injectable anesthetic that works by inhibiting NMDA receptors. Gammaitoni<sup>41</sup> reports the effectiveness of ketamine gel on refractory neuropathic pain in 5 patients. Doses of 0.13-0.37 mg/kg (generally 10 to 20 mg doses) were applied topically to the affected area. Four of the five patients reported significant pain relief at initial application. Reduction in numerical pain scores after application of the ketamine gel ranged from 53%-100% using a 0-10 numerical pain intensity scale in as little as 15 minutes post application. The higher doses resulted in positive responses. The average pain score pre-application was 8.8, while the average 15 minute post application score was 1.6. Patients reported alterations in temperature sensation, feelings of relaxation and decreased tension in the area of application, in addition to pain relief. The only side effect noted was slight sedation in one patient at the 0.37 mg/kg dose.

However, this patient was also receiving high-dose opioids and therefore, this side effect might not have been solely due to the ketamine. Lower doses did not appear to have produced any negative effects.

The use of topical amitriptyline in combination with ketamine for diabetic neuropathy, postsurgical/posttraumatic neuropathic pain with allodynia, hyperalgesia, pinprick hyperesthesia<sup>42-44</sup> or postherpetic neuralgia<sup>42-45</sup> has been described. Amitriptyline is a tricyclic antidepressant that may have a role in neuropathic pain due to several characteristics. It can inhibit NMDA, it can activate adenosine A<sub>1</sub> receptors, and it can alter the sodium channels, providing local analgesic action<sup>46</sup>.

A double-blind, placebo controlled trial evaluated the efficacy of topical 2% amitriptyline, 1% ketamine, and a combination of both in treating patients with neuropathic pain. A reduction in pain scores of 1.1-1.5 units was observed in all groups, and there was no difference between groups<sup>43</sup>. Subjects who were interested were then enrolled in an open label prospective trial examining perceived analgesic effects, patient satisfaction, and safety of topical amitriptyline 2%/ketamine 1% cream. At the end of 6 months, subjects reported an average long-term reduction in pain of 34% (SD = 37%); 5 subjects (25%) achieved 50% or greater reduction in pain, and 1 subject achieved 100% reduction in pain<sup>44</sup>. At the end of 12 months the average pain reduction was 37% (SD = 40%); 7 subjects (40%) achieved 50% or greater reduction in pain and 2 (11%) achieved 100% reduction in pain. The majority of subjects (89%) rated their satisfaction as 3/5 or greater (good-excellent). Five subjects were able to discontinue oral analgesics (including opioids) due to the decreased pain they attributed to the use of the topical cream<sup>44</sup>. In both studies, blood concentrations revealed no significant systemic absorption and minimal side effects were reported.

A recent randomized, placebo-controlled trial (reported only in abstract form), used a higher dose of topical amitriptyline and ketamine (4% and 2% respectively) for the treatment of post herpetic neuralgia. 118 patients were randomized to receive either high dose (4% amitriptyline/2% ketamine) or low dose (2% amitriptyline/1% ketamine) therapy or placebo. Investigators reported a 30% or greater reduction in pain intensity in 46% of subjects treated with the high dose versus 26% on low dose and 19% of subjects on placebo (p= .025 high dose vs. placebo). This effect was seen over 3 weeks. The topical cream was well tolerated. This latest study as well as data reported previously strongly suggests that there is a dose dependent effect on analgesia. Plasma concentrations of either drug were detected in less than 10% of subjects and, when measurable, were well below therapeutic levels<sup>45</sup>.

#### 1.42 Baclofen

The partial ligation of the sciatic nerve is a widely used animal model of peripheral neuropathic pain. It is generally accepted that this model may mimic many important characteristics of neurogenic pain in patients after peripheral nerve injury<sup>47-49</sup>. The anti-nociceptive effects of baclofen in a rat model of chronic peripheral neuropathic pain were measured and the results suggest that baclofen increases the pain threshold. However, the baclofen induced increase in

latency was significantly higher in the intact hind limbs compared to the ligated ones in CCI rats. Based on these results, the authors concluded that “baclofen has antinociceptive action, which is attenuated in the model of chronic neuropathic pain probably due to the degeneration of GABA interneurons after chronic constriction injury”<sup>48</sup>.

L-baclofen has shown superiority over gabapentin for relieving neuropathic pain and inflammation in rat models. These findings confirm previous studies showing an inhibition by D,L-baclofen of hyperalgesia and allodynia in the chronic constriction injury and spinal nerve ligation models of chronic neuropathic pain<sup>50-52</sup>.

Baclofen, an agonist of the metabotropic GABA receptor, is used in clinical practice for the treatment of spasticity of skeletal muscles, and some studies suggest it may also exert an analgesic effect<sup>48</sup>. Anghinah<sup>53</sup> reported two cases involving patients with chronic severe painful diabetic neuropathy refractory to chlorpropamide and carbamazepine/amitriptyline. The patients were started on 10mg/day, orally, of baclofen (subsequently increased to 20mg/day), with complete elimination of pain reported after 4 months and 15 months respectively. Both patients tolerated the baclofen without side effects.

Therefore, there are data suggesting baclofen can be helpful with respect to neuropathic pain in both animals and people, but the baclofen tested thus far has been systemically administered. The rationale for using baclofen topically, as in the case of both ketamine and amitriptyline, lies in the fact that the target of baclofen, gaba receptors, both a and b, have been found to exist in the peripheral nervous system<sup>87, 88,89</sup>. In fact, the action of gaba b agonists and antagonists has been demonstrated both in vitro<sup>87</sup> and in animal organs<sup>88</sup> with respect to peripheral activity. Therefore, since gaba is a major inhibitory neurotransmitter, and the combination of ketamine and baclofen is hypothesized to work together to decrease glutamate at the cellular level and therefore decrease pain signal transmission, if all receptors exist in peripheral nerves, then this action might be local, as opposed to systemic<sup>40</sup>.

#### 1.43 Pharmacology of topical absorption

According to pharmacology experts, the permeability of a compound is due primarily to the concentration in the vehicle and its ability to cross the stratum corneum of the skin<sup>54</sup>. Compounding pharmacists have much experience with mixing compounds in vehicles and cite Lipoderm or PLO gel as the most penetrable (personal communication Gateway Pharmacy, Mike Riepl, RPh). Numerous peer review articles discuss topical mechanisms of action for amitriptyline, ketamine and baclofen and how they differ from systemic effects including the fact that topical agents exhibit a lack of unwanted toxicities that are seen with systemic absorption<sup>46, 55-56</sup>. In addition, researchers have used topical application of these agents to explore various properties<sup>57-59</sup>. Therefore, though extensive studies have not been done to definitively determine the local absorption rate for various compounds, the pilot and randomized data are convincing that the agents are being absorbed and having an effect in neuropathic pain.

The use of a compounded base that contains penetration enhancers is the preferred method of administration of topical analgesics and has been found to be more efficacious than simple creams, gels, and ointments. One example is Pluronic lecithin organogel (PLO).<sup>40</sup> Several studies have used ketamine in PLO gel without appreciable systemic side effects.<sup>41,58,59</sup> Studies investigating the combination of ketamine and amitriptyline have used creams. Several of these have evaluated serum levels of agents<sup>43,44,45</sup>, and found no systemic absorption. In one study alone evaluating the combination of ketamine and amitriptyline, in 21 patients, there was no detectable ketamine or norketamine and in 14 patients, no amitriptyline or nortriptyline detected in the serum<sup>44</sup>. Since we are proposing a mixture of three agents in a penetration enhancing gel, we will evaluate serum concentrations of the drugs in a subset of participants; and in all participants, we will monitor adverse events commensurate with systemic administration of opioids (specifically, somnolence/depressed level of consciousness and confusion -- see Adverse Event Stopping Rule in Section 16.8).

A recent abstract presented at the American Pain Society Meeting in May, 2007 describes a study looking at the bioavailability of morphine in PLO gel. This study, done by pain experts at Northwestern University, demonstrates that the bioavailability of morphine in PLO gel was less than 2% of that of morphine administered subcutaneously.<sup>90</sup> In addition, pharmacokinetic data over 96 hours in 36 healthy adults found topical 4% amitriptyline and topical 2% ketamine to have systemic concentrations well below that of systemically administered agents. The highest single concentration of amitriptyline was 5.91 ng/ml and of ketamine was 10.7 ng/ml. For example, CNS depressant effects of ketamine are seen at concentrations of 0.6 to 2.0 micrograms/ml. This is 600 nanograms/ml and is far above the highest single concentration found when topically applied<sup>91</sup>.

#### 1.44 Summary and Rationale for use of combination analgesia gel

Compounding pharmacists, including those at the Mayo Clinic, have been mixing amitriptyline and ketamine in a gel to treat neuropathic pain of various etiologies for some time (personal communication Gateway Pharmacy and Roger Warndahl, Mayo Clinic Pharmacy). There have been one case report manuscript, three pilot trials and two randomized trials evaluating topical amitriptyline and ketamine for various types of neuropathic pain. The two randomized trials present a nice contrast as one used low dose (2% amitriptyline/1% ketamine) and one used both high (4% amitriptyline/2% ketamine) and low dose versus placebo. The highest dose had the most efficacy and was statistically significantly better than placebo.

The following case study of a patient in Bismarck, ND, who had a history of painful neuropathy in her feet of unknown etiology, is interesting. She was treated with a combination gel of amitriptyline, ketamine and baclofen with total resolution of her symptoms (personal communication, Tammy Fischer, Bismarck, ND). Although baclofen has less pilot data, consisting of one case study manuscript, the animal model provides evidence that it offers a different mechanism of action than amitriptyline or ketamine. The combination of the three products, having different mechanisms of action, makes this combination an intriguing option to test in chemotherapy-induced peripheral neuropathy.

Expert compounding pharmacists propose as a best evidenced base combination for neuropathic pain, 3 agents in a base that is a penetration enhancer, such as Pluronic lecithin organogel (PLO). The three agents recommended are first and foremost, an NMDA antagonist, second, a glutamate/AMPA antagonist and third, a GABA<sub>b</sub> agonist. In this study, we propose two of the three recommended agents (ketamine and baclofen) with amitriptyline instead of with gabapentin (a glutamate/AMPA (NA channel) antagonist). The reason for this is that preliminary positive results have been published with amitriptyline as a topical agent and previous studies in NCCTG have not found benefit with gabapentin for peripheral neuropathy.

Therefore, based on expert opinion and literature in compounding pharmacy as well as the complex physiology of neuropathic pain involving GABA and NMDA, we feel it is essential to study the combination product, ketamine, baclofen and amitriptyline.

This combination of analgesics represents two innovations in chemotherapy-induced peripheral neuropathy studies in NCCTG. The first is that this is a topical, as opposed to a systemic, application affording higher doses that have a greater chance of efficacy without unwanted side effects. The second is that there are two novel mechanisms of action being evaluated: NMDA and GABA<sub>b</sub> agonist action. Previous agents evaluated for CIPN have been sodium/calcium channel modulators. Though it is hypothesized that relief of neuropathic pain occurs at the dorsal nerve root ganglion in the animal model, agents that have been successful in animal models have not been effective when tested in randomized, placebo-controlled trials (ie: gabapentin, lamotrigine). It is time to test different mechanisms. Therefore, based on randomized pilot data of efficacy with neuropathic pain in humans and a compelling anecdotal experience, these three agents (amitriptyline, ketamine and baclofen) are being tested.

#### 1.45 Side effects of ketamine, amitriptyline, and baclofen

Previous studies using amitriptyline (1-2%) and ketamine (1%) demonstrated no significant systemic absorption and minimal side effects. Reported side effects included intermittent drowsiness, dry mouth, intermittent rapid heart rate and palpitations without clinically significant abnormalities on ECG or vital signs<sup>44</sup>, minor temporary skin irritation, sedation, tinnitus, peeling skin at application site, facial acne, burning feet, swollen feet<sup>43</sup>, burning skin irritation and rash at the site of application<sup>42</sup>.

There are no published data on the use of topical baclofen. However, safety and efficacy of oral and intrathecal baclofen has been established. Topical baclofen is available through compounding pharmacies in doses ranging from 0.5% to 2%. It is often used in combination with amitriptyline or ketamine. There are no reported side effects of topical baclofen. The most common side effects of oral baclofen include drowsiness (10-63%), dizziness (5-15%), weakness (5-15%), and fatigue (2-4%). Other side effects may include confusion (1-11%), headache (4-8%), insomnia (2-7%), hypotension (0-9%), nausea (4-12%), constipation (2-6%), and urinary frequency (2-6%). Hallucinations and seizures have been reported in rare instances following abrupt withdrawal<sup>58</sup>. However, since we are

using topical baclofen and therefore do not anticipate systemic effects, we expect any side effects to be minimal.

#### 1.46 Study design and dosing

A randomized, placebo-controlled, two arm clinical trial is proposed based on preclinical, pilot and case study data to evaluate the ability of a ketamine/amitriptyline/baclofen gel to alleviate the pain, numbness, and/or tingling of chemotherapy-induced peripheral neuropathy. Based on previous studies, effects on local pain receptors should be immediate but there is some thought that for consistent pain relief, saturation of the receptors needs to occur. Therefore, prolonged use is the better test of efficacy and results should be evident within 4 weeks. Since this is a placebo controlled trial that offers the option of a continuation phase, we will limit the randomized, double-blind portion of the trial to 4 weeks to avoid a prolonged period of placebo use for participants assigned to that arm. We will use the continuation phase to evaluate longer term effects of the topical treatment in terms of efficacy and side effects. The dose of the components of the gel is also based on previous data from the positive randomized trial<sup>45</sup>. Each application of active gel will contain 40 mg amitriptyline HCl, 20 mg ketamine and 10 mg of baclofen. This will be used on up to 4 sites at maximum of twice daily. Therefore, the daily dose to be delivered will not exceed 320 mg of amitriptyline HCL, 160 mg of ketamine and 80 mg of baclofen.

## 2.0 Goals

### 2.1 Primary Goal

2.12 To compare sensory neuropathy as measured by the sensory scale of the EORTC QLQ-CIPN20 for the topical amitriptyline HCl/ baclofen/ ketamine and placebo arms to determine whether topical amitriptyline HCl/ baclofen/ ketamine is effective in improving sensory neuropathy in patients with CIPN.

### 2.2 Secondary Goals

2.21 To compare motor and autonomic symptoms and functioning (EORTC QLQ-CIPN20); mood states (POMS-B); pain (BPI); and peripheral neuropathy (Peripheral Neuropathy Question); in patients in the two treatment arms.

2.22 To assess the adverse event profile of topical amitriptyline HCl/ baclofen/ ketamine by CTCAE v3.0 and by a weekly patient-completed Symptom Experience Diary.

2.23 To explore whether topical amitriptyline HCl/ baclofen/ ketamine is absorbed systemically.

## 3.0 Patient Eligibility

### 3.1 Required Characteristics

3.11 Received, or are currently receiving, neurotoxic chemotherapy (including but not limited to taxanes such as paclitaxel or docetaxel; platinum-based compounds such as carboplatin, cisplatin, or oxaliplatin; or vinca alkaloids such as

vincristine or vinblastine, or other neurotoxic chemotherapy agents such as bortezomib, lenalidomide or thalidomide). Note: Patients on daily chemotherapy will not be eligible for this trial.

- 3.12 Pain or symptoms of peripheral neuropathy of duration  $\geq 1$  month attributed to chemotherapy.
- 3.13. A score of  $\geq 4$  out of 10 on the numbness/tingling/pain numeric analogue scale (see Appendix VII).
- 3.14  $\geq 18$  years of age.
- 3.15 Ability to sign informed consent and understand the nature of a placebo-controlled trial.
- 3.16 ECOG Performance Status (PS) of 0, 1, or 2. (This form is now on the NCCTG website <https://ncctg.mayo.edu/ncctg/formsNonProtocolSpecificForms/>.)
- 3.17 Ability to complete questionnaires by themselves or with assistance.
- 3.18 Life expectancy  $\geq 4$  months.

Add 1

- 3.19a Women who are not able to bear children. Note: This is defined by those who are menopausal (12 months and no menstrual period if natural menopause), have had a hysterectomy and/or oophorectomy, permanent surgical sterilization (tubal ligation).
- 3.19b Creatinine  $\leq 1.5 \times$  UNL obtained  $\leq 90$  days prior to registration.
- 3.19c Neuropathy limited to either hands or feet (or both) where gel can be applied.

### 3.2 Contraindications

- 3.21 Pre-existing or history of peripheral neuropathy due to any cause other than chemotherapy (diabetes, alcohol, toxin, hereditary, etc.).
- 3.22 History of an allergic reaction to amitriptyline HCl, baclofen, and/or ketamine.
- 3.23 Treatment  $\leq 30$  days with anticonvulsants, tricyclic antidepressants, MAO inhibitor, or other neuropathic pain medication agents such as carbamazepine, phenytoin, valproic acid, gabapentin, lamotrigine, topical lidocaine patch or gel, capsaicin cream, amifostine, etc.

**Note:** Patients who have taken any of these agents for peripheral neuropathy for  $\leq 1$  week during the past 30 days, but are no longer taking the agent, are not excluded.

- 3.24 Diagnosis of coronary artery disease including but not limited to MI, PTCA, or CABG  $\leq 5$  years or diagnosis of congestive heart failure of any NY heart class I-IV (this form is now on the NCCTG website <https://ncctg.mayo.edu/ncctg/formsNonProtocolSpecificForms/>). Note: Valve

replacements are permitted as long as patient has fully recovered from the surgery.

- 3.25 Other medical conditions, which in the opinion of the treating physician/allied health professional would make this protocol unreasonably hazardous for the patient.
- 3.26 Current use of any of the study agents in any manner.
- 3.27 Skin abnormalities at the intended application sites (hands and feet) of study gel (i.e.: skin breakdown)
- 3.28 Any of the following:
  - Pregnant women
  - Nursing women
  - Women of childbearing potential.

Add 1

**4.0 Test Schedule**

Tests and procedures	Active-Monitoring Phase			
	Double-Blind Phase			Optional Continuation Phase
	≤30 days prior to registration	Baseline	Weekly x 4 weeks (weeks 1-4)	Weekly x 8 weeks (weeks 5-12)
History and exam, weight, performance status, including mental status exam and skin examination of hands and feet <sup>2</sup>	X			
Creatinine Blood Test	X <sup>1</sup>			
Peripheral Neuropathy Question (Appendix VII)	X <sup>11</sup>			
Patient questionnaire booklet completion <sup>3</sup> EORTC QLQ-CIPN20 (Appendix III) <sup>10</sup> BPI (Appendix V) <sup>10</sup> POMS-B (Appendix IV) <sup>10</sup> Symptom Experience Diary (Appendix II) Peripheral Neuropathy Question (Appendix VII) Subject Global Impression of Change (Appendix VI) <sup>8</sup>		X	X	X <sup>6,7</sup>
Adverse Event Assessment <sup>4,5</sup>		X	X	X <sup>6</sup>
Research Blood Draw ( <b>MCR Participants ONLY</b> )			X <sup>R</sup>	
CRA/Nurse phone call <sup>12</sup> (Appendices VIII and IX), Neurotoxicity Evaluation (Appendix XI)		X <sup>9</sup>	X <sup>5</sup>	X <sup>5,6</sup>

1. Must be obtained ≤ 90 days prior to registration and is considered standard treatment to evaluate renal function.
2. Skin assessment of hands and feet must be done ≤7 days prior to registration.
3. Patient questionnaire booklets **must** be used and completed weekly; copies are not acceptable for this submission. A self-addressed, stamped envelope will be provided for patients to return questionnaires to the healthcare provider and/or study staff.
4. May be completed over the phone or at in-person visit. When the patient is seen in the clinic, health care personnel are to (in person) evaluate skin integrity of hands and feet as well as mental status using the CTC.
5. On weeks when the patient is not seen in the clinic, the CRA/Nurse phone call is used to evaluate compliance and adverse events, answer questions, and encourage questionnaire completion and return.
6. Continuation on the study can only occur after the treatment site has received completed patient questionnaires from the double-blind phase of the study.
7. Appendices II (SED) and VII (Peripheral Neuropathy Question) to be completed weekly during weeks 5-12. Appendix III (EORTC QLQ-CIPN20) to be completed at weeks 6, 8, 10, and 12. Appendix IV (POMS-B) to be completed at weeks 8 and 12. Appendix V (BPI) does not need to be completed during the continuation phase.
8. To be completed at the end of week 4 only (i.e., before unblinding occurs).
9. For the Provider Rated Peripheral Neuropathy Scale (CTC) only.

10. During double blind phase – Appendices III, IV, and V need to be completed at baseline and week 4. For time points during the continuation phase (weeks 5-12), see footnote 7.
  11. Use this as the baseline measure for Appendix VII.
  12. Any comments pertinent to the study evaluation from the patient during the phone call (or in person) should be recorded in the comments section of the Evaluation/Treatment form.
- R Mayo Clinic Rochester only - research funded optional blood draw. Single blood draw to be completed one time at any time during weeks 3 or 4 of double blind phase (see Section 14.0).

## 5.0 Stratification Factors

- 5.1 Chemotherapy with a neurotoxic agent: Active vs. non-active (i.e. completed or discontinued).
- 5.2 Use of opioids or oral pain medications: Yes vs no.
- 5.3 Eligibility pain rating: 4-7 vs. 8–10 (see Section 3.13 and Appendix VII).
- 5.4 Previous ineffective pharmacologic treatment for peripheral neuropathy: Yes vs. no

In reviewing the need for stratification factors and the literature, several revisions have occurred. The stratification factors are based on variables that may affect sensory changes and pain relief response. Since participants will already have to have peripheral neuropathy, risk factors for neuropathy are not necessary as stratification factors (such as types of chemotherapy, cumulative dose, etc.). Continued exposure to a neurotoxic agent, current use of pain medications and severity of pain at the beginning of the trial are variables that present potential confounding effects for the primary outcome of this study. Finally, stratifying by previous ineffective treatment is to ensure refractory neuropathies are equally represented in each arm.

## 6.0 Registration/Randomization Procedures

### 6.1 Double-Blind Phase

#### 6.11 Registration Procedures

- 6.111 To register a patient, access the NCCTG web page at <https://ncctg.mayo.edu/training> and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If you are unable to access the website, call the NCCTG Registration/Randomization Center at (507)284-4130 between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the NCCTG web page and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an NCCTG subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

- Contact the NCCTG Registration/Randomization Center (507)284-4130. If the patient was fully registered, the Registration/Randomization Center staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.112 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: [www.ctsu.org/rss2\\_page.asp](http://www.ctsu.org/rss2_page.asp). Guidelines can be found under Quick Fact Sheets.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

- 6.113 Prior to accepting the registration/randomization, the remote registration/randomization application will verify the following:
- IRB approval at the registering institution
  - Patient eligibility
  - Existence of a signed consent form
  - Existence of a signed authorization for use and disclosure of protected health information (*USA institutions only*)
- 6.114 Treatment on this protocol must commence at the accruing membership under the supervision of an NCCTG member physician or allied health professional.
- 6.115 Treatment cannot begin prior to registration and must begin  $\leq 28$  days after registration.
- 6.116 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.
- 6.117 All required baseline symptoms (see Section 10.3) must be documented and graded.
- 6.118 Study drug availability checked.
- 6.119 Patient questionnaire booklet availability checked; copies are not acceptable for this submission.

6.12 Randomization Procedures:

After the patient has been registered into the study, the values of the stratification factors (Section 5.0) will be recorded, and the patient will be randomly assigned to one of the following treatment groups:

- Topical gel of amitriptyline HCl, baclofen, and ketamine bid
- Identical placebo gel bid

#### 6.13 Translational Research (Mayo Clinic Rochester patients only)

Add 1

An optional translational research component is part of the study for Mayo Clinic Rochester patients only. There will be an option to select if the patient is to be registered onto this component (Section 14.0).

- Patient has/has not given permission to give a blood sample for research testing.

#### 6.14 Procedures for Double-Blinding the Treatment Assignment

6.141 After the treatment assignment has been ascertained by the remote registration/randomization application, the patient's study medication code number will be displayed on the confirmation of registration screen.

6.1411 The data manager/nurse/pharmacist at the patient's institution must contact the randomization center for a code number when additional study product is needed for the patient.

6.142 The number of the treatment assigned to the patient will be recorded on the dosing form.

6.143 Randomization Center personnel will monitor the supply of coded bottles at each participating institution and will arrange for the Research Base oncology pharmacist to send further supplies to the participating institutions as needed.

#### 6.2 Optional Continuation Study

6.21 The double-blind phase of the study must be completed prior to the treatment code being broken; that is, after the treating site has received the completed patient questionnaire booklet.

6.22 If the patient and physician want to continue with the active gel, or if on placebo, begin the active gel, call (507/284-4130) or fax (507/284-0885) a completed continuation phase eligibility checklist to the Randomization Center between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.23 Treatment cannot begin prior to registration and must begin  $\leq 28$  days after registration.

Add 1 **7.0 Protocol Treatment**

## 7.1 Treatment Schedule

Agent	Dose Level	Route	Day	Duration of Treatment
Amitriptyline HCl/ ketamine/baclofen gel	1.31 grams of compounded gel = 40 mg amitriptyline HCl, 10 mg baclofen, 20 mg ketamine. Contents of one level measuring spoon which will be supplied.	Apply one level spoonful of gel topically to <u>each area</u> of pain, numbness, and/or tingling <sup>1</sup>	Twice daily (in morning and before bedtime)	4 weeks; study gel will not be applied on days patients are receiving chemotherapy treatment
Placebo gel	1.31 grams of gel = Contents of one level measuring spoon which will be supplied	Apply one level spoonful of gel topically to <u>each area</u> of pain, numbness, and/or tingling <sup>1</sup>	Twice daily (in morning and before bedtime)	4 weeks; study gel will not be applied on days patients are receiving chemotherapy treatment

1. No more than 4 areas of pain, numbness, and/or tingling should be treated at a single time point (i.e. max 4 spoonfuls of gel per application).

See Appendix X for Patient Instructions for Pain/Placebo Gel Application.

Refer to 14.0 if a Mayo Rochester patient is participating in optional blood draw.

- 7.2 In the event of an emergency, call the Randomization Center at (507) 284-4130 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. central time.

## 7.3 Optional Continuation Phase

Agent	Dose Level	Route	Day	Duration of Treatment
Amitriptyline HCl/ ketamine/baclofen gel	1.3 grams of compounded gel = 40 mg amitriptyline HCl, 10 mg baclofen, 20 mg ketamine. Contents of one level measuring spoon which will be supplied.	Apply one level spoonful of gel topically to <u>each area</u> of pain, numbness, and/or tingling <sup>1</sup>	Twice daily (in morning and before bedtime)	8 weeks

1. No more than 4 areas of pain, numbness, and/or tingling should be treated at a single time point (i.e. max 4 spoonfuls of gel per application).

Participants may choose to continue on the active gel or if on placebo, begin the active gel for an additional 8 weeks. Participants may not start on the continuation phase of the study until questionnaire data from the double-blind phase has been received by the

treatment site.

## 8.0 Dosage Modification Based on Adverse Events

Dermatology/Skin	Rash: hand-foot skin reaction grade $\geq 2$	Stop treatment
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During the double-blind phase, if the patient develops any symptoms attributed to the study gel that are considered by the patient and/or physician to be of unacceptable severity then the patient will be taken off study and the study code can be broken (after all adverse event decisions have been made and the patient has completed questionnaires up to stopping) if the physician feels that it would be helpful to know whether the patient was on a placebo.

## 9.0 Ancillary Treatment

Management of other symptoms allowed as needed. Changes in the use of pain medications should be noted on the Concurrent Treatment Form. No other topical agents should be used on areas where study gel is applied.

## 10.0 Adverse Event (AE) Reporting and Monitoring

10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be accessed from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2). Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.3 and 18.0).

Expedited adverse event reporting requires submission of an Adverse Event Expedited Reporting System (AdEERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.12 Expected vs. Unexpected

- The determination of whether an AE is expected is based the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

## 10.2 Expedited Adverse Event Reporting Requirements

### 10.21 Standard Expedited Reporting for Commercial Agents

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE <sup>1</sup>
Submit a full expedited commercial report via AdEERS within 7 working days <sup>2</sup>	X	X

1. Any increased incidence of a known AE (as reported in the package insert or the literature), including adverse events resulting from a drug overdose.
2. In the rare event when Internet connectivity is disrupted, a report may be prepared using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (accessible from the CTEP Home Page at <http://ctep.cancer.gov>). Contact the NCCTG SAE Coordinator (as identified on the NCCTG Protocol Resources page) for back-up submission instructions.

### 10.22 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	Reporting for this event required during and after completion of study treatment.  Submit the NCI/CTEP Secondary AML/MDS Report form within 15 days via fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628. The Operations Office will submit to NCI.

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	<p>Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form.</p> <p>If an AdEERS report has been submitted, this form does not need to be submitted.</p> <p>Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.</p>

10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

Category	Adverse Event/Symptoms	Baseline	Each evaluation
Dermatology/Skin	Rash: hand-foot skin reaction	X	X
Gastrointestinal	Constipation	X	X
	Dry mouth/salivary gland (xerostomia)	X	X
Neurology	Confusion	X	X
	Somnolence/depressed level of consciousness	X	X

10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3:

10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment

10.313 Grade 5 AEs (Deaths)

10.3131 Any death within 30 days of the patient’s last study treatment or procedure.

10.3132 Any death more than 30 days from the patient’s last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as

applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation

11.1 The primary endpoint for this study is total sensory neuropathy (area under the curve [AUC]) as measured by the sensory scale of the EORTC QLQ-CIPN20 at 4 weeks. The EORTC QLQ-CIPN20 is described below.

### 11.11 EORTC QLQ-CIPN20 (Appendix III)

The EORTC QLQ-CIPN20 is a 20-item CIPN-specific questionnaire which includes three scales assessing sensory (9 items: #31-36, 39, 40, 48), motor (8 items: #37, 38, 41-45, 49), and autonomic (3 items: #46, 47, 50) symptoms and functioning with each item measured on a 1-4 scale (1 – not at all; 4 – very much) The EORTC QLQ-CIPN20 has been tested in cancer patients receiving a variety of chemotherapies and has been shown to have internal consistency reliability based on Cronbach's alpha coefficients of 0.82, 0.73, and 0.76 for the three scales, respectively<sup>63</sup>.

11.2 Secondary endpoints include the assessment of motor and autonomic symptoms and functioning (EORTC QLQ-CIPN20); mood states (POMS-B); pain (BPI); peripheral neuropathy (Peripheral Neuropathy Question); and functional abilities. The EORTC QLQ-CIPN20 is described in Section 11.11 and the POMS-B, BPI, Peripheral Neuropathy Question and questionnaire administered at end of study evaluation are described below.

### 11.21 POMS-B (Appendix IV)

The Profile of Mood States - Brief (POMS-B)<sup>64-66</sup> is a shortened version of the original 65-item POMS with 30 items each asking the patient to select how he/she has been feeling during the past week with respect to an adjective such as “tense”, “angry”, “worn out”, etc., on a 0-4 scale (0=not at all; 4=extremely). The POMS-B consists of six identifiable mood states (tension, dejection, anger, vigor, fatigue, and confusion) and measures the patient's total mood disturbance. The POMS-B exhibits high internal consistency and high content validity<sup>65</sup>. Because of its brevity and number of mood states that it measures, the POMS-B has been extensively used in cancer research studies.

### 11.22 BPI Short Form (Appendix V)

The Brief Pain Inventory (BPI) short form is a pain assessment tool used with cancer patients to measure both severity of pain (first 4 items) and interference caused by pain (item 7 with 7 components) on 0-10 scales (0=does not interfere; 10=completely interferes)<sup>67</sup>. The reliability has been estimated with Cronbach's alpha ranging from 0.77 to 0.91 and the BPI has been validated in 25 different languages.

### 11.23 Peripheral Neuropathy Question (Appendix VII)

The peripheral neuropathy question is administered at baseline as part of eligibility criteria and will be completed weekly as a supplemental measure of peripheral neuropathy. It is a single-item numeric analogue scale assessing the level of numbness, tingling or pain in the patient's fingers and/or toes (0=no numbness, tingling or pain in fingers and/or toes; 10=numbness, tingling or pain in fingers and/or toes as bad as you can imagine). This approach has been validated in general by Cleeland et al in the development of the BPI<sup>80,81</sup>, and in cancer patients<sup>82,83</sup>. This peripheral neuropathy question will be analyzed as a separate individual construct.

#### 11.24 Subject Global Impression of Change (Appendix VI)

This questionnaire is completed by the patient at the end of the double-blind portion of the study (before the patient is unblinded). Perception of benefit from the medication will be evaluated with the Subject Global Impression of Change Scale (Appendix VI) and efficacy of blinding will be assessed by asking participants what treatment assignment they thought they had. The Subject Global Impression of Change Scale (also called the Subjective Significance Scale) has been used as an anchor for determination of minimally clinically significant differences in numerous oncology clinical trials within the NCCTG (N00C3, N01C3, N01CB, N03CA) and beyond<sup>85,86</sup>. The patient rates the change in his/her overall quality of life; physical condition; emotional state; social life; and numbness, tingling or pain in the hands and/or feet since starting the study (ranging from very much better, moderately better, a little better, about the same, a little worse, moderately worse, to very much worse).

- 11.3 Adverse events will be assessed via the health care provider in an ongoing fashion according to the CTCAE v3.0 and reported on AE forms. Additionally, adverse events will be reported via the Symptom Experience Diary (Appendix II) which patients will complete weekly. The Symptom Experience Diary asks patients to assess whether he/she has experienced a particular symptom (e.g., dizziness) using a 0-10 scale (0=not at all; 10=as bad as it can be).

### 12.0 Descriptive Factors

- 12.1 Neurotoxic chemotherapy agent exposure (check all that apply): Oxaliplatin, vincristine, other vinca alkaloids, taxanes, platinums, thalidomide, other (please note).
- 12.2 Duration of pain or neuropathy symptoms in months at baseline:  
1 to ≤ 3 vs. > 3 to ≤ 6 vs. > 6.
- 12.3 Age: < 70 vs. ≥ 70
- 12.4 Gender: Male vs female.
- 12.5 Exposure to neurotoxic agents over lifetime: Single agent vs. multiple agents.

### 13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 A patient is deemed *ineligible* if, at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.
- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted and patient should be taken off study.
  - If the patient never received treatment, initial material must be submitted.
- The patient may continue non protocol treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.
- 13.2 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient may continue non-protocol treatment at the discretion of the healthcare provider as long as there are no safety concerns, and the patient was properly registered.
- 13.3 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted.
- 13.4 During the double-blind phase of the study, if, in the judgment of the attending physician or allied health professional, it would be helpful for the future clinical care of the individual patient, the code may be broken. The Randomization Center may be called to find out which study therapy the patient was receiving. Participants may choose to continue on the active gel or if on placebo, begin the active gel for an additional 8 weeks. Assessments of efficacy per the EORTC QLQ-CIPN20 (Appendix III), Peripheral Neuropathy Question (Appendix VII), and side effects per the Symptom Experience Diary (Appendix II) will be collected. The POMS-B (Appendix IV) will be assessed at weeks 4 and 8 of the continuation phase. Participants may NOT receive gel and start on the continuation phase until questionnaire data has been received by the treatment site.

### 14.0 Non-solid Tissue (Body Fluid) Biospecimens

Add 1

- 14.1 Non-solid Tissue Biospecimen Submission – **MAYO CLINIC ROCHESTER (MCR) PARTICIPANTS ONLY.**

NOTE: Participants must have consented to submission of the following tissue(s).

Type of biospecimen to submit	Mandatory or optional	When to submit <sup>1</sup>	Reason for submission (background/methodology section)	Where to find specific details for specimen submission
Blood/blood products (serum and plasma)	Optional <b>MCR participants ONLY</b>	One time during weeks 3 or 4.	Determination of study drug concentrations (Section 14.4)	Section 14.2

**Draws must be collected within 8 hours of last gel application.**

14.2 Blood/Blood Products

14.21 **Kits are not required for this study.**

14.22 All specimens must be collected and processed **Monday-Friday ONLY.**

14.23 Verify ALL sections of the NCCTG Blood Specimen Submission Form are completed and filled in correctly. Enter information from the NCCTG Blood Specimen Submission Form into the remote data entry system within 7 days of specimen collection (see Forms Packet).

14.24 Provide the participant with a pink card and direct the participant to have their blood drawn at any MCR phlebotomy laboratory.

14.25 The phlebotomy laboratory will collect blood/blood products in the order listed in the table that follows and forward the specimens and pink card to Special Study Processing (Laboratory Medicine and Pathology Department, Hilton CL) for processing.

Summary Table of Research Blood/Blood Products to Be Collected for This Protocol

Indicate if specimen is mandatory or optional	Collection tube description and/or additive (color of tube top)	Volume to collect per tube (number of tubes to be collected)	Blood product being processed	One time during weeks 3 or 4 <sup>1</sup>	Process at site?
Optional	None (red)	10 mL (3)	Serum	X	Yes
Optional	EDTA (purple)	10 mL (1)	Plasma	X	Yes

<sup>1</sup> **Blood draw must be within 8 hours of last gel application.**

14.26 Special Study Processing will process the whole blood in no additive (red-top) tubes into serum and the whole blood in EDTA (purple-top) tube into plasma per standard institution protocols.

14.261 Special Study Processing will forward 3.0 mL EDTA plasma to the Drug Laboratory (Hilton 7) to determine amitriptyline HCl concentrations, test code #8125.

14.262 Special Study Processing will forward 3.0 mL serum to the Drug Laboratory (Hilton 7) to determine baclofen concentrations, test code #81255.

14.263 Special Study Processing will forward 6.0 mL serum to National Medical Services to determine ketamine/norketamine concentrations, test code #90366.

14.27 Residual serum and plasma specimens will be discarded.

## 14.3 Other Body Fluids (None)

## 14.4 Background/Methodology Information

14.41 Blood/blood product samples will be collected for the following research:

14.411 Blood will be collected one time during weeks 3-4 of the double-blind phase (draw must be within 8 hours of last gel application) to determine if this combination and dose of three opioids is absorbed systemically.

14.4111 Amitriptyline HCl levels will be measured by reverse phase high performance liquid chromatography (HPLC) in the Drug Lab at Mayo Clinic Rochester (test code #8125).

14.4112 Ketamine and norketamine will be measured by liquid chromatography/mass spectrometry at National Medical Services (test code #90366).

14.4113 Baclofen concentrations will also be measured by HPLC in the Drug Lab at Mayo Clinic Rochester (test code #81255).

## 14.5 Return of Genetic Testing Research Results

No genetic specimens will be collected from non-solid tissue (body fluid) biospecimens for this study.

**15.0 Drug Information**

Add 1

- IND 78,250

## 15.1 Amitriptyline HCl, baclofen, and ketamine gel and matching placebo gel

15.11 Preparation and storage: An amitriptyline HCl/baclofen/ketamine PLO based gel will be compounded for use in this trial. The gel will contain the following:

Amitriptyline HCl (3.05%)

Baclofen (0.77%)

Ketamine (1.53%)

Pluronic lecithin organogel (PLO) 30%

One level spoonful contains 1.31 grams of the gel and will provide 40 mg amitriptyline HCl, 10 mg baclofen, and 20 mg ketamine.

The gel will be compounded at Gateway Compounding Pharmacy in Bismarck, North Dakota. The gel will be in wide mouthed jars and will be stored at room temperature, 59 to 86°F. The product beyond-use date will be a maximum of 6 months.

Calculations for the formulation and dose of the gel were computed by the expert compounding pharmacist at Gateway Compounding Pharmacy. The baclofen and ketamine were converted to base formulations and amitriptyline HCl will

remain expressed as a salt in order to better evaluate potency. A potency over time analysis will be completed by an independent company, Eagle Analytical. 30% PLO will be used as it is more stable with respect to temperature changes. In addition, a certificate of analysis for each lot of chemical will be available.

15.12 Known potential adverse events:

Reported side effects of amitriptyline HCl and ketamine have included intermittent drowsiness, dry mouth, intermittent rapid heart rate and palpitations without clinically significant abnormalities on ECG or vital signs<sup>44</sup>, minor temporary skin irritation, sedation, tinnitus, peeling skin at application site, facial acne, burning feet, swollen feet<sup>43</sup>, burning skin irritation and rash at the site of application<sup>42</sup>.

The most common side effects of oral baclofen include drowsiness (10-63%), dizziness (5-15%), weakness (5-15%), and fatigue (2-4%). Other side effects may include confusion (1-11%), headache (4-8%), insomnia (2-7%), hypotension (0-9%), nausea (4-12%), constipation (2-6%), and urinary frequency (2-6%). Hallucinations and seizures have been reported in rare instances following abrupt withdrawal<sup>58</sup>.

15.13 Drug procurement: The NCCTG research base pharmacist will obtain the drug from Gateway Compounding Pharmacy in Bismarck, North Dakota. Each institution will order the drug for the double-blind and/or continuation phase from the NCCTG research base pharmacist. Submit the NCCTG Clinical Drug Order/Return Form request to:

Medical Oncology Pharmacist  
Mayo Clinic  
Gonda 10-178  
Rochester, MN 55905  
FAX (507) 284-3464

*Outdated or remaining drug/product should be destroyed on site. Do not return outdated or remaining drug/product to the research base pharmacy unless specifically requested.*

15.14 Nursing guidelines

15.141 Patients may experience a slight “burning” sensation when applying the gel. This should be mild in nature and short-lived.

15.142 Instruct patients to rub gel into skin very well. As it becomes sticky, the patients should dip their fingers in water and continue rubbing until the gel is rubbed in.

15.143 Patients should not handle food, rub their eyes, or touch their hands or fingers to any mucous membrane until the gel is completely dry for about 1 hour.

15.144 Patients should avoid washing hands or feet until the gel is completely

dry, for about one hour.

- 15.145 Instruct patient to concentrate the gel to the area of pain only.
- 15.146 Systemic absorption is not expected, however instruct patients to report any dizziness, drowsiness, rapid heart rate or palpitations as these may be signs of systemic effects.
- 15.147 Instruct patients to report any skin irritation, peeling or rash at the site of application. Advise patients that if they are allergic to egg whites, they may have a skin reaction to the base.
- 15.148 Instruct patients to not use the study gel on days they are receiving chemotherapy.
- 15.149 Review with the patient in detail the instruction sheet for applying the gel.

- 15.2 Placebo PLO gel – Pluronic F 127, lecithin, isopropyl palmitate and preserved water

The placebo will consist of pluronic lecithin organogel without any additives. It will be prepared by Gateway Health Mart Pharmacy North in Bismarck, North Dakota and will be packaged in wide mouth jars identical to the active treatment and will be stored at room temperature. The color and shelf life will also be identical to that of the active gel.

## 16.0 Statistical Considerations and Methodology

- 16.1 This two-arm placebo-controlled double-blind randomized phase III trial will use a dynamic allocation to allocate an equal number of patients to one of two treatment regimens: topical amitriptyline HCl/ baclofen/ ketamine versus placebo for CIPN. This procedure will balance the marginal distributions of the stratification factors between these two treatment regimens<sup>74</sup>. All hypothesis testing will be carried out using a two-sided  $\alpha=0.05$  including all patients meeting the eligibility criteria who have signed a consent form and who did not cancel prior to receiving treatment.
- 16.2 Primary and secondary endpoints
  - 16.21 The primary endpoint for this study is total sensory neuropathy (area under the curve [AUC]) as measured by the sensory subscale of the EORTC QLQ-CIPN20 (items 31-36, 39, 40 and 48) at baseline and weeks 1 to 4, adjusting for baseline.
  - 16.22 Secondary endpoints for this study are:
    - Motor neuropathy as measured by the EORTC QLQ-CIPN20 (Items 37, 38, 41-45).
    - Autonomic symptoms and functioning as measured by the EORTC QLQ-CIPN20 (Items 46, 47, and 50).

- Mood states and total mood disturbance as measured by the POMS-B. Items comprising the tension-anxiety subscale include 1, 6, 12, 16 and 20. Items for the anger-hostility subscale are 2, 9, 14, 25 and 28. Vigor-activity are 4, 8, 10, 27 and 30. Fatigue-inertia; 3, 13, 19, 22 and 23. Confusion-bewilderment is 18, 24, 26 and 29. Depression-dejection (not clinical depression) is comprised of items 7, 11, 15, 17 and 21.
- Pain severity and interference as measured by the BPI. Pain severity is the summed score of the first 4 items and the interference score is the sum of the 7 components of item 7.
- Numbness, tingling and pain as measured by the Peripheral Neuropathy Question (yielding a 0 to 10 score).
- Perception of benefit per the Global Impression of Change described in 11.24.
- Frequency and severity of adverse events reported by the patient in the Symptom Experience Diary and evaluated through clinical assessment per the CTCAE v3.0

### 16.3 Analysis plans

#### 16.31 Primary analysis

The primary endpoint for goal 2.12 will be total sensory neuropathy (AUC) as measured using the sensory neuropathy scale of the EORTC QLQ-CIPN20. The specific items are listed above in 16.21. The AUC summary statistic will be calculated for each patient using the baseline and weeks 1 to 4 data. If a patient fails to provide week 4 data, the AUC summary statistic will be pro-rated. If a patient cancels or only provides baseline data, he/she will be excluded from the analysis. The primary endpoint analysis of the total AUC sensory neuropathy scores will compare the average AUC for the placebo arm to the average AUC for the topical amitriptyline HCl/ baclofen/ ketamine arm using a single two-sample independent samples *t*-test or Wilcoxon rank sum test as appropriate. Confidence intervals will be constructed for the mean difference in total AUC sensory neuropathy score between the placebo and topical amitriptyline HCl/ baclofen/ ketamine arms.

Supplementary analyses will compare (1) the average sensory neuropathy score at baseline, (2) the average sensory neuropathy score at week 4, and (3) the average change from baseline sensory neuropathy score at week 4 for the placebo arm to that of the topical amitriptyline HCl/ baclofen/ ketamine arm using single two-sample independent samples *t*-tests or Wilcoxon rank sum tests as appropriate. Further confirmatory analyses of the primary analysis will be undertaken by use of analysis of variance (ANOVA) modeling of the total sensory neuropathy score at week 4 as the dependent variable. Baseline sensory neuropathy score, as well as the baseline patient characteristics, will be included in the modeling process.

Supplementary graphical procedures associated with the sensory neuropathy scores of the EORTC QLQ-CIPN20 will include a stream plot of individual scores over time and a plot of average scores over time for the placebo and topical amitriptyline HCl/ baclofen/ ketamine arms.

16.32 Secondary analyses to meet goal 2.21:

All endpoints will be transformed to a 0-100 point scale where applicable to aid in ease of comparison of secondary endpoints. This transformation is standard practice in NCCTG Cancer Control trials with numerous secondary endpoints<sup>84</sup>.

16.321 The analysis of total motor neuropathy (AUC) as measured using the motor neuropathy scale of the EORTC QLQ-CIPN20 will follow as specified for the primary analysis in 16.31.

16.322 The analysis of total autonomic symptoms and functioning (AUC) as measured using the autonomic symptoms and functioning scale of the EORTC-CIPN20 will follow as specified for the primary analysis in 16.31.

16.323 Data from the POMS-B will be analyzed identical to the primary endpoint in 16.31. Each mood scale will be analyzed as an endpoint as will the total mood disturbance score.

16.324 Pain severity, defined by the four items addressing worst, least, and average pain and pain right now as measured by the BPI will be analyzed identical to the primary endpoint. Additionally, total pain interference as measured by the BPI will be transformed onto a 0-100 point scale and analyzed identical to the primary endpoint.

Supplementary analysis of the worst and average pain data from the BPI will be undertaken using the classification system recommended by Serlin et al<sup>75</sup> for pain scores of 0-4, 5-6 and 7-10 representing mild, moderate and severe pain, respectively. Chi-square test will be used to test the equality of pain distributions across the two study groups.

16.325 The Peripheral Neuropathy Question and the provider CTC rating of sensory neuropathy will be analyzed identically to the primary endpoint.

16.326 Related to goal 2.22: For each adverse event type reported via the CTCAE v3.0, the maximum grades reported by patient during weeks 1 to 4 of the study will be compared between treatment arms using a single two-sample independent samples *t*-test or Wilcoxon rank sum test as appropriate. Incidence rates (grade  $\geq 1$ ) at baseline and during weeks 1-4 will be compared between the treatment arms using Fisher's exact test.

For each symptom captured on the Symptom Experience Diary, (1) change from baseline scores will be compared between treatment arms using a single two-sample independent samples *t*-test or Wilcoxon rank sum test as appropriate; and (2) maximum scores reported by patient during weeks 1 to 4 of the study will be compared between treatment

arms using a single two-sample independent samples *t*-test or Wilcoxon rank sum test as appropriate. Also for each symptom, incidence rates (score  $\geq 1$ ) at baseline and during weeks 1-4 will be compared between the treatment arms using Fisher's exact tests.

- 16.327 Correlational analyses will be done using primary and secondary endpoints to determine the relationships between various endpoints such as CTCAE v3.0 sensory neuropathy grades and EORTC QLQ-CIPN20 sensory neuropathy scale scores. Such correlations will be done at single data points such as baseline and weeks 1 to 4.
- 16.328 The Subject Global Impression of Change Scale data will be summarized via relative frequencies of responses by treatment arm and compared between treatment arms using chi-squared testing. An anchor-based analysis similar to that present by Osoba et al.<sup>85</sup> will be performed using the Subject Global Impression of Change items with the EORTC QLQ-CIPN20 and the Peripheral Neuropathy Question. In particular, the Spearman rank correlations will be computed between change from baseline subscale scores (at week 4) of the EORTC QLQ-CIPN20 and the Peripheral Neuropathy Question and the scores of the Subject Global Impression of Change items. Further, the small ("a little"), moderate ("moderately"), and large ("very much") effect sizes will be computed for each subscale using the appropriate (i.e., matching) Subject Global Impression of Change item. The effect size will be computed as the mean change from baseline subscale score at week 4 divided by the standard deviation of the subscale scores at baseline.

The appropriate 95% confidence interval for the proportion of patients by treatment arm identifying the actual treatment received will be computed. If the confidence interval does not contain 50% (the percentage expected if all patients are randomly guessing), it will be concluded that the blinding was ineffective. The proportion of patients on each treatment arm continuing onto the continuation phase will also be computed.

Data from the continuation phase will be descriptively presented including summary statistics (N, mean, standard deviation, median, quartiles, and range) and plots of average scores and individual patient scores over time for each endpoint (summary statistics and plots for all patients participating on the continuation phase together and separately by original treatment arm assignment).

- 16.329 Related to goal 2.23: Because participation in the translational component is expected to be small (since it is limited to patients at Mayo Rochester), the investigation of systemic absorption is exploratory. The proportion of patients with any detectable (i.e., non-zero) level will be computed for each of the three components of the gel (amitriptyline HCl, baclofen, and ketamine/norketamine). The patients on placebo will be compared with patients on active agent, descriptively. Since the sample sizes are likely to be no larger than 5 each, we are only looking for evidence of systemic absorption in a descriptive manner, not looking for statistically significant differences between groups in any way.

#### 16.4 Sample size and power calculations

We have little preliminary information about the likely variability of the AUC sensory neuropathy summary score. In such circumstances, we have pioneered a sample size estimation process known as the empirical rule effect size (ERES) procedure<sup>76-78</sup>. We have demonstrated the applicability of this procedure to numerous oncology clinical trials, including previous NCCTG studies. Using the empirical rule, we can produce a conservative estimate of the standard deviation for the AUC sensory neuropathy summary score to be roughly 16.7 percentage points based on a transformed scale of 0 to 100 units. Defining a clinically meaningful effect size as roughly equivalent to one half of this standard deviation, we are intending to detect a difference between treatment arms of 8.35 units in the average AUC sensory neuropathy summary score. We believe any smaller effect would be more a function of measurement error than true efficacy and so we set level of 10 units for a conservative estimate of the practical clinical significance to reflect the precision of the measurement<sup>76-78</sup>.

The primary analysis will be undertaken by a single *t*-test using a two-sided  $\alpha=0.05$  to compare the topical amitriptyline HCl/ baclofen/ ketamine arm versus the placebo arm. A two-sample *t*-test with 64 patients in the topical amitriptyline HCl/ baclofen/ ketamine arm and 64 patients in the placebo arm will have 80% power to detect a difference of 50% times the standard deviation. This is considered a moderate effect size by Cohen<sup>79</sup>.

Sample size will be inflated by 15% to account for missing data (e.g., patient ineligibility, cancellation, or other reasons). The total number of patients accrued hence will be 148 patients, 74 per arm.

#### 16.5 Accrual rate and time to completion

We anticipate accruing approximately 10 patients per month, based on our previous experience with similar neuropathy trials. This would mean completing accrual within 15 months from study initiation and completing double-blind data collection 16 months from study initiation.

#### 16.6 Missing data

Previous experience with imputation in NCCTG clinical trials have demonstrated that the use of various imputation methods compared to analysis of all available data provides evidence of the degree of robustness of the results relative to the assumptions of the analytical procedure. We expect the amount of missing data to be about 15% and, therefore, will adjust the accrual accordingly. This rate is determined based on the fact that this study can include patients with more advanced stages of cancer who may have unexpected changes in their health during the course of the trial. We will examine the data for any influence that would be likely to cause data to be missing for any other reason than simple random chance. In other words, we will explore the data for evidence to suggest that any concomitant influence may cause the data to not be missing completely at random.

#### 16.7 Monitoring

16.71 This study will be monitored by the NCCTG External Data Monitoring Committee (DMC), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DMC every six months as per NCI guidelines.

16.72 This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

#### 16.8 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following criteria:

- If 6 or more of the first 20 treated patients (or 25% of all patients after 20 patients have been accrued) experience a grade 3 or higher non-hematologic adverse event\* and the non-hematologic adverse event rate is higher in the active treatment arm as compared to the placebo arm.
- If 6 or more patients of the first 20 patients (or 10% of all patients after 20 patients have been accrued) experience a grade 2 or higher dermal AE on areas of study gel application or if one person experiences a Grade 3 or higher dermal AE on areas of study gel application and the adverse event rate is higher in the active treatment arm as compared to the placebo arm.

\*Sensory neuropathy is excluded, as this rate is likely to be high given the patient population being studied. Additionally, sensory neuropathy will be monitored as part of the efficacy analysis reviewed by the DMC every 6 months.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

#### 16.9 Minority accrual

This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects of topical amitriptyline HCl/ baclofen/ ketamine in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist.

Based on prior NCCTG neuropathy studies, we expect about 10% of patients will be classified as minorities by race and about 65% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

**Accrual Estimates by Gender/Ethnicity/Race**

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	5	3	0	8
Not Hispanic or Latino	91	49	0	140
<b>Ethnic Category: Total of all subjects*</b>	96	52	0	<b>148*</b>
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	1	1	0	2
Black or African American	4	3	0	7
Native Hawaiian or other Pacific Islander	0	0	0	0
White	91	48	0	139
More than one race	0	0	0	0
Unknown	0	0	0	0
<b>Racial Category: Total of all subjects*</b>	96	52	0	<b>148*</b>

**Ethnic Categories:** **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

**Not Hispanic or Latino**

**Racial Categories:** **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

**Asian** – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

**Black or African American** – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

**Native Hawaiian or other Pacific Islander** – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**White** – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

**17.0 Pathology Considerations/Tissue Biospecimens:** None.

Add 1

**18.0 Records and Data Collection Procedures**

## 18.1 Submission Timetable

Forms	Active-Monitoring Phase (Compliance with Test Schedule)			At each occurrence	
	Initial Material	Follow-up Material			
	≤4 weeks after registration	At each evaluation (Weekly)	At end of treatment	Grade 4 or 5 Non-AER Reportable Events/Hospitalization	ADR/AER
On-Study Form	X				
Baseline Adverse Events Form	X				
Concurrent Treatment Form	X	X	X		
Evaluation/Treatment Form <sup>3</sup>		X	X		
End of Active Treatment/Cancel Notification Form	X <sup>1</sup>		X <sup>6</sup>		
Adverse Event Log		X	X		
NCCTG Blood Specimen Submission Form (Section 14.0) <b>(Mayo Rochester patients only)</b>		X <sup>8</sup>			
Patient Questionnaire Booklet <sup>2</sup> (Appendices II through VII)	X <sup>5</sup>	X <sup>5</sup>	X <sup>7</sup>		
Patient Questionnaire Booklet Compliance Form <sup>4</sup>	X	X	X		
ADR/AER (see Section 10.0)					X
Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form				X	

1. Submit this form only if withdrawal/refusal prior to beginning protocol therapy occurs.
2. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
3. The CRA/Nurse Worksheets (Appendix VIII and IX) as well as Appendix XI can be used as guides when making phone calls to assist in completing this form. Any comments pertinent to the evaluation of the study should be recorded in the comments section of the form.
4. This form must be completed **only** if the Patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
5. Appendices III, IV and V to be completed at baseline and Week 4 of the double-blind phase. Appendix VI to be completed at week 4 only (i.e., before unblinding occurs). Appendices II and VII to be completed at baseline and weekly during the double blind phase.
6. Submit after 4 weeks if patient does not go on continuation phase. If patient goes on continuation phase, submit after 12 weeks. Form is completed only one time.
7. If patient goes on continuation phase, Appendices II and VII need to be completed weekly for weeks 5-12. Appendix III to be completed at weeks 6, 8, 10, and 12 only. Appendix IV to be completed at weeks 8 and 12 of the continuation phase. Appendix V does not need to be completed for the continuation phase.
8. Blood will be collected one time during weeks 3-4 for Mayo Rochester patients only.

**19.0 Budget**

## 19.1 Costs charged to patient: routine clinical care.

- 19.2 Tests to be research funded: one time optional blood draw for Mayo Clinic Rochester patients (see Sections 4.0 and 14.0).
- 19.3 Other budget concerns: drug and placebo to be supplied at no cost to the patient via NCCTG Research Base.

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# NCI Informed Consent Template for Cancer Treatment Trials (English Language)

## **\*NOTES FOR LOCAL INVESTIGATORS:**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer... What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

\*These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

N06CA, The Use of Topical Baclofen, Amitriptyline HCl, and Ketamine (BAK) in a PLO Gel vs. Placebo for the Treatment of Chemotherapy Induced Peripheral Neuropathy: A Phase III Randomized Double-Blind Placebo Controlled Study

**This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.**

This is a clinical trial, a type of research study. Your healthcare provider will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your healthcare provider for more explanation.

You are being asked to take part in this research study because you have taken or are taking a type of chemotherapy that is causing you to have peripheral neuropathy. Peripheral neuropathy is an injury to the nerves that supply sensation to the arms and legs. Some symptoms you might be experiencing may include tingling, numbness, shooting, burning, or cramping sensations in your fingers and toes.

### **Why is this research study being done?**

The purpose of this research study is to:

- See if using BAK gel rubbed into the skin will improve symptoms of peripheral neuropathy caused by chemotherapy.
- See how the use of BAK gel affects your body, mood, pain, and quality of life.
- See the effects (good or bad) of using BAK gel.

BAK represents three medications that may be useful in relieving tingling, numbness and/or pain in your hands and feet as a result of chemotherapy. B stands for baclofen which is a muscle relaxant. A stands for amitriptyline HCl which is an antidepressant often used for nerve related pain. K stands for ketamine which is an anesthetic which is thought to relieve nerve related pain when rubbed into the skin.

### **How many people will take part in the research study?**

About 148 people will take part in this study.

## **What will happen if I take part in this research study?**

Before you begin the study you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your healthcare provider.

- Medical history (you will be asked to rate your pain and any problem with numbness, tingling or pain in your fingers and/or toes)
- Physical examination
- Routine blood test to check your kidney function.

You will be "randomized" into one of the study groups to receive either medication in a Pluronic Lecithin Organogel (PLO) or plain Pluronic Lecithin Organogel (PLO) described below. PLO is a type of gel designed to serve as a base gel to which medicines can be added when they are to be used on the skin. Randomization means that you are put into a group by chance (as in the flip of a coin). A computer program will place you in one of the study groups. Neither you nor your healthcare provider can choose the group you will be in. You will not be told if you are using the active gel or the placebo. You will have an equal chance of being placed in either group.

**If you are in group 1** You will apply the BAK gel to the skin in the area where you are experiencing pain, tingling, or other effects from your peripheral neuropathy twice a day (in the morning and before bedtime) for 4 weeks.

**If you are in group 2** You will apply the placebo gel to the skin in the area where you are experiencing pain, tingling, or other effects from your peripheral neuropathy twice a day (in the morning and before bedtime) for 4 weeks. A placebo is an inactive gel used to compare the study results with the gel listed above.

You will also be asked to complete some study questionnaires before you begin to use the gel and then each week for 4 weeks after you start using the gel. The questions will ask you about your health, mood, pain, and quality of life. You will be given a questionnaire booklet to take home with you. These questionnaires should take you approximately 30 minutes to complete.

A nurse or research assistant will also call you weekly (during the weeks you do not see your healthcare provider) to ask you about any side effects you might have from the gel and to see if you have any questions about the study or the questionnaires you are completing.

## **How long will I be in the research study?**

You will be asked to use the gel for 4 weeks. After you are finished with the 4 weeks of the study, you will find out if you were using the BAK gel or the placebo gel. You may choose to enter a continuation phase of the study and start using the BAK gel if you were on the placebo gel (or continue using it) for an extra 8 weeks. If you decide to start or continue the BAK gel after the first 4 weeks of the study, a member of the study team will call you weekly for 8 weeks and you will also be asked to complete weekly questionnaires similar to those you completed during the first 4 study weeks.

### **Can I stop being in the research study?**

Yes. You can decide to stop at any time. Tell your healthcare provider if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your healthcare provider if you are thinking about stopping so any risks from the BAK gel can be evaluated by your healthcare provider. Another reason to tell your healthcare provider that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The healthcare provider may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

### **What side effects or risks can I expect from being in the research study?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. Since the medications in this study are not being given in their usual form (by mouth or through a shot), healthcare professionals don't know whether or not side effects may happen. In previous studies, side effects from using these drugs on the skin (topically) have been none to minimal. Side effects may be mild or very serious. Your healthcare team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the BAK gel. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your healthcare provider about any side effects that you have while taking part in the study.

#### More Likely Risks (when ketamine and amitriptyline have been mixed together and used topically):

- Drowsiness
- Dizziness
- Dry mouth
- Burning skin irritation, peeling, or rash at site of application
- Occasional increased heart rate
- Ringing in the ears
- Facial acne

#### Less Likely Risks (Seen with oral baclofen) and may occur if baclofen is absorbed into your system:

- Drowsiness
- Dizziness
- Weakness
- Fatigue
- Confusion
- Nausea (feeling sick to your stomach)
- Low blood pressure
- Constipation

- Increased need to urinate
- Inability to sleep
- Headache

Rare but serious Risks:

- Allergic reaction for any of the medications
- Hallucinations or seizures when stopping oral baclofen

Reproductive risks: Pregnant women or those that can become pregnant are not eligible of this study. Women should not breastfeed a baby while on this study.

The risks of drawing blood include pain, bruising, or rarely, infection at the needle site.

For more information about risks and side effects, ask your healthcare provider.

**Are there benefits to taking part in the research study?**

Taking part in this study may or may not make your health better. While doctors hope the BAK gel will be useful against peripheral neuropathy, there is no proof of this yet. We do know that the information from this study will help doctors learn more about BAK gel as a treatment for chemotherapy-induced peripheral neuropathy. This information could help future cancer patients.

**What other choices do I have if I do not take part in this research study?**

You do not have to be in this study to receive treatment for your peripheral neuropathy.

**Your other choices may include:**

- Getting treatment or care for your peripheral neuropathy without being in a study
- Taking part in another study
- Getting no treatment

Talk to your healthcare provider about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- North Central Cancer Treatment Group (NCCTG) researchers

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

### **What are the costs of taking part in this research study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The study agent, BAK or placebo gel, will be provided free of charge while you are taking part in this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage> . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

### **What happens if I am injured because I took part in this research study?**

It is important that you tell your healthcare provider, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the healthcare provider in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### **What are my rights if I take part in this research study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

### **Who can answer my questions about the research study?**

You can talk to your healthcare provider about any questions or concerns you have about this study. Contact your healthcare provider \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

### ***The following section regarding biological samples for research should only be used to consent patients enrolled at Mayo Clinic Rochester***

Please note: This section of the informed consent form is about an additional research study that is being done with people who are taking part in the main study. You may take part in this additional study if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional study.

You can say “yes” or “no” to the following study. Please mark your choice for the study.

#### **About Using Biological Samples for Research**

Add 1

During the first part of the study (the first 4 weeks) when you are receiving either placebo or the active gel, you will be asked to participate in a laboratory test that will use a small sample of blood. A blood sample will be done by drawing some blood (3 Tbsp or 40 ml) from a vein. The blood will be taken one time during weeks 3 or 4 of the study.

The blood samples will be sent to laboratories associated with the Mayo Clinic, Rochester, where the test will be done. The test will be done in order to understand how the gel is absorbed into your body. The results of the test will not be sent to you or your healthcare provider and will not be used in planning your care. This test is for research purposes only and you will not have to pay for it. Your samples will be used as described for this study. When the study is done, they will be destroyed.

You can take part in the treatment portion of this study without taking part in this research laboratory test.

**Please read the following statements and mark your choice:**

1. I agree to provide a blood sample to laboratories associated with Mayo Clinic Rochester for research testing planned as part of this study.

Yes     No    Please initial here: \_\_\_\_\_    Date: \_\_\_\_\_

**Benefits**

The benefits of research using blood include learning more about how these medications are absorbed through your skin. You will also learn whether the medications in the BAK gel are being absorbed into your blood stream or whether they are staying at local sites in your hands and feet.

**Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Where can I get more information?**

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your healthcare provider.

**Signature**

**I have been given a copy of all \_\_\_\_\_ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Printed Participant Name:** \_\_\_\_\_

**Participant Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Printed name of person obtaining informed consent:**

\_\_\_\_\_

**Signature of person obtaining informed consent:**

\_\_\_\_\_

**Date** \_\_\_\_\_

**This model informed consent form has been reviewed by DCP/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.**

**Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.**

N06CA - Appendix II

**Symptom Experience Diary -- Topical Analgesics**

**Please let us know what symptoms you have experienced over the past week. Please circle one number for each item.**

1. Are you experiencing any drowsiness?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

2. Are you experiencing any trouble concentrating?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

3. Are you experiencing any pain in your hands and/or feet?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

4. Are you experiencing any skin irritation (redness or rash) on your hands and/or feet?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

5. Are you experiencing any swelling in your hands and/or feet?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

6. Are you experiencing dry mouth?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

7. Are you experiencing any dizziness?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

8. Are you experiencing any constipation?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

9. Are you experiencing any nausea?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

10. Are you experiencing any headaches?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

11. Are you experiencing any trouble sleeping?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

12. Do you feel confused?

Not at all

0 1 2 3 4 5 6 7 8 9 10 As bad as it can be

**Baseline SED ONLY :**

13. I expect that the pain gel in this study will be very helpful in getting rid of my pain, numbness or tingling.

Totally Disagree

0 1 2 3 4 5 6 7 8 9 10

Somewhat agree

Totally agree

N06CA - Appendix III

**EORTC QLQ – CIPN20**

ENGLISH



**EORTC QLQ – CIPN20**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

<b>During the past week :</b>	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
31 Did you have tingling fingers or hands?	1	2	3	4
32 Did you have tingling toes or feet?	1	2	3	4
33 Did you have numbness in your fingers or hands?	1	2	3	4
34 Did you have numbness in your toes or feet?	1	2	3	4
35 Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36 Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37 Did you have cramps in your hands?	1	2	3	4
38 Did you have cramps in your feet?	1	2	3	4
39 Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40 Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41 Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42 Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43 Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44 Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

ENGLISH

**During the past week :**

	<b>Not at All</b>	<b>A Little</b>	<b>Quite a Bit</b>	<b>Very Much</b>
45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46 Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47 Did you have blurred vision?	1	2	3	4
48 Did you have difficulty hearing?	1	2	3	4

**Please answer the following question only if you drive a car**

49 Did you have difficulty using the pedals?	1	2	3	4
--	---	---	---	---

**Please answer the following question only if you are a man**

50 Did you have difficulty getting or maintaining an erection?	1	2	3	4
--	---	---	---	---

N06CA - Appendix IV  
POMS-B

NAME \_\_\_\_\_ DATE \_\_\_\_\_

SEX: Male (M) Female (F) Identification No. \_\_\_\_\_

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases.

- 0 = Not at all
- 1 = A little
- 2 = Moderately
- 3 = Quite a bit
- 4 = Extremely

	Not at all A little Moderately Quite a bit Extremely		Not at all A little Moderately Quite a bit Extremely		Not at all A little Moderately Quite a bit Extremely
1. Tense .....	0 1 2 3 4	12. Uneasy .....	0 1 2 3 4	23. Weary .....	0 1 2 3 4
2. Angry .....	0 1 2 3 4	13. Fatigued .....	0 1 2 3 4	24. Bewildered .....	0 1 2 3 4
3. Worn out .....	0 1 2 3 4	14. Annoyed .....	0 1 2 3 4	25. Furious .....	0 1 2 3 4
4. Lively .....	0 1 2 3 4	15. Discouraged ...	0 1 2 3 4	26. Efficient .....	0 1 2 3 4
5. Confused .....	0 1 2 3 4	16. Nervous .....	0 1 2 3 4	27. Full of pep .....	0 1 2 3 4
6. Shaky .....	0 1 2 3 4	17. Lonely .....	0 1 2 3 4	28. Bad-tempered .	0 1 2 3 4
7. Sad .....	0 1 2 3 4	18. Muddled .....	0 1 2 3 4	29. Forgetful .....	0 1 2 3 4
8. Active .....	0 1 2 3 4	19. Exhausted .....	0 1 2 3 4	30. Vigorous .....	0 1 2 3 4
9. Grouchy .....	0 1 2 3 4	20. Anxious .....	0 1 2 3 4		
10. Energetic .....	0 1 2 3 4	21. Gloomy .....	0 1 2 3 4		
11. Unworthy .....	0 1 2 3 4	22. Sluggish .....	0 1 2 3 4		

**MAKE SURE  
YOU HAVE ANSWERED  
EVERY ITEM.**

POMS-B, by Douglas M. McNair, Ph.D., Joan Lorr Ph.D., Leo F. Droppleman, Ph.D.

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SHORT FORM







N06CA - Appendix VI  
Subject Global Impression of Change

**1. Since starting this study, the overall quality of life is: (please circle one)**

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

**2. Since starting this study, my physical condition is: (please circle one)**

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

**3. Since starting this study, my emotional state is: (please circle one)**

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

**4. Since starting this study, my ability to enjoy social life is: (please circle one)**

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

**5. Since starting this study, the numbness, tingling or pain in my hands and/or feet is: (please circle one)**

-3	-2	-1	0	+1	+2	+3
very much worse	moderately worse	a little worse	about the same	a little better	moderately better	very much better

**6. During this study, I think that I was on: (please circle one)**

A. Pain relieving gel (*active agent*)

B. Placebo gel (*inactive agent*)

N06CA - Appendix VII  
Peripheral Neuropathy Question

1. How much of a problem has numbness, tingling or pain in your fingers and/or toes been in the past week?

0	1	2	3	4	5	6	7	8	9	10
No numbness, tingling or pain in fingers and/or toes										Numbness, tingling or pain in fingers and/or toes as bad as you can imagine

PLACE LABEL HERE

Protocol #:     N06CA    

Patient ID #: \_\_\_\_\_ Initials:     L    F    M    

Local ID #: \_\_\_\_\_ Institution: \_\_\_\_\_

**APPENDIX VIII  
CRA/NURSE WORK SHEET  
DOUBLE-BLIND STUDY  
DOCUMENTATION OF PHONE CALLS**

Physician: \_\_\_\_\_

Patient Phone No. \_\_\_\_\_ Best Dates/Times to call: \_\_\_\_\_

**AT STUDY ENTRY:**

1. Double check eligibility criteria.
2. Date treatment started: \_\_\_\_\_
3. Instruct patient in the use of questionnaires, especially in documenting.

**FOLLOW-UP:**

1. Call patient at home weekly during weeks 1-4 to assess compliance and answer questions. (Phone calls may be eliminated if patient is seen in clinic that week.)
  - Document all information below and on the **Evaluation/Treatment Form**.
  - Write in side effects not specified in patient questionnaires.
  - Grade AE's on the AE form per Section 10.3.

Date of Phone Call	Side effects: ▪ Which ones? ▪ How severe?	Questionnaires: ▪ Going OK? ▪ Any problems?	Questions/Comments	Nurse Signature

3. Date of last treatment dose: (mm/dd/yyyy)   /  /



N06CA – Appendix X

Patient Instructions for Pain/placebo Gel Application

- 1) Before applying gel, have a small bowl of water ready.
- 2) Apply one spoonful of gel to each area of pain, numbness, or tingling on your feet and/or your hands and rub into the skin very well. **Do NOT apply to any area other than your hands or feet.**
- 3) As gel becomes sticky, dip your fingers in water and continue rubbing until the gel is totally rubbed in. Note: A Q-tip is helpful in getting all of the gel out of the spoon.
- 4) Do not wash hands or feet for 1 hour after applying.
- 5) Apply only once in the morning and once in the evening.
- 6) Do not handle food or rub your eyes for an hour after applying.
- 7) You may experience slight burning when applying the gel.
- 8) Report any skin irritation, peeling or rash to your healthcare provider responsible for this study.
- 9) Report drowsiness, dizziness or rapid heart beat to your healthcare provider responsible for this study.
- 10) Protect hands and/or feet from sun while using the study gel.
- 11) Do not use any other creams, lotions or other topical products on the same areas as the study gel throughout the study period.
- 12) Do not put the gel in the refrigerator or other cold area. Keep at room temperature, 59-86°F.
- 13) **Do NOT use on the days you are receiving chemotherapy.**

If you have any questions about how to use this gel or any side effects you are having, please contact your study personnel.

## N06CA - Appendix XI

## Neurotoxicity Evaluation

Grade	I	II	III	IV
NCI-CTCAE v3.0	loss of deep tendon reflexes or paresthesia, including tingling, but not interfering with function	objective sensory alteration or paresthesia, including tingling, interfering with function, but not with activities of daily living	sensory alteration or paresthesia interfering with activities of daily living	permanent sensory losses that are disabling