Academic and Community Cancer Research United (ACCRU)

Treatment of Established Chemotherapy-Induced Neuropathy with N-Palmitoylethanolamide, a Cannabimimetic Nutraceutical: A Randomized Double-Blind Phase II Pilot Trial

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site ([redacted]).

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FDA IND Sponsor/Investigator: [redacted]

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Statistician: [redacted]

Drug Availability
Drug Company Supplied: *OptiPEA® (NSC # 760371)* – IND# 155458 or Placebo

√ Study contributor(s) not responsible for patient care.
* Grant holder

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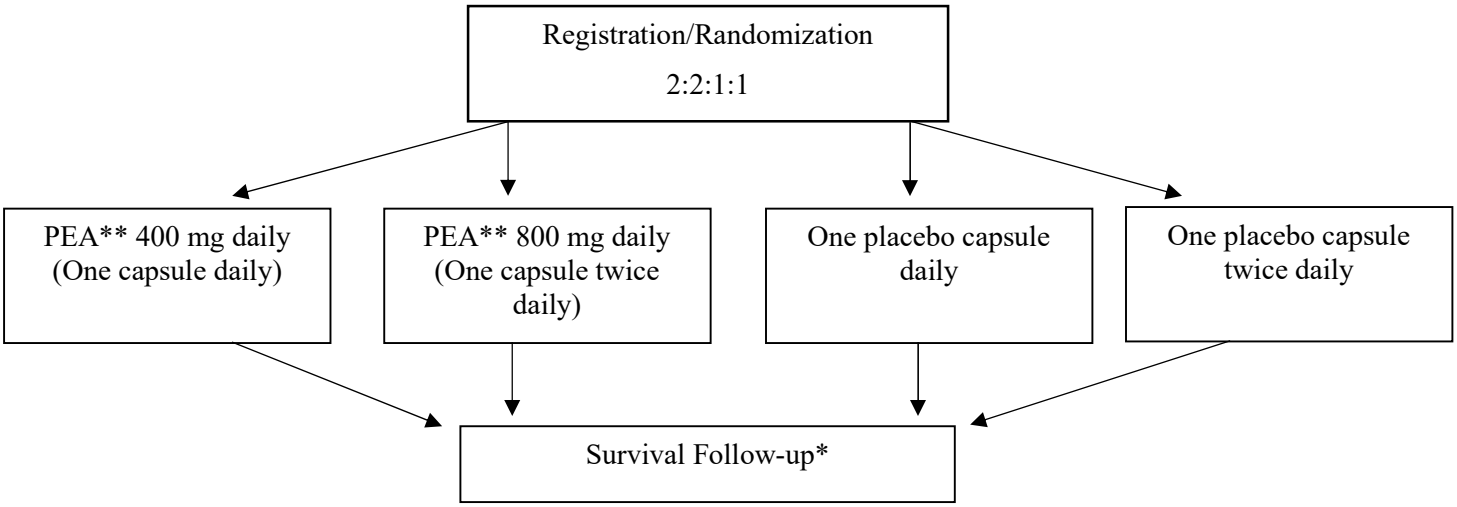
Schema



Treatment for a maximum of 8 weeks or unacceptable adverse events.
*Survival follow-up, every 6 months until 1 year after registration.

**Generic name: N-Palmitoylethanolamide
Brand name(s): OptiPEA®
Availability: McKesson

1.0 Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a major and growing problem as cancer survivor- ship grows and patients are living longer with advanced cancer[1-3].This topic has been identified as being of high priority by NCI's Symptom Management/Quality of Life Steering Committee. Chemotherapy agents, such as oxaliplatin and paclitaxel, cause long-term toxicity for many patients, which can last for years without reprieve and reduce function and quality of life. Resultant chronic pain leads to psychological distress and depression [4]. There are no pharmacological agents that are proven to be efficacious in preventing or limiting the neurotoxicity to chemotherapy. Only duloxetine has been found to have modest benefits in reducing CIPN [5], while gabapentin, pregabalin and tricyclic antidepressants are relatively ineffective [1].

1.1 Cannabis and Neuropathic pain

Cannabis has moderate quality evidence for moderate relief of neuropathic pain [6]. Analgesic mechanisms of cannabis involve inhibition of active neurotransmitter release and neuropeptides from presynaptic nerve endings, postsynaptic modulation of neuron excitability, activation of descending inhibitory pain pathways, and reduction of neural inflammation[7]. Cannabidiol (CBD) produces analgesia through the vanilloid receptor TRPV1 activation, reduces anxiety associated with pain through serotonin 5-HT1A receptor activation, and rescues 5-HT (serotonin) neurotransmission impaired under neuropathic pain conditions [8]. Cannabis also influences brain connectivity altered by pain, which can lead to analgesia. The anterior cingulate cortex and dorsal lateral prefrontal cortex are 2 major cognitive-emotional pain modulating areas influenced by cannabis, and their connections to somatosensory areas are important to the experience of pain. These two sites are functionally involved in the analgesic effect of (tetrahydrocannabinol) THC [9].

A systematic review and meta-analysis of cannabis focused on neuropathic pain relief reported that cannabis-based medicine increased the number of people achieving 50% or greater pain relief compared with placebo (21% versus 17%); the risk difference (RD) for benefit was 0.05 (95% confidence interval (CI) 0.00 to 0.09). The number needed to treat to benefit (NNTB) a single individual was 20 (95% CI 11 to 100). The evidence for improvement in Patient Global Impression of Change (PGIC) with cannabis was felt to be of very low quality [10].

The National Institute for health and Care Excellence (NICE) guidelines recommend against using commercial phytocannabinoids products for chronic pain. The committee found evidence that showed that "CBD reduced chronic pain, but the treatment effect was modest (an average improvement of about 0.4 on a scale ranging from 0 to 10)". Cannabis utility is limited by side effects and dose tolerance; classical phytocannabinoids have a narrow therapeutic margin. Having stated this, there may be specific cannabis products that, eventually, will be shown to be beneficial and well tolerated.

1.2 Rationale for study and introduction to PEA

N- palmitoylethanolamide (PEA) differs from cannabis since it is an endogenous cannabimimetic nutraceutical, a saturated fatty acid which does not directly target classical cannabinoid receptors (CB1 and CB2) but significantly reduces pain. PEA has been found to have no serious side effects and appears to have a greater therapeutic margin, compared to phytocannabinoids [11-15]. PEA analgesic targets include peroxisome proliferator-activated receptors (PPAR), vanilloid receptors, and the orphan receptor GPR-55. PEA impairs mast cell degranulation and blunts neuropathic pain-

causing neuroinflammation [16-25]. PEA competitively inhibits fatty acid amide hydrolase thus increasing anandamide, which activates CB1 receptors [26]. Another entourage effect is the activation and down-regulation of TRPV1 when PEA and anandamide bind to TRPV1 [27-30]. PEA also increases spinal serotonin levels, which has been shown to reduce neuropathic pain [31, 32].

1.3 PEA utility for human pain

PEA has been studied in prospective randomized studies involving patients with multiple pain phenotypes, including CIPN pain. In one meta-analysis, involving 1289 patients in eight trials which included an inactive control group, there was a significantly greater pain reduction with PEA compared to inactive control conditions (WMD = 2.03, 95% CI: 1.19 - 2.87, $z = 4.75$, $P < 0.001$) [33]. In a second meta-analysis involving 1,484 patients in twelve studies of which three were double-blind trials comparing active comparators vs placebo, two open-label trials vs standard therapies, and seven open-label trials without comparators, PEA elicited a progressive reduction of pain intensity, significantly greater than was seen in control arms. The magnitude of reduction with PEA was 1.04 points (on a 10-point scale) every two weeks with a 35% response variance explained in the linear model. The control group pain reduction intensity was 0.20 points every two weeks with only 1% of the total variance explained by the regression. The Kaplan-Meier estimator showed a pain score ≤ 3 out of 10 in 81% of PEA treated patients compared to only 40.9% in control patients at 60 days of treatment [15].

1.4 Animal Models of PEA Regarding CIPN

There are several studies which have used PEA in animal models of CIPN. PPAR activation reduces oxaliplatin neurotoxicity in a rat model [34]. In the same model, a single dose of PEA (30mg/kg IP) reduced oxaliplatin pain and, when administered at the beginning of oxaliplatin, prevented the lowering of pain thresholds associated with oxaliplatin. PEA normalized the electrophysiological activity of spinal nociceptive neurons. Importantly, it did not impair the oxaliplatin-induced human colon cancer cytotoxicity (HT-29) [35].

In a paclitaxel-induced CIPN model, mice received PEA (9.2mg/kg) which significantly reduced allodynia caused by paclitaxel. The PPAR-alpha antagonist GW6471 reversed the anti-nociception of PEA in this model. PEA with gabapentin (67.4mg/kg) synergistically reduced neuropathic pain in this mouse model. The analgesic actions appeared to occur at multiple sites along the peripheral and central nervous system. Analgesic tolerance was not observed [36].

1.5 PEA Utility for Human CIPN

There are multiple human published studies of PEA for various pain phenotypes. What has been noted was analgesia with very little to no toxicity observed [12, 13, 33, 37-44]. A pilot study, involving 20 patients with CIPN from thalidomide and bortezomib were treated with PEA 300mg twice daily which resulted in improved subjective pain and neurophysiological parameters after two months of therapy. PEA was very well tolerated in this population and reduced pain from 4.5 to 3.4 on the Douleur Neuropathique en 4 (DN4) questionnaire. EMG sensory action potentials from sural and ulnar nerves and motor action potentials from ulnar and peroneal nerves improved, indicating objective recovery of myelinated nerve function and conduction which was associated with subjective improvement in pain [45].

1.5.1 Tolerability of PEA

In the experience of 1590 treated patients, there were no 'very common' or 'common' adverse drug reactions (ADRs) being found with PEA following <49 days treatment times, however there are insufficient data to give information in the 'uncommon' or 'rare' categories [12]. ADRs occurring this early on in treatment would likely to have been seen for an incidence of 1/200 or greater. In randomized trials, there were no differences in ADR compared to placebo [46]. The number needed to benefit from PEA for sciatic pain to reach 50% pain reduction appears to be 1.5 and the number needed to harm is in the hundreds, but for the time being not calculable due to the absence of serious and troublesome side effects leading to dropouts in clinical trials [39].

1.6 Should the Current Trial Explore CIPN Prevention vs the Treatment of Established CIPN?

As noted above, the animal data show marked benefit in both the prevention of neuropathic pain from PEA and also in the treatment of established neuropathic pain. The current protocol is designed to look at the treatment of established CIPN issue. In part, this is because we do not know if the reason this product looks good in animal model prevention trials is because the analgesic effect of this drug is masking neuropathic damage from chemotherapy versus whether it is actually preventing the neuropathic damage from happening. If the former is true, then it may be that we would be causing more neuropathic damage but not know about it until later on in the clinical course.

1.6.1 What dose(s) of PEA should we study?

Given that this is a pilot trial, we decided to explore the use of two different doses of PEA. In a variety of human pain trials, PEA doses have ranged from 300 mg to 1200 mg per day [11]. We opted to study 400 mg/day and 800 mg/day, as these represent the lower and higher ranges of studied doses and one reasonably sized capsule can only contain 400 mg of PEA. A dose response relationship has not been established with PEA. Therefore, it is rationale to explore two dose levels in this pilot trial to explore this issue.

1.6.2 Should we measure the effect of PEA on cognitive function?

Some studies have reported an association between higher levels of neuro-inflammation and lower general cognitive function in cancer survivors [47]. Since PEA, in Alzheimer's disease patients, has shown promise regarding an improvement of cognitive dysfunction [48-50], we will explore whether it has any suggestion of improving cognitive function in patients with a history of cancer.

1.7 Palmitoylethanolamide Pharmacology Efficacy and Safety

1.7.1 Pharmacology

N-(2-acylethanolamine)-exadecanamide, commonly called palmitoylethanolamide (PEA), and is a prominent member of the n-acylethanolamine (NAE) family. It is an Autacoid Local Injury Antagonist amide (ALIAmide); ALIAmides are endogenous bioactive ethanolamides with anti-inflammatory properties.[51, 52] These compounds are produced as a reaction to injury and are generated and metabolized in the same cells and tissue that developed the injury. The Nobel Prize winner Rita Levi Montalcini first described the accumulation of NAE under pathologic and degenerative

conditions, resulting in down-modulation of cellular inflammation and mast cell activation.[24, 53, 54] The down-modulation of inflammation, neuroinflammation and mast cell activation has been found to be associated with antinociception in animals and analgesia in clinical studies.[15, 55]

1.7.2 Pharmacodynamics

The pharmacodynamics of PEA, protean as related to analgesia, are : 1. Down modulation of mast cell responses to tissue injury, 2. Activation of peroxisome proliferator activated receptor-alpha, 3. Activation and desensitization of the vanilloid receptor, TRPV1, 4. An entourage effect with anandamide through competition with fatty acid amide hydrolase catabolism resulting in indirect activation of the cannabinoid receptors CB1 and CB2 by increasing anandamide, and 5. Inhibition of microglia activation within the central nervous system.[29, 56-63]

1.7.3 Pharmacokinetics

There are advantages to using ALIAmides over traditional analgesics in that ALIAmides influence metabolic pathways within tissues rather than targeting a single receptor. Since ALIAmides have no toxic metabolites and do not interact with mixed function oxidases or conjugases, they do not have drug-drug interactions. Traditional analgesics, on the other hand, alter physiologic processes and cause" collateral" damage through toxic metabolites or off-target effects, as seen with opioid analgesics.[38, 64]

Micronization of PEA, a highly lipophilic compound, to less than 10 microns increases both bioavailability and efficacy.[65-67] Almost all trials published in the literature have used micronized PEA.

There are barriers to achieving accurate estimates of PEA pharmacokinetics. PEA is normally found in blood and tissue; levels may change with diseases and vary independent of oral pharmacokinetics. Levels can be expressions of second and third order pathways or local and circulating levels may be influenced by the presence of competing endocannabinoids for fatty acid amide hydrolase and the expression of enzymes responsible for PEA production.[28, 42, 59, 68]. There are few human pharmacokinetic studies. Fortunately, though, there are a sizable number of animal studies which used radiolabeled micronized PEA in oral and parenteral forms which has provided useful information about PEA bioavailability and distribution after administration.[65]

Concentrations of PEA in tissues are generally higher than in plasma. Circulating levels markedly vary during the day.[65] Concentrations in tissues and plasma change with injury, particularly with inflammation and in disease processes associated with neurodegeneration.[69-74] In the pig brain, PEA levels far exceed those of anandamide (205 ng / gram versus 6 ng / gram brain tissue).[75]

Human intestinal Caco-2 cell lines are widely used in vitro to estimate drug bioavailability. By this method, micronized PEA absorption starts at 30 minutes and approximately 20-30% of PEA is projected to be bioavailable. Maximum absorption by this method was observed at 3 hours.[29, 65] in a small study of 10 healthy individuals, 300 mg of micronized PEA produced peak concentrations at 2 hours; there was a 2-fold increase in circulating PEA levels over baseline. A

second peak was noted later, which was assumed to be due to enterohepatic recirculation.[42]

Animal studies used both parenteral and oral radiolabeled micronized PEA to determine oral bioavailability, plasma and tissue levels. Oral micronized PEA in corn oil in rats, at a dose of 100 mg/kg, produced plasma levels within 15 minutes with levels that were 20-fold higher in concentration, relative to baseline. Plasma levels returned to baseline at approximately 2 hours.[76] Beagle dogs given 30mg/kg of micronized PEA had a 6-fold increase in circulating PEA levels.[29] Animals with inflammatory pain have greater absorption of oral micronized PEA than healthy animals. PEA plasma levels are 4.3-fold higher at 15 minutes than healthy animals and overall circulating levels are 4.9-fold higher than healthy controls.[59] Spinal cord levels are 26-110-fold higher, as measured by $[^{13}C]_4$-micronized PEA. Inflammation appears to alter the spinal cord barrier, allowing greater amounts of PEA to enter the central nervous system.[77].

A 4-arm randomized trial involving Sprague Dawley rats illustrates this point. Standardized and micronized radiolabeled PEA was used in healthy animals and animals subject to carrageenan paw injections resulting in pain and inflammation.[59] The standardized and micronized radiolabeled ($[^{13}C]_4$-micronized PEA) PEA dose was 30mg/kg in healthy rats and rats subject to carrageenan. The inflammatory state significantly increased radiolabeled PEA levels relative to healthy controls and oral bioavailability of micronized PEA was greater than standardized PEA at the same dose.[59] Significant tissue (paw) levels of radiolabeled PEA were seen at 15, 30, and 60 minutes. Tissue levels were significantly higher in the carrageenan-treated animals, relative to controls, measured at 15, 30, 60 and 360 minutes after PEA administration. Tissue levels in those receiving micronized PEA and subject to carrageenan were 6-fold higher than healthy controls receiving the same dose. Rats subjected to carrageenan had radiolabeled PEA levels in the spinal cord that were 110-fold higher than normal controls (11.1 pmol/gm tissue versus 0.10 pmol/gm tissue). Brain levels of radiolabeled PEA in rats receiving micronized PEA increased over baseline at 5 minutes through 60 minutes after administration. Levels though were not higher than those seen in healthy controls receiving the same dose of micronized PEA. Biopsies of the carrageenan injected paw in animals given oral micronized PEA at a dose of 10mg/kg demonstrated reduced mast cell degranulation, reduced TNF-alpha levels, IL-6 levels and IL-1 beta levels. Expression of NF-kappa-B p65 and cyclooxygenase-2 levels were also reduced compared to controls. These histologic findings correlated with reduced edema and hyperalgesia.[59] Injections of PEA at a dose of 10mg/kg produces significant levels in the bowel and prevents radiation enteritis in mast cell deficient, but not wild type, rats, suggesting that significant tissue levels are achieved by systemic administration and that paradoxically mast cells are needed to reduce radiation injury. PEA benefits in this study appeared to be independent of mast cell modulation.[78]

Intraperitoneal emulsified micronized PEA at a dose of 10mg/kg in DBA/2 mice produces significant brain, blood, heart and retina levels, which persist at 24 and 48 hours.[79] Brain levels in rodents after oral administration of 30mg/kg micronized PEA produces levels, ranging between 21 and 16pmol/gm brain tissue, within 15 minutes of administration.[59, 80] Oral administration of

radiolabeled micronized PEA at a dose of 100mg/kg produced significant levels within the pituitary, hypothalamus and adrenal gland within 20 minutes.[12]

In summary, though human studies are limited, oral micronized PEA appears to be bioavailable and produces measurable plasma levels. Bioavailability by standard in vitro studies is estimated to be 20-30%. In multiple animal models, micronized PEA is rapidly absorbed, and bioavailability is improved by disease state. PEA penetrates tissues and produces measurable levels both in the peripheral tissues and central nervous system. PEA is catabolized by 2 enzymes in tissues (fatty acid amide hydrolase and N-acylethanolamine acid amidase) and is not subject to drug-drug interactions. Pharmacokinetics have not been done in end-organ failure, but PEA is likely to be safe in hepatic, renal and heart failure because of its unique metabolism, absence of active metabolite and its safety.

1.7.4 Safety

PEA has been found to be quite safe by standard in vitro tests, in animal studies and clinically. In vitro, PEA does not induce drug-dependent or a 2-fold increase in revertant colonies at 30, 90, 300, and 3000 mcg per plate cultures in the Ames test.[14] PEA does not induce biologically significant increases in the percentage incidence of micronuclei in binucleated cells at any dose.[14] PEA does not cause cytotoxicity as measured by the cytokinesis-block proliferation index.[14]

PEA does not induce mortality in Sprague Dawley rats at doses as high as 2000 mg per kg for 15 days.[14] There is no NOEL effect (no observed effect level) at doses greater than 1000 mg per kg twice daily. There was no toxicity noted using doses of a 1000 mg per kg for 90 days.[14] Survival was 100% at 90 days. There was no significant loss or gain in weight. There were no differences in blood counts when compared to controls. There was no biologically significant changes in blood chemistries.[14] There was no gross anatomical or histopathological changes noted in treated animals.[14]

There have been a large number of micronized PEA human trials, largely centered on pain. Daily doses ranged from 300-1200 mg per day. Thirteen studies listed below reported no adverse events, though one study noted an adverse event, but was unrelated to PEA.[14]

Table 1 Clinical Toxicity Noted in PEA Trials

Study	Days on Treatment	Number of Participants	Toxicity
Canteri (2010)	21	112	0
Guida (2010)	21	626	0
Schifilliti (2014)	60	30	0
Bacci (2011)	15	26	1 -unrelated to PEA
Pescosolido (2011	15	15	0
Truini (2011)	60	20	0
Costaglioda (2014)	180	32	0
Marini (2012)	14	12	0

Barbieri (2010)	4	90	0
Calabro (2010)	14	1	0
Conigliaro (2011)	30	26	0
Affini (2010)	60	50	0
Desio (2010)	45	30	0

Three publications are particularly illustrative of the safety and efficacy of PEA in treating pain. A post hoc analysis of a multi-center double-blind, placebo-controlled, 3-armed trial involved patients with lumbosacral pain; the two treatment arms were micronized PEA, 300 and 600mg daily and the third was placebo.[81] The duration of treatment was 21 days. The outcomes were the change in the visual analog scale (VAS) (0 no pain 10 severe pain) and the Rolan-Morris Disability Questionnaire (RMDQ). The number needed to treat to benefit a single individual (NNT) was calculated using the response criteria of a 50% improvement in pain relief and a 50% improvement in the RMDQ. Attrition due to side effects was determined and the number needed to harm due to discontinuation for reasons of adverse effects was the safety outcome. The study registered 626 patients of which 619 were evaluable. Both treatment arms were superior to placebo ($P<0.001$). Efficacy was particularly superior in the subgroup with neuropathic pain. For the 300 mg arm, the NNT for pain relief was 9 (95% confidence intervals 5-29) and the RMDQ NNT was 6.4 (95% confidence interval 4-14) ($P<0.02$). For the 600 mg treatment arm the NNT for pain relief was 1.7 (95% confidence intervals 1.4 -2) and the RMDQ NNT was 1.5 (1.4 - 1.7) ($P<0.001$). The NNH was not different between treatment arms. Dropouts were 19 from placebo treatment, 2 from the 300mg treatment arm and 1 from the 600mg treatment arm.[81]

There are two meta-analysis published recently. The first was a meta-analysis of pulled raw data available from clinical trials of micronized PEA.[15] The study involved trials published between 2010 and 2014. Patients has had either chronic pain or neuropathic pain. Pain reduction over time was the main outcome. Timeframes were divided into baseline (T0), days 7-10 (T1), days 11-14 (T2), days 15 through 21 (T3), days 22-45 (T4), and days 46-60 (T5). Analysis used Generalized Linear Mixed Modeling and linear regression. Cox modeling was used to assess the influence of gender, age, pain etiology and study design on pain outcomes. Of 26 clinical trials, 12 met the inclusion criteria. The number of participants were 1484 and doses ranged from 300-1200 mg daily. Pain reduction was seen in both the active and control groups. The pain reduction was superior with PEA and differences were evident at T1 ($P<0.05$ and) and increased over time ($P<0.001$). The average reduction in pain using a numerical rating scale (0 =no pain 10 = severe pain) was 0.2 points every 2 weeks for controls and 1.04 points every 2 weeks for PEA ($P<0.001$). Placebo accounted for 1% in pain variability over time, whereas PEA accounted for 35% of the variability. Age, gender and pain etiology did not influence responses. The average pain score at 60 days was < 3/10 (0 no pain 10 severe pain) in 81.9% of PEA treated individuals, compared to 40.9% for those treated with placebo.[15]

The second meta-analysis was published in 2017 and involved controlled trials using PEA for pain.[33] Randomized trials published up to May 1, 2015 were included. Trials could have either placebo or inactive comparator. The primary

outcome was the change in the VAS. Random effects modeling was used for the primary outcome and fixed effect modeling was performed for a sensitivity analysis. Publication bias was assessed by funnel plot and Egger's analysis. Trials were grouped by dose, duration of study and trial characteristic. Meta-regression was used to assess the effects of dose on outcomes. Of 25 references, 10 randomized trials were included in the meta-analysis. Daily doses ranged from 300-800 mg with the majority receiving 600 mg daily. Of the 1298 patients in the meta-analysis, 786 received micronized PEA; 46% of studies had an inactive control. PEA was superior to the inactive comparator (WMD = 2.03, 95% CI: 1.19 – 2.87, z = 4.75, $P < 0.001$). By a fixed effect modeling the WMD = 2.20, 95% CI: 2.00 – 2.41, z =21.4, $P < 0.001$). There was no publication bias. Stratified subgroup analysis did not show differences based on trial design. There was no response differences between doses. There was no association of efficacy with duration of treatment. In regard to tolerability, all-cause dropouts were reduced in the PEA treated groups, but this was not statistically significant, relative to placebo or the inactive comparator (P =0.11). All-cause dropouts were 1.1% of patients on PEA and 4.3% in the inactive controls/ placebo treated patients. Adverse effects reported with PEA were gastrointestinal upset in 2 patients, drowsiness in 1 and heart palpitations in 1 individual.

In summary, based on two meta-analysis and a large clinical trial, micronized PEA is safe, tolerable and efficacious. There are discrepancies in the two meta-analysis centered dose-response and efficacy over time which will need clarification in future studies.

With regards to the effect of PEA on blood tests, the following information is available. Hematology, blood chemistry, and urine analyses have been carried out at baseline and at treatment end in 427 patients receiving PEA and showed no clinical and statistical differences. (101, 102) In a randomized trial of PEA in osteoarthritis versus placebo, (N = 188), the hematological and biochemical parameters were in the healthy reference range for all groups at baseline and remained stable over the 8 weeks. (103) Extensive testing has also been done in vitro and in animals, demonstrating no toxicity despite very high doses. (104)

1.8 CIPN endpoint measurement tools

Given that this is a pilot trial, we will evaluate neuropathy with a variety of patient-reported outcome (PRO) tools. (See Section 11.1)

1.9 Toxicity and QOL Endpoint Measurement Tools

We will utilize the symptom experience diary (Appendix V) and CTCAE version 5.0 criteria to look for any evidence of toxicity from PEA, understanding that substantial past work has suggested that this product does not cause any significant toxicity. This questionnaire will also evaluate QOL changes. (See Sections 11.2 and 11.3 for a detailed description of the measurement tools)

2.0 Goals

2.1 Primary

The primary objective is to look for evidence of the efficacy of PEA at two different doses relative to placebo responses, as a treatment for CIPN. This is being done to

inform the design of a subsequent phase III trial of PEA for treating bothersome established CIPN.

2.2 Secondary

2.2.1 To assess the safety of PEA at the two study doses.

2.2.2 To evaluate changes in patient-reported quality of life from baseline to the end of 8 weeks.

2.3 Exploratory

2.3.1 To explore whether PEA appears to affect cognition in the study patients.

2.3.2 To explore the weekly trajectory of CIPN from baseline to 8 weeks.

2.3.3 To explore the weekly trajectory of pain using the single-item numerical rating scale from baseline to 8 weeks.

2.3.4 To explore the weekly patient global impression of change in each treatment arm from baseline to 8 weeks.

2.3.5 To explore the weekly chemotherapy induced peripheral neuropathy in each treatment arm from baseline to 8 weeks.

2.3.6 To explore the PEA effects on CIPN20 between two PEA dosage arms.

2.3.7 To explore the number of recurrent cancer events by study arm

2.3.8 To explore the overall survival by study arm

3.0 Patient Eligibility

NOTE: Waivers to eligibility criteria are not allowed per ACCRU policy

3.1 Registration -- Inclusion Criteria

3.1.1 Age ≥ 18 years.

3.1.2 ECOG Performance Status 0, 1, 2 (Form available on ACCRU website).

NOTE: Patients with a history of metastatic cancer or an ECOG Performance Status of 2 must have lab work (see Section 3.1.9) completed ≤ 28 days prior to registration.

3.1.3 Pain, numbness, tingling or other symptoms of CIPN of ≥ 3 months (90 days) duration for which the patient is seeking an intervention.

3.1.4 Neurotoxic chemotherapy must have been completed ≥ 3 months (90 days) prior to registration and there must be no further planned neurotoxic chemotherapy for > 2 months after registration.

Note: The study is limited to those with taxane- and/or platinum-based neuropathy.

3.1.5 Patient must note tingling, numbness or pain symptoms of at least a four out of ten ≤ 7 days prior to registration.

Note: On a 0-10 scale where zero was ‘no problem’ and ten being ‘as bad a problem that could be imagined’: *how much of a problem has numbness, tingling,*

and/or pain in your fingers and/or toes been in the past week? (patient verbal report utilizing question 1 in Appendix VI "Peripheral Neuropathy Questions").

3.1.6 Patient must be able to speak, read and comprehend English.

3.1.7 For women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 14 days prior to registration is required.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

NOTE: If the urine test cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.8 Life expectancy ≥ 6 months.

3.1.9 Required Initial Laboratory Values: Following completion of chemotherapy, patients must have had a CBC and serum chemistries, including the following:

- Platelet count > 100,000/mm^3
- Absolute neutrophil count (ANC) ≥ 1,000/mm^3
- Hemoglobin > 11 g/dL
- Serum transaminase [ALT or AST] ≤ 1.2 x upper limit of normal (ULN)
- Alkaline phosphatase ≤ 1.2 x ULN
- Serum creatinine ≤ 1.2 x ULN

NOTE: Patients with a history of metastatic cancer or an ECOG Performance Status of 2 must have these labs completed ≤ 28 days prior to registration.

3.1.10 Able to swallow oral medication.

3.1.11 Provide written informed consent ≤ 28 days prior to registration.

3.2 Registration – Exclusion Criteria

3.2.1 Currently receiving neurotoxic chemotherapy for a second cancer or recurrence of the primary cancer.

3.2.2 Impaired decision-making capacity (such as with a diagnosis of dementia or memory loss).

3.2.3 Evidence of residual cancer, per routine clinical practice-based parameters.

3.2.4 Comorbid conditions:

a) Previous diagnosis of diabetic or another non chemotherapy induced peripheral neuropathy.

b) Previous history of peripheral neuropathy prior to receiving neurotoxic chemotherapy.

c) Neuropathy from HIV infection. Note: Patients with HIV infections are eligible as long as they do not have a neuropathy from their viral illness.

3.2.5 Concurrent use of a cannabis product (THC and/or CBD). Patients should have discontinued these products ≥ 4 weeks prior to registration.

3.2.6 Current or previous use of PEA.

3.2.7 Currently receiving or planning to start any of the following agents: opioids, duloxetine, gabapentin or pregabalin. Patients are eligible if they discontinue these medications ≥ 1 week prior to registration.

3.2.8 Any of the following because the study involves an investigational agent whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception

4.0 Test Schedule

	Screening			Active Monitoring Phase	
	Prior to Registration			Prior to Start of Treatment (baseline)	End of each weekly cycle (for 8 weeks)
	≤ 28 Days	≤ 14 Days	≤ 7 Days		
Tests & Observations					
History	X				
CBC and serum chemistries, including serum transaminase [ALT or AST], alkaline phosphatase and Cr[1]	X[1]				
ECOG PS	X				
Laboratory Studies					
Serum or Urine HCG[2]		X[2]			
Patient reported measures**					
EORTC QLQ-CIPN 20 (Appendix II)				X	X
Patient Global Impression of Change (Appendix III)					X
Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (Appendix IV)				X	X

Symptom experience diary (Appendix V)				X	X
Peripheral Neuropathy Question (Appendix VI)			X[4]	X	X
Cognitive Functioning Assessment (Appendix VII)				X	X
Adverse Event Assessment[3]					X[3]
Nurse telephone contact[3] (Appendix VIII)					X[3]

** To be completed using paper booklets. Patient questionnaire booklets are to be available prior to the registration of any patients. The booklet order form is located on the ACCRU website under 'Manuals and Forms'. Patients are to complete these booklets prior to the end of each week of treatment (See Section 7.2). See appropriate Appendices for samples of the booklets.

1 This blood testing is required within the 28 days prior to registration if the patient has a history of metastatic cancer or currently has an ECOG Performance Score of 2 (See eligibility criteria 3.1.9). For patients who do not have a history of metastatic cancer or a current ECOG Performance Score of 2, this blood testing is to have been completed after the patient finished their chemotherapy per eligibility criteria 3.1.4.

2 For women of childbearing potential. Must be done ≤ 14 days prior to registration.

3 Nurse/Research Coordinator will contact the patient at the end of each weekly cycle (+ 2 days) to remind the patient to complete questionnaires, answer questions, and to query adverse events.

4 To be collected orally (per eligibility criteria 3.1.5) and the response will be documented on the eligibility checklist and in the clinic note (per section 18.5).

4.1 Survival Follow-up

After completing 8 weeks of treatment, patients will proceed to survival follow-up. A Nurse/Research Coordinator will contact the patient to inquire about neuropathy status, disease status, and survival at both 6 months (± 30 days) and 12 months (± 30 days) after registration. There will be no additional follow-up after these two timepoints. (Appendix IX)

5.0 Stratification Factors:

- Gender: Male vs Female
- Prior Chemotherapy Received: Any **Taxane ± carboplatin ±** other agents versus **Oxaliplatin** based versus **other** (never received a taxane nor oxaliplatin)

6.0 Registration/Randomization Procedures

6.1 Site Procedures

6.1.1 Study staff will need to complete the required training prior to gaining access to the registration application. This is located on the ACCRU web page at [redacted] Refer to Study Resources → Applications. Near the bottom of the page there will be a link to the "Research Registration Application Training." After training is complete, study staff must complete the "Attestation of Training" and send to the ACCRU Registration Office at [redacted]

6.1.2 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using Florence online.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the Florence online. If the necessary documentation is not submitted in advance of attempting patient registration, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Submission of annual IRB approvals is required until the study has been closed through your IRB.

6.2 Registration Procedures

6.2.1 To register a patient, access the ACCRU web page at [redacted] go to the Study Resources → Application section and click on "Registration" and enter the registration application. The registration 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 unable to access the Web site, email the Academic and Community Cancer Research United (ACCRU) Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration application are available on the above web page under the Study Resources → Application section. Please refer to the "Research Registration Application Training" or Quick Reference Guide for instructions.

Prior to initiation of protocol treatment, this process must be completed in its entirety and an ACCRU 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 registration application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Officer [redacted] If the patient was fully registered, the ACCRU Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to the Research Registration Application training on the ACCRU website under Study Resources → Applications.

6.2.2 Prior to accepting the registration/randomization, the 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

6.2.3 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.2.4 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.2.5 Treatment on this protocol must commence at an ACCRU institution under the supervision of an oncologist.

6.2.6 Study drug is available on site.

6.2.7 Patient questionnaire booklet is available on site.

6.3 Randomization Procedures

6.3.1 The factors defined in Section 5.0 will be used as stratification factors.

6.3.2 After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups [105].

- Palmitoylethanolamide: 400 mg (1 capsule daily) PO for 8 weeks
- Palmitoylethanolamide: 800 mg (1 400mg capsule twice daily) PO for 8 weeks

- Placebo: 1 capsule PO daily for 8 weeks
- Placebo: 1 capsule PO twice daily for 8 weeks

6.4 Procedures for Double-Blinding the Treatment Assignment

6.4.1 After the treatment assignment has been ascertained by the registration/randomization application, the registration specialist will notify the designated unblinded data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be entered in the designated space on the eligibility checklist, so the Registration Office personnel have it for each patient at the time of randomization. Make sure this contact person will be available at the time of randomization so he or she can take a call from the registration specialist if necessary. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. The last page of the Eligibility Checklist Form should provide the e-mail address and the appropriate contact information (including phone number). The registration specialist will then communicate the treatment assignment to the designated contact at the patient's institution.

6.4.2 The treatment assignment will be to palmitoylethanolamide 400 mg once daily, palmitoylethanolamide 400 mg twice daily, placebo once daily, or placebo twice daily. Innexus Nutraceuticals will provide supplies labeled for investigational use to McKesson Specialty Pharmacy's Clinical Research Services. Each participating institution will order the drug from McKesson using the protocol-specific Drug Order Request Form. Each participating institution will be responsible for monitoring drug supplies and will use the Drug Order Request Form to order additional supplies as needed. Upon receipt of orders, McKesson Specialty Pharmacy's Clinical Research Services will send bulk supply to participating institutions. The palmitoylethanolamide/placebo drug supplies will be prepared and labeled by the unblinded pharmacist per Section 7.1 so that the contents are not discernible to the person administering the treatment.

6.4.3 The unblinded pharmacist will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

7.0 Treatment Plan/Intervention

Protocol treatment is to begin ≤ 14 days of registration.

This is a randomized double-blind trial. See Section 15.1 for drug procurement instructions.

Patients with peripheral neuropathy either from a platinum or taxane based chemotherapy will be randomized if eligible to one of four treatment arms:

Agent	Dose	Route	Day
Palmitoylethanolamide (PEA)	400 mg (1 capsule daily)	PO	Daily for 8 weeks
Palmitoylethanolamide (PEA)	800 mg (1 400 mg capsule twice daily)	PO	Daily for 8 weeks
Placebo	1 capsule daily	PO	Daily for 8 weeks
Placebo	1 capsule twice daily	PO	Daily for 8 weeks

Medications will be taken once or twice daily depending on randomization. Assessment of neuropathy, side effects and cognitive function will occur weekly.

7.1 Palmitoylethanolamide (PEA)/Placebo

Beginning on Day 1 of the study, and for eight weeks, patients will be instructed to take one of the following:

- Palmitoylethanolamide (400 mg) or placebo: 1 capsule by mouth once in the morning daily for 8 weeks

  OR

- Palmitoylethanolamide (400 mg) or placebo: 1 capsule by mouth once in the morning and once in the evening daily for 8 weeks

7.2 Submission of Patient Completed Measures (Booklets)

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients. The booklet order form is located on the ACCRU website under 'Manuals and Forms. Samples of questionnaire booklets are available in Appendices II-VII for reference and IRB submission only. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient responses into Medidata Rave. At visits in which booklets are to be completed, the booklet should be given to and completed by the patient before any discussion of the patient's health status or test results. The PRO submission schedule is provided in the Study Calendar.

Baseline Booklet: The baseline questionnaire booklet should be completed in clinic on the same day as registration and returned to study staff. In the event the patient is unable to complete while in the clinic, the patient may complete at home and return by mail prior to starting the study medication.

Weekly Booklets: Questionnaire booklet(s) will be provided to patients to complete at home on a weekly basis for a total of eight weeks. Before the booklets are given to the patients, the nurse/study assistant will label each booklet with the week number and the anticipated 7-day weekly cycle start dates, in chronological order. Patients should be instructed to return the booklets by mail weekly. If, by chance, the patient has a regularly scheduled clinic visit at any time during the study period, the patient could return that

week's questionnaire during the clinic visit. Institutions must provide patients with sufficient self-addressed stamped envelopes for this purpose. Site staff will enter patient responses into Rave upon receipt of the completed booklets.

Verbal administration of the measures for visually impaired patients is permitted if the measure and verbal administration of the measure is conducted in a language understandable to the patients.

7.3 Unblinding Procedures

Unblinding during active study treatment can be done only in cases of an emergency. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

7.3.1 Emergency Unblinding Procedures

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose.

In the event of an emergency, email the ACCRU Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Send an email to the ACCRU Registration Office informing them of the need to un-blind a patient. Provide your contact information so that ACCRU Registration Office personnel can respond to the email the next business day.

7.3.2 Study Completion Unblinding

On a case by case basis, if in the judgement of the treating physician, it would be helpful for the future clinical care of the individual patient, the code may be broken *after* the patient has completed the study. That is, after the patient has completed study treatment and mailed in all of the required study questionnaires. The ACCRU Registration Office may be contacted to find out which study therapy the patient was receiving. This would allow for the individual patients to choose whether to continue taking active PEA or to start it. This treatment would be considered off study and patients should discuss with their primary cancer physician. Patients would need to purchase palmitoylethanolamide on their own terms.

8.0 Dose and Treatment Modifications

8.1 Dose Modifications

There are no known toxicities related to the study medication. However, patients who have an unacceptable toxicity which they attribute to the study medication, should discontinue study treatment. Clinical investigators may use clinical judgment to stop treatment for suspected adverse events. This should be decided and done prior to breaking the study code for an individual patient.

9.0 Ancillary Treatment/Supportive Care

9.1 Prohibited Concomitant Medications/Therapy

Patients should not receive any other treatment which would be considered treatment for peripheral neuropathy or impact the primary endpoint. This includes opioids, duloxetine, gabapentin, pregabalin, or PEA obtained outside of this study.

Patients should not receive other cannabinoids (CBD or THC) by any route for 4 weeks prior to registration or during the eight-week study period. If it's discovered a patient is receiving a cannabinoid while on active study treatment, this will need to be reported in the case report forms. Patients will be asked to discontinue the cannabinoid, if patient declines, they will be removed from study and proceed to Survival Follow-up (Section 13.0).

Patients should not receive other PPAR- α agonists used to treat high triglycerides including clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate as these may interact with the investigational agent, PEA.

Patients should not receive any neurotoxic chemotherapy ≥ 3 months (90 days) prior to registration or for > 2 months after registration. If the patient develops disease recurrence whereby such treatment is indicated, the patient will be taken off active study treatment and proceed to Survival Follow-up (see Section 13.0).

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 5.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).
NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

10.3 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).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.3.1 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.

  - Death Neonatal: A disorder characterized by cessation of

life during the first 28 days of life.

- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of General Disorders and Administration Site Conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.3.2 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.3.3 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.3.4 New Malignancies

- All new malignancies must be reported whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

    - Whenever possible, the expedited report for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

10.3.5 Pregnancy

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting [redacted] the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.4.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Special Instructions:

- Follow site-specific reporting guidelines.
- Submit the ACCRU Adverse Event Expedited Report Form to the ACCRU SAE Coordinator via email [redacted]. The ACCRU SAE Coordinator will forward to [redacted] via email: [redacted]
- The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.5.1 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.5.2 Baseline and Adverse Events Evaluations

Not applicable.

10.5.3 Submit via appropriate Academic and Community Cancer Research United (ACCRU) Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.5.3.1 Grade 1 and 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.5.3.2 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure

10.5.3.3 Grade 5 AEs (Deaths)

10.5.3.3.1 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5.3.3.2 Any death more than 30 days after 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.

11.0 Treatment Evaluation/Measures

A description of the patient reported measures is included below. It will take patients approximately ten to fifteen minutes to complete the questionnaires.

11.1 CIPN endpoint measurement tools

We will evaluate neuropathy with a variety of patient-reported outcome (PRO) tools. These include the following three assessment items.

11.1.1 EORTC QLQ-CIPN20 (Appendix II)

The EORTC QLQ-CIPN20 [82-85] (CIPN20) is a 20-item PRO questionnaire originally designed to supplement the EORTC Quality of Life Questionnaire. Based on the initially hypothesized factor structure, it contains 9 items assessing sensory neuropathy items, 8 assessing motor function, and 3 assessing autonomic neuropathy. Items are scored from 1-4 with 1 representing "not at all" and 4 "very much." Item scores are summed to obtain subscale scores. However, given conflicting evidence regarding the validity of this three-factor structure, recent evidence suggests that all items can be summed to obtain a total CIPN score. Scores can be linearly converted to a 0-100 scale with higher scores reflecting less CIPN. The published literature provide evidence of its internal consistency and stability reliability, sensitivity, convergent and contrasting group validity, and responsiveness; nine studies conducted across multiple countries support its strong psychometric properties [86, 87]. This is completed prior to treatment and at the end of every week of treatment for eight weeks.

11.1.2 Patient Global Impression of Change (Appendix III)

The Patient Global Impression of Change (PGIC) is a tool that came out of the Clinical Global Impressions scale (CGI). The CGI was initially published in 1976 by the National Institute of Mental Health (US). The PGIC tool was taken from the CGI and adapted to be completed by patients, therefore becoming a PRO measurement tool [88]. This is completed at the end of every week of treatment for eight weeks

11.1.3 Chemotherapy-Induced Peripheral Neuropathy Assessment Tool (Appendix IV)

The Chemotherapy-Induced Peripheral Neuropathy Assessment Tool consists of 14 items that might be affected by peripheral neuropathy. Patients are asked to complete a numerical rating score from 0-10 related to symptoms "not at all interfering" to "completely interfering" based on the patient's neuropathy symptoms. This tool has been validated [89, 90]. This is completed prior to treatment and at the end of every week of treatment for eight weeks.

11.2 Toxicity and QOL Endpoint Measurement Tools

We will utilize the symptom experience diary (Appendix V) and CTCAE version 5.0 criteria to look for any evidence of toxicity from PEA, understanding that substantial past work has suggested that this product does not cause any significant toxicity. This questionnaire will also evaluate QOL changes.

11.2.1 Peripheral Neuropathy Questions (Appendix VI)

This appendix provides the question that is to be verbally asked, to prospective protocol candidates, to judge whether or not they have enough neuropathy to participate in this clinical trial. This question will be asked prior to enrollment, and this question and the specific question with regard to pain in fingers/hand and toes/feet will be asked at the end of every week.

11.2.2 Cognitive Function

PEA (N-Palmitoylethanolamide) may have an influence on cognitive function by indirect evidence. There are multiple scales that have been used to assess cognitive function [91-97]. We have decided to have patients complete two questions to assess this (Appendix VII). This assessment will be completed prior to treatment and at the end of every week of treatment for eight weeks.

11.3 Nurse, clinician, or study assistant Telephone Contact (Appendix VIII)

All patients will receive weekly phone calls from study staff, to document compliance with study drug, encourage completion of requisite study questionnaires, and address any patient concerns or problems and assess adverse events.

12.0 Descriptive Factors

- None

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Treatment Duration/Off protocol treatment

Protocol treatment is to continue for eight weeks. If patient discontinues treatment for any reason prior to the end of the eight weeks, they will proceed to Survival Follow-up per Section 4.1 until 1 year post-registration. All attempts should be made to collect patient questionnaires until the last date the patient received any protocol treatment.

13.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.

13.3 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, the patient may continue treatment at the discretion

of the physician as long as there are no safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

- If the patient never received treatment, on-study material and the Off Treatment form must be submitted. No further data submission is necessary.

13.4 Major Violation

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. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol, and all data submission should continue per protocol. If the patient does not continue with treatment, the patient will go off treatment and be followed in Survival Follow-up.

13.5 Cancel

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 Off Treatment form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

None.

15.0 Drug Information

15.1 Palmitoylethanolamide (OptiPEA®)

IND number 155458

- Investigator brochure available on ACCRU website

15.1.1 **Background:**

Palmitoylethanolamide, or PEA, is a naturally occurring fatty acid amide and belongs to the class of organic compounds known as carboximidic acids. It is an Autacoid Local Injury Antagonist amide (ALIAmide) which are endogenous bioactive ethanolamides with anti-inflammatory properties. These compounds are produced as a reaction to injury and are generated and metabolized in the same cells and tissue.

15.1.2 **Formulation:**

Palmitoylethanolamide (OptiPEA®) is supplied as capsules containing 400 mg of non-micronized PEA. There are no excipients in the PEA capsules.

15.1.3 **Preparation and storage:**

Store at room temperature. Keep container tightly closed. Store in accordance with information listed on the product insert.

15.1.4 **Administration:**

Palmitoylethanolamide (OptiPEA®) will be provided as 400 mg capsules supplied in bottles containing 30 capsules. It can be administered either once or twice daily as directed by the protocol, with food to maximize absorption. Capsules should be swallowed whole and not crushed or opened.

15.1.5 **Pharmacokinetic information:**

a) Absorption – Human intestinal Caco-2 cell lines are widely used in vitro to estimate drug bioavailability. For micronized PEA, initial absorption starts at 30 minutes and maximum absorption peaks at 3 hours. Bioavailability is approximately 20-30%. This study uses non-micronized PEA. Most clinical studies have used some form of micronized (e.g., co- or ultra-micronized) PEA. However, there are no head-to-head clinical comparisons of non-micronized vs. micronized formulations of PEA, and so evidence for superiority of one formulation over the other remains lacking according to the latest reviews. Unmicronized, micronized, and ultra-micronized PEA formulations have all shown to be absorbed following oral administration but there is little data available concerning the actual absorption phase or whether the rate of absorption can be improved. There is no information in the literature about the bioavailability of PEA or, arguably more importantly, how bioavailability varies between individuals.

b) Distribution – PEA is likely to show considerable plasma protein binding. It does penetrate peripheral tissue and the central nervous system

c) Metabolism – Tissue enzymatic degradation from PEA → palmitic acid → incorporation into phospholipids. The extent to which orally or topically administered PEA is hydrolyzed to palmitic acid prior to its excretion from the body, is unclarified.

d) Excretion – Unknown.

15.1.6 **Potential Drug Interactions:** Based on its mechanism, PEA may be considered likely to interact with other PPAR- α agonists use to treat high triglycerides including clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate. However, no data on interactions with PEA are available and none have been reported.

15.1.7 **Known potential toxicities:** PEA is generally considered safe, and without adverse drug reactions. Infrequent reports of gastrointestinal upset, drowsiness, and heart palpitations were noted in studies with PEA. Individual cases of urinary tract infection, paralytic ileus, cholecystolithiasis, fungal infection, and erysipelas (bacterial skin infection) causing hospitalization have also been reported.

15.1.8 **Drug procurement:** Innexus Nutraceuticals will supply palmitoylethanolamide (PEA) free of charge to study participants. This agent will be supplied to McKesson Specialty Pharmacy's Clinical Research Services. Each participating ACCRU treating location will order the drug from McKesson Specialty Pharmacy's Clinical Research Services. Submit the Drug Order Request Form (found on the ACCRU website) :

[redacted]

Each participating ACCRU treating location will be responsible for monitoring the supply of palmitoylethanolamide (PEA) and will use the Drug Order Request Form to order additional supplies as needed.

Outdated or remaining drug is to be destroyed on-site as per institutional procedures.

15.1.9 Each participating institution may ship Study Product/Placebo directly to their patients. If the site's standard operating procedures allow. All local site procedures should be followed, and accurate accountability logs should be maintained.

NOTE: All sites are responsible for shipping material and shipping cost.

15.2.0. **Nursing guidelines:**

15.2.0.1.1PEA may interact with other similar drugs (such as gemfibrozil, fenofibrate, and clofibrate). Assess patients' concomitant medications and any over the counter supplements.

15.2.0.2Overall PEA has been well-tolerated with no major side effects, instruct patient to report any side effect to the study team immediately.

15.2 Placebo

15.2.1 **Formulation:** Matched placebo capsules are provided in identical PEA-Placebo labeled bottles for dispensing. Each placebo capsule contains 400mg dextrose in a size 0 transparent Hydroxypropyl methylcellulose (HPMC) capsule.

15.2.2 **Storage:** Products are to be stored in the original container below 25°C. Containers should be stored tightly closed.

16.0 Statistical Considerations

16.1 Statistical Design

This trial is designed as a randomized placebo-controlled pilot trial with the primary objective of estimating the efficacy of two dose levels of PEA to inform the design of a future phase III trial for treatment of chemotherapy-induced peripheral neuropathy (CIPN). Patients will be randomized 2:2:1:1 to receive either 400 mg of PEA (one 400 mg capsule), 800 mg PEA (two 400 mg capsules), 1 placebo capsule, or 2 placebo capsules, respectively. The two placebo arms are included in this study to ensure that there is a matched number of capsules for each of the PEA arms; however, all placebo patients will be analyzed as one group (a combined placebo arm). The efficacy of the two dose levels of PEA will be estimated as the difference between each dose level of PEA compared to the combined placebo arm.

16.2 Sample size, Accrual time and Study Duration

16.2.1 Sample size

As this is a pilot trial to estimate the efficacy of PEA, the sample size is based on feasibility considerations and estimation precision. We plan to accrue a total of 88 patients (consisting of 78 evaluable patients + 10% dropout due to cancellation or ineligibility). Based on our previous trial experience [98], by assuming the standard deviation of the 0-100 scale transformed CIPN20 change score is 15 in each treatment arm. With this assumption, 26 patients per PEA arm and 26 total patients for the combined placebo arm (pooling all patients receiving

placebo together for statistical analysis) allows estimation of the difference between two arms, of the CIPN20 score change from baseline to 8 weeks, with a 95% two-sided confidence interval width of 16.8 points.

16.2.2 Accrual time and study duration

We assume that the accrual rate will be about 6 patients per month; if true, the anticipated study period for accruing 88 patients will be 15 months. With data from the primary endpoint maturing 8 weeks later, the primary analysis can begin approximately 17 months after the trial begins; as soon as all patients have completed 8 weeks of treatment and submitted QOL booklets or have gone off protocol treatment.

16.3 Primary Endpoint Analysis Plan

16.3.1 Primary endpoint analysis

The primary endpoint is the CIPN20 score (Appendix II). The CIPN20 questionnaire will be scored and summarized at each time point for each patient (see Section 11.1). The change from baseline to 8 weeks will then be calculated for each patient. The mean (standard deviation) and median (range) of the change will be calculated for each PEA arm and the combined placebo arm. The difference in change scores between each PEA arm and the combined placebo will be estimated along with a 95% confidence interval. For the primary analysis, the CIPN20 analysis dataset will include all eligible patients who are randomized, initiated treatment, and completed the baseline questionnaire. For patients who go off protocol treatment before 8 weeks, the score at their final observation will be used to calculate the change. For patients who do not have any post baseline data, they will be considered to have no change from baseline. Sensitivity analysis based on imputation of missing data as described in Section 16.5 will be performed using similar methods.

16.3.2 Interim analysis for primary endpoint

Because this study is a pilot randomized parallel group trial to look for evidence of the efficacy of PEA, no interim data analysis is planned.

16.4 Secondary/Exploratory Analysis Plans

The safety analysis dataset is defined as all eligible patients who are randomized and had at least one dose of treatment (PEA or placebo).

The efficacy analysis dataset for the secondary/exploratory analysis will be based on the CIPN20 primary endpoint analysis dataset.

16.4.1 Secondary endpoint analysis

16.4.1.1 Adverse events by patient will be summarized by frequencies and severity using CTCAE v5.0. The proportion of patients who experience at least one grade 3+ adverse event (regardless of attribution) will be reported. The overall adverse event rates for grade 3 or higher adverse events will be compared across the three arms (the two PEA arms and combined placebo) using a Chi-squared or Fisher's Exact tests as appropriate.

16.4.1.2 The difference in change of QOL (Question 3 Appendix V, PRO-QOL) from baseline to 8 weeks will be calculated for each patient. The mean and standard deviation of the change will be reported for each PEA arm

and the combined placebo arm. Additional analysis using data collected from the Symptom Experience Diary may be performed. For patients who go off protocol treatment before 8 weeks, the question 3 response at their final observation will be used to calculate the change. For patients who do not have any post baseline data, they will be considered to have no change from baseline.

16.4.2 Exploratory endpoint analysis

16.4.2.1 The two cognitive items of the Cognitive Functioning Assessment (Appendix VII) will be summarized by mean (SD) and median (range) at each time point for each PEA arm and the combined placebo arm. The mean change from baseline to 8 weeks will be estimated along with the 95% confidence interval for each PEA arm and the combine placebo arm.

16.4.2.2 The weekly CIPN20 scores will be summarized at each time point by mean (SD) and median (range) and will be plotted longitudinally for each PEA arm and the combine placebo arm.

16.4.2.3 The weekly pain scores (Appendix VI) will be summarized at each time point by mean (SD) and median (range) and will be plotted longitudinally for each PEA arm and the combined placebo arm.

16.4.2.4 Items of the Global Impression of Change tool (Appendix III) will be summarized by frequency (percentage) of each level at each time point for each PEA arm and the combine placebo arm. Bar plots for each PEA arm and the combined placebo arm of frequency over time will be constructed.

16.4.2.5 The Chemotherapy Induced Peripheral Neuropathy Assessment Tool (Appendix IV) will be summarized by mean (SD) and median (range) at each time point for each PEA arm and the combine placebo arm.

16.4.2.6 Using the changes scores constructed for the primary endpoint, the difference in CIPN20 change scores between the two PEA dosage arms will be estimated along with a 95% confidence interval.

16.4.2.7 Evidence of disease recurrence and the date of recurrence will be asked by nurse at the 6 and 12 months' follow-up (Appendix IX). The number of events and percentage will be reported by each PEA arm and combined placebo arm. No hypothesis test will be performed between arms.

16.4.2.8 Overall survival is defined as the time from registration to death due to any cause. For each PEA arm and combined placebo arm, the distributions of OS time will be estimated using the Kaplan-Meier method. Log-rank test will be used to compare the survival distributions between each PEA and the combined placebo arm.

16.5 Missing Data

We will examine the mechanisms of missing data if the proportion of missing assessments for the primary endpoint is not small (≥ 10%). Graphical presentation, correlation analysis (Kendall's) and logistic regression will be performed to examine whether the missing data mechanism depends on the covariates (patient characteristics

and other baseline risk factors), observed patient-reported outcome (PRO) scores, and missing PRO scores.

If the missingness is completely at random (MCAR), complete case analysis will be conducted.

If the missingness depends on covariates and observed PRO scores (missing at random, MAR) [99] [100], the data will be analyzed using the (generalized) linear mixed models with patient as the random effect and treatment along with all factors associated with data missingness will be included as predictors in the models. [100].

If there are indications that the missingness is not at random (MNAR),, we will explore advanced models that consider both longitudinal PRO assessments and missing data mechanism, such as pattern mixture model and selection model[100].

16.6 Study Monitoring

16.6.1 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:

- If 2 or more patients in the first 10 treated patients in any study arm (or 20% of all patients after 10 are accrued) experience a grade 3 or higher adverse event and the event rate is higher in the active treatment arm.

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.

16.7 Study Reporting

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

This study will be monitored by the Mayo Data Safety Monitoring Board (DSMB). Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every 6 months as per NCI guidelines.

Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the “ClincialTrials.gov” web site. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov.

16.8 Inclusion of Women and Minorities

We expect about 17% of patients will be classified as minorities by race and ethnicity. Expected sizes of race by ethnicity subsets for patients randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	5	5	0	0	10
White	42	31	2	1	76
More Than One Race	0	0	0	0	0
Total	48	37	2	1	88

Ethnic Categories:

- Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, 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.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

NOTE: If a patient is still alive 1 year after registration, no further follow-up is required.

18.2 Survival Follow-up

See Section 4.1

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. All PHI must be redacted from any documentation.

18.5 Supporting documentation

Upload a copy of documentation in RAVE on the Supporting Documentation Form.

Baseline: The following documents are required for diagnosis and eligibility verification: Clinic note including description of prior chemotherapy and neuropathy status. These documents should be submitted within 14 days of registration.

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the ACCRU website. Only site staff rostered with the Rave CRA role will have access to these reports.

All data must be entered by Remote Date Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [redacted] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [redacted]

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

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Appendix I: ACCRU-SC-2102 PATIENT INFORMATION SHEET

Patient Completed Questionnaire Booklet

Baseline

You will be given booklets to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed on the day you enroll in the study.
2. This booklet contains the following questionnaire(s):
    a. EORTC QLQ-CIPN20 Instrument
    b. Chemotherapy Induced Peripheral Neuropathy Assessment Tool
    c. Symptom Experience Diary (Baseline)
    d. Peripheral Neuropathy Question
    e. Cognitive Functioning Assessment
3. Directions on how to complete each set of questions are written at the top of the page.
4. You will be given the nurse's or study coordinator's name and telephone number. You can call any time with any concerns or questions.
5. Please complete the booklet and return it to your study staff. If returning by mail, please use the self-addressed and stamped envelopes provided with the questionnaires. It is very important that you return the booklet to us.

Thank you for taking the time to help us.

Appendix I: ACCRU-SC-2102 PATIENT INFORMATION SHEET

Patient Completed Questionnaire Booklet

During Treatment

You will be given booklets to complete for this study. This booklet contains some questions about your 'quality-of-life' as a patient receiving treatment for cancer. Your answers help us to better understand how the treatment you are receiving is affecting the way you feel.

1. You are being asked to complete a questionnaire booklet for this study. This booklet must be completed at the end of each week, prior to the start of another week of treatment.
2. This booklet contains the following questionnaire(s):
    a. EORTC QLQ-CIPN20 Instrument
    b. Patient Global Impression of Change
    c. Chemotherapy Induced Peripheral Neuropathy Assessment Tool
    d. Symptom Experience Diary – During Treatment
    e. Peripheral Neuropathy Question
    f. Cognitive Functioning Assessment
3. Directions on how to complete each set of questions are written at the top of the page.
4. You will be given the nurse's or study coordinator's name and telephone number. You can call any time with any concerns or questions.
5. Please complete the booklet and return it, by mail, to your study staff weekly. Please use the self-addressed and stamped envelopes provided with the questionnaires. It is very important that you return the booklet to us.

Thank you for taking the time to help us.

Appendix II: EORTC QLQ-CIPN20 Instrument

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.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
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

During the past week :	Not at All	A Little	Quite a Bit	Very Much
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

Appendix III: Patient Global Impression of Change

1. Since starting this study, my *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, 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

3. Would you recommend this therapy, to try to prevent or treat neuropathy, to other patients with problems similar to yours?

☐ No

☐ Yes

☐ Unsure

Comments:

_____
_____
_____
_____
_____

Appendix IV: Chemotherapy Induced Peripheral Neuropathy Assessment Tool (Quantitative Items)

Over the last week, how much have your neuropathy symptoms interfered with:	**Not at all Interfering**										**Completely Interfering**
Dressing (buttoning, zipping, etc)	0	1	2	3	4	5	6	7	8	9	10
Walking	0	1	2	3	4	5	6	7	8	9	10
Picking up objects	0	1	2	3	4	5	6	7	8	9	10
Holding onto objects	0	1	2	3	4	5	6	7	8	9	10
Driving	0	1	2	3	4	5	6	7	8	9	10
Working	0	1	2	3	4	5	6	7	8	9	10
Participating in hobbies or leisure activities	0	1	2	3	4	5	6	7	8	9	10
Exercising	0	1	2	3	4	5	6	7	8	9	10
Sleeping	0	1	2	3	4	5	6	7	8	9	10
Sexual activity	0	1	2	3	4	5	6	7	8	9	10
Relationships with other people	0	1	2	3	4	5	6	7	8	9	10
Writing	0	1	2	3	4	5	6	7	8	9	10
Usual household chores	0	1	2	3	4	5	6	7	8	9	10
Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10

Appendix V: Symptom Experience Diary –Baseline ONLY

Note to study staff: Remove the 'Symptom Experience Diary – Baseline ONLY' from patient questionnaire booklets for Weeks 1-8. Patients will complete the 'Symptom Experience Diary -during treatment' for Weeks 1-8 following baseline.

Note to Patient: This form is to be completed only at baseline prior to the start of your study medication. If you have started your study medication, please complete the 'Symptom Experience Diary – during treatment' instead.

Please circle **ONE** number for each item that best describes you **over the past 7 days**.

1. Over the past week, did you experience nausea and/or vomiting?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

2. Over the past week, did you experience diarrhea?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

3. Over the past week, please rate your quality of life:

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

Symptom Experience Diary –during treatment

The following questions should be answered only after you start the study medication.

Please circle **ONE** number for each item that best describes you **over the past 7 days**.

1. Over the past week, did you experience nausea and/or vomiting?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

2. Over the past week, did you experience diarrhea?

0	1	2	3	4	5	6	7	8	9	10
Not at all										As bad as it can be

3. Over the past week, please rate your quality of life:

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

4. How many doses of the study medication did you miss over the past week?

0 times 1-2 times 3-4 times More than 5 times

Appendix VI: Peripheral Neuropathy Question

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

Being more specific, how much of a problem has pain in your fingers/hand and/or toes/feet been in the past week?

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

Appendix VII: Cognitive Functioning Assessment

1. How much of a problem have you had concentrating on things, in the past week?

0	1	2	3	4	5	6	7	8	9	10
No trouble at all										Trouble as bad as you can imagine

2. How much of a problem have you had remembering things, in the past week?

0	1	2	3	4	5	6	7	8	9	10
No trouble at all										Trouble as bad as you can imagine

Appendix VIII Nurse/CRP Weekly Phone Contact Guide

Patient Phone No._____
Best Dates/Times to call_____

FOLLOW UP:

1. Please make an appointment to call the patient at home the end of each study week. The purpose of this contact is to remind the patient of dose schedule, document compliance, encourage completion of the booklet, and address problems.

    - It is important to reinforce completion of weekly questionnaires. Regarding potential side effects, please ask about nausea, vomiting and diarrhea. In addition, determine whether there are any reportable adverse events (Section 9.0).

2. Items to document on the Nurse/CRP Evaluation form in the forms packet include, but are not limited to the following:
    - Date of phone call
    - Study week
    - Side effects:
        - Type of side effect, severity and attribution, if applicable
    - Any changes in medications or other treatments (i.e. behavioral, diet, etc.)
    - Has the participant taken the proper amount of study medication each day? Choose one:
        - Always (6-7 doses out of 7 for once daily dosing; 11-14 doses out of 14 for twice daily dosing) __ _____,
        - Usually (3-5 doses out of 7 for once daily dosing; 5-10 doses out of 14 for twice daily dosing) __ _____,
        - Rarely (1-2 doses out of 7 for once daily dosing; 1-4 doses out of 14 for twice daily dosing) __ _____, or
        - Never (0 doses taken) _____
    - Questions/Comments

3. Reinforce compliance with study medication.

4. Ask about use of other cannabinoid products such as CBD and/or THC, noting that they are not supposed to be taking them. If they are, then document and state/suggest that they stop such agents. If patient agrees to discontinue, they may remain on active study treatment. If they decline to discontinue the cannabinoid, they will be taken off study.

5. Reinforce completion of questionnaires and request return of them. NOTE: If patient decides to stop study before Week 8, ask the patient to fill out the questionnaires up to that point at the end of the booklet and return in the envelope provided.

Appendix IX: Nurse/study assistant phone call at months 6 and 12.

Patient Phone No._____

FOLLOW UP:

1. Please call the patient at home at 6 and 12 months.

2. Ask about neuropathy status and what medications that the patient might be taking for CIPN:

_____
_____

3. Ask about whether they have had any recurrent cancer problems:

☐Yes ☐ No

If Yes, please describe:

_____
_____