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Topical Cannabidiol (CBD) for the Treatment of Chemotherapy-induced Peripheral Neuropathy: A Randomized Placebo-controlled Pilot Trial

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Mayo Clinic Cancer Center

Topical cannabidiol (CBD) for the treatment of chemotherapy-induced peripheral neuropathy: a randomized placebo-controlled pilot trial

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Protocol Resources

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Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
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Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility allowed

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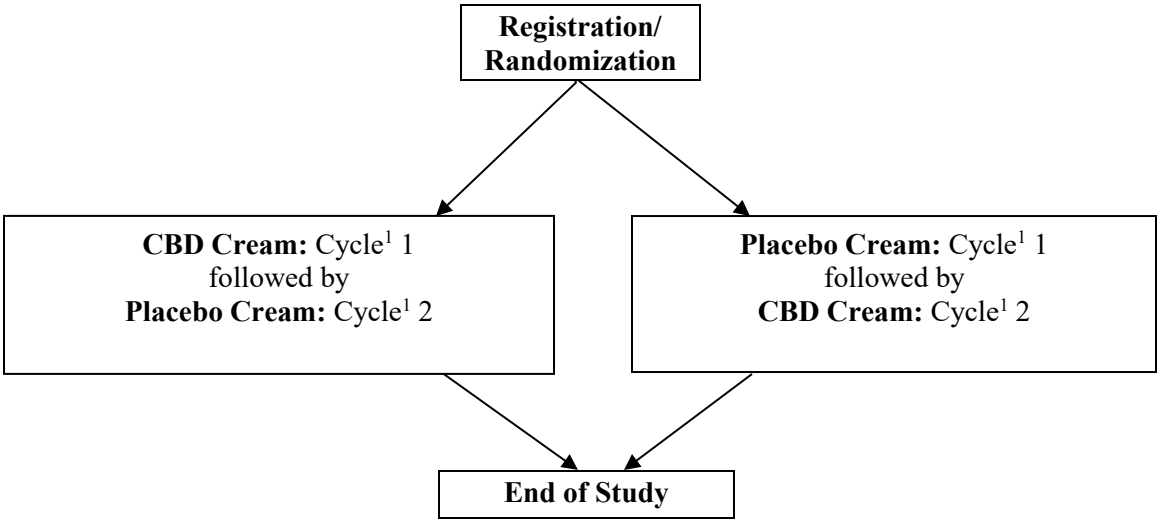
Schema



[1] Cycle length = 14 days

1.0 Background

Chemotherapy-induced peripheral neuropathy (CIPN) is a dose and age-dependent side-effect associated with six main antitumor agent drug classes: platinum-based drugs, (e.g., oxaliplatin), taxanes (e.g., paclitaxel and docetaxel), vinca alkaloids (e.g., vincristine), epothilones (e.g., ixabepilone), the proteasome inhibitors (e.g., bortezomide) and immunomodulatory drugs (e.g., thalidomide)[1]. In a review of over 30 clinical studies, CIPN prevalence was reported to be approximately 68% when measured in the first month after finishing a variety of chemotherapy agents, most of which had been associated with CIPN; it was 60% at three months and 30% at 6 months or more [2].

CIPN remains a challenge to treat, as most agents used in practice, such as tricyclic antidepressants, anticonvulsants (gabapentin and pregabalin), or serotonin-norepinephrine reuptake inhibitors (SNRIs), primarily duloxetine, provide limited benefit to most patients and can have significant side effects[3-5].

The mechanism of CIPN broadly includes the production of neuronal toxicity and inflammation[6]. The six main classes of antitumor agents, discussed above, cause damage to peripheral sensory, motor, and autonomic neurons, through such mechanisms as microtubule disruption, oxidative stress and mitochondrial damage, altered ion channel activity, and myelin sheath and DNA damage [7]. In addition, the cumulative damage leading to increased activation of the immune system ultimately promotes cell damage and death in peripheral neurons, leading to a sensitization to nociceptive responses[6].

The cannabinoids, delta-nine-tetrahydrocannabinol (THC) and cannabidiol (CBD), derived from the plant *Cannabis sativa* (*Cannabis*) have shown some efficacy in the treatment of pain [8, 9], including neuropathic pain[3, 10]. THC interacts with the endocannabinoid system primarily through the activation of cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) receptors[11]. CBD does not efficiently interact to activate known cannabinoid (CB_1 and CB_2) receptors [12]. CBD, however, can antagonize the activity of CB_1 and CB_2 receptor agonists [13].

THC and additional CB_1 and CB_2 receptor agonists, have been shown to be effective at reducing CIPN in multiple preclinical models [6, 14]. THC and additional cannabinoids, through CB1 and/or CB2 receptors, have the potential to modulate pain through a variety of mechanisms, including inhibition of calcium channel activity, transient receptor potential (TRP) channels, serotonin, GABA and glutamate receptor signaling, and modulation of the immune system, leading to anti-inflammatory activity [15-17]. Inhaled cannabis has also been reported to be effective for treating HIV-associated neuropathy, possibly via CB_1 agonism [18].

Neuropathic pain may also involve abnormal hyper-excitability in skin afferent nerves. Skin cells express CB2 and endothelin receptors, and when activated, they release B-endorphin, which can reduce hyperalgesia, that is mediated by pro-inflammatory pathways [19, 20].

CBD has been shown to have pleotropic effects that ultimately lead to reduction in oxidative stress and inflammation [21]. Increasingly, preclinical evidence demonstrates that CBD has anti-neuropathic pain effects in multiple rodent models, including models of CIPN [21-25]. Also, there is significant overlap with mechanisms controlling pain when CBD and THC are compared. CBD has been shown to inhibit pain through modulation of calcium and TRP channels, serotonin receptors, glycine receptors, and modulation of the immune system [6], in particular, microglia and macrophage function [26], leading to anti-inflammatory activity.

Similar to CB_1 and CB_2 receptor agonists, the neuroprotective and anti-inflammatory properties of CBD provide a potential mechanism for the protective effects of CBD in neuropathic pain, including CIPN [27]. For example, CBD has been shown to directly or indirectly modulate several receptors involved in modulating pain signaling, including 5-HT_{1A} [25], and transient receptors TRPV1 and TRPA1

[16, 22]. TRPV1 receptors are present in sensory peripheral nerves as well as in keratinocytes and are activated by capsaicin, as well as by endogenous cannabinoids [28]. Capsaicin is a TRPV agonist that has been extensively studied in pain and appears to have activity in treating neuropathic pain. This agonist leads to overstimulation and desensitization of nociceptors and may lead to nerve regeneration and restoration [29]. A placebo-controlled, double-blinded, cross-over trial of a capsaicin cream demonstrated that it substantially decreased chronic post-surgical scar pain and its benefit persisted after stopping the capsaicin [30].

CBD can also act as a neuroprotective agent as a result of direct antioxidant activity [31]. During secondary injury, CBD can reduce intracellular calcium levels and have neuroprotective effects [32]. CBD reduces mitochondrial damage during events of cellular stress, thereby diminishing generation of inflammatory and oxidative products [33]. CBD also inhibits microglial proliferation and pro-inflammatory cytokines and increases anti-inflammatory cytokine production in vivo [22, 23, 34].

Given that many patients do not have access to systemic *Cannabis*, and/or want to avoid the psychoactive effects of THC, a more local means of providing cannabinoids might be preferable. Cannabinoids happen to be lipophilic agents and, thus, can permeate skin [35, 36]. Taking advantage of this delivery technique, a small pilot clinical trial evaluated a topical cannabinoid cream, reporting data that supported that it improved neuropathic pain [37].

In addition to the promising-appearing data noted above, we recently analyzed data from a case series of 22 patients with chemotherapy-induced peripheral neuropathy, who reported symptomatic benefit from using topical cannabinoid-based creams containing the delta-nine-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), derived from *Cannabis sativa* (manuscript submitted for publication). These cases are summarized in the following table.

Table 1. Patients reporting benefit from topical cannabis.

Pt	Cancer type	Chemotherapy	Location of symptoms	Treatments tried/failed	Cannabis type
1	Myeloma	RVD/transplant	Feet	Duloxetine, Gabapentin, pregabalin, acupunture	CBD
2	Breast	AC-T	Feet	Gabapentin	CBD/THC 1:1
3	Pancreatic	FOLFOXIRI	Hands/feet		CBD/THC 1:1
4	Primary peritoneal	Taxol/carboplatin	Feet		CBD
5	Breast	Capecitabine/eribulin	Feet		CBD/THC
6	Lymphoma	R-CVAD	Hands and feet		CBD
7	Breast	AC-T	Feet	Gabapentin	CBD
8	Breast	AC-T	Feet, legs		CBD/THC
9	Ovarian	Paclitaxel/carboplatin /bevacizumab	Feet		CBD oil
10	Breast	AC-T	Feet	Acupuncture	CBD
11	Uterine	Paclitaxel	Hands		CBD/THC 1:1

12	Colorectal	FOLFOX	Burning in feet, hands	gabapentin	CBD/THC 1:1
13	Ovarian	Paclitaxel/carboplatin	Hands/feet	gabapentin	CBD/THC 1:1
14	Pancreas	FOLFOX	Feet		CBD oil
15	Pancreas	FOLFOX	Hands		CBD/THC 1:1 cream
16	Breast	Paclitaxel/carboplatin	Feet		CBD/THC
17	Ovarian	Paclitaxel/carboplatin	Hands and feet	Gabapentin	CBD
18	Breast	TC	Hands		CBD
19	Primary peritoneal cancer	Paclitaxel/carboplatin	Feet		CBD oil
20	Breast	AC-T	Hand and feet	Duloxetine, acupuncture, hydrotherapy	CBD oil
21	Pancreatic	FOLFOXIRI	Feet		CBD
22	Ovarian	Paclitaxel	Hands and feet		CBD/THC

Abbreviations: RVD-lenalidomide/bortezomib/dexamethasone; AC-T: doxorubicin, cyclophosphamide/paclitaxel; TC:docetaxel and cyclophosphamide; FOLFOXIRI: 5-florouracil/leucovorin/oxaliplatin/irinotecan; FOLFOX: 5-florouracil/leucovorin/oxaliplatin

As this table indicates, patients in this case series were using either a topical CBD alone or a topical combination of CBD/THC. Given that CBD is a negative modulator of CB1, it would seem that topical THC, working via a CB1 mechanism, might not be needed for the benefit observed with anti-nociception.

The data reported above, supporting that topical-based cannabis products decrease CIPN pain in humans, call for the conduct of a prospective trial to evaluate a topical cannabis-based product as a treatment of established painful CIPN. We have chosen to study a cream with CBD alone, as opposed to a product that contains THC. This should simplify the conduct of this trial, given the barriers to conducting studies using THC products and varying laws and regulations regarding the use of THC in different states in the USA.

2.0 Goals

This is a pilot randomized double blinded placebo controlled cross-over trial. This pilot study will randomize 40 patients with chemotherapy-induced peripheral neuropathy to receive, for 14 days, either 1) a CBD cream or 2) a placebo. Patients initially receiving the placebo will cross over to receive the CBD cream, while those receiving the CBD creams will cross over to receive the placebo, for 14 days. Patients will apply cream to the affected area (hands and/or feet) twice daily (morning and evening). This cross-over will allow all patients to eventually receive the CBD cream and will allow us to determine whether any benefit derived from a CBD preparation will diminish or persist after the CBD preparation is stopped (that is in the patients who initially received the CBD product and then were changed to receive a placebo, while still being blinded to what they received).

No washout period is planned with the cross-over because a) no washout is needed in patients going from placebo to CBD cream, and b) we want to determine what happens after patients stop cannabis cream, i.e., do the effects persist after the patient starts the placebo portion, as was prominently seen in a prior trial of ours evaluating capsaicin cream [30].

2.1 Primary Objective

The aims of the proposed project include:

1. To evaluate whether topical CBD improves chemotherapy-induced peripheral neuropathy (CIPN), compared to placebo
2. To evaluate side effects from topical CBD cream use, compared to placebo

The data obtained from this trial are designed to provide information to allow for a larger phase III, placebo-controlled, randomized, clinical trial.

Primary endpoint

The primary endpoint is change in CIPN from baseline to the end of week 2. CIPN will be measured by the sensory subscale of the EORTC QLQ-CIPN20 which is composed of 9 individual items.

2.2 Secondary Goals

Secondary endpoints include other measures of neuropathy as measured by the EORTC QLQ CIPN20 motor subscale, the EORTC QLQ CIPN20 autonomic scale, and the total CTCAE neuropathy scale. Adverse event profiles will also be assessed using symptom questionnaires and CTCAE v5.0.

3.0 Registration Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥18 years

3.12 English speaking

3.13 Cancer diagnosis of any tumor type with chemotherapy-induced neuropathy

3.14 At least 4 out of 10 severity of neuropathy pain and/or tingling per appendix IV

3.15 Stable for at least 7 days prior to registration on medications for neuropathy, if any are being used

3.16 ECOG Performance Status (PS) 0, 1 or 2 (Appendix VIII).

3.17 **Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.**

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

3.18 Able to provide written informed consent

3.19a Ability to complete questionnaire(s) by themselves or with assistance.

3.19b No evidence of residual cancer

3.19c 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

3.2 Registration - Exclusion Criteria

3.21 Any of the following because this 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

3.22 Any medical condition that would prohibit use of a topical cream (skin infection or open wound in the area of the neuropathy)

3.23 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.24 Pre-existing neuropathy prior to chemotherapy that would confuse the issue of CIPN

3.25 Currently on chemotherapy or received chemotherapy treatment within the prior 3 months.

3.26 Use of other cannabis products within 30 days prior to registration

3.27 History of allergy to cannabis products

4.0 Test Schedule

4.1 Test schedule for Chemotherapy-Induced Peripheral Neuropathy

Study Visit	1	2	3	4	5	6	7
Study Time Point	Screening /Baseline (Day -30 to Day 1)	Day 1	End of Week 1	End of Week 2[c] (+3 Days)	End of Week 3	End of Week 4	End of study
CLINCAL ASSESSMENTS							
Informed consent	X						
Inclusion/exclusion criteria	X[g]						
Demographics/ Medical history	X						
Pregnancy testing [a]	X						
Randomization	X						
Dispense Study Product/Placebo		X		X			
Collect questionnaires							X
Adverse event assessment [b]			X	X	X	X	
STUDY TESTING							
EORTC QLQ-CIPN 20 instrument (Appendix I)	X		X	X	X	X	
Global impression of change (Appendix II)			X	X	X	X	
Chemotherapy Induced Peripheral Neuropathy Assessment Tool (Appendix III)	X		X	X	X	X	
Symptom experience diary (Appendix Va & Vb)	X[d]		X[e]	X[e]	X[e]	X[e]	
NCI-CTCAE neuropathy scale [f] (Appendix VI)	X		X	X	X	X	

Cycle = 14 days

[a] For individuals of childbearing potential. Must be done ≤7 days prior to registration.

[b] Research nurse or clinician to call patient. Including inquiry about skin toxicity and to assess for suicidal thoughts (Appendix IX). Ask the patient if they have missed any doses of the study

medication and provide education if necessary. Note any other pertinent information that the patient provides.
[c] After subject completes week 2 they will turn in completed questionnaire diary and start the next supply of cream within 1-3 days after completing the first 2 weeks, ideally.
[d] Appendix Va: System Experience Diary used for baseline assessment. Must be completed prior to application of study medication.
[e] Appendix Vb: System Experience Diary used for weekly assessments. Must be completed at the end of each week.
[f] To be completed during research nurse or clinician call to patient per Appendix VI.
[g] Required Initial Laboratory Values per inclusion criteria 3.19c can be done any time after the patient has completed their chemotherapy and prior to study registration.

5.0 Stratification Factors:

- Gender (Male, Female, or Other)

6.0 Registration/Randomization Procedures

6.1 Registration (Step 1):

6.11 Registering a patient

To register a patient, access the Registration Application at [redacted] The Registration Application is available 24 hours a day, 7 days a week. If unable to access the application, contact the Mayo Clinic Research Registration Office [redacted] between the hours of 8am and 4:30 pm Central Time, Monday through Friday. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC Subject ID number (R######) must be assigned. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent.

6.2 Verification of materials

Prior to accepting the registration, 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

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

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

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

6.4 Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.4a Study drug

Study drug is available on site. Each site will have a supply of both investigational product and placebo that will be sent from Nightingale Remedies. After randomization at Mayo, the local site pharmacist will re-label the product per randomization instructions. Research staff, other than pharmacy, are blinded, and will dispense the cream to the patient at the site.

6.4b Patient questionnaire booklets need to be available for patients

Patient questionnaire should be ordered using the Patient Questionnaire Order Form. PDF versions of the questionnaires will be sent electronically for printing.

Patient questionnaire booklets should be provided to the patients. They may be provided to the patient during a routine visit, via mail or electronically. They will be available as follows:

- Questionnaires for Baseline (this should be completed prior to application of study medication)
- Questionnaires for week 1 & 2 (a self-addressed and stamped envelope should be provided the patient to mail this back at the end of week 2)
- Questionnaires for week 3 & 4 (a self-addressed and stamped envelope should be provided the patient to mail this back at the end of week 4)

Before the questionnaires are provided to the patient, the patient initials and appropriate dates of when they are to be completed should be written on each of the questionnaires.

6.4c Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

6.4d Randomization Procedures: The factor defined in Section 5.0 (gender) will be used as the only stratification factor

6.4e Procedures for Double-Blinding the Treatment Assignment

6.4e1 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 at the time of registration. Make sure this contact person will be available at the time of registration so he or she can be contacted by 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 sources of communication, either fax or e-mail, and the appropriate contact information. The registration specialist will then communicate the treatment assignment to the designated contact at the patient's institution.

6.4e2 The treatment assignment will be to *active or placebo*. The unblinded pharmacist should only give one supply of study cream at a time according to the treatment assignment from the registration specialist. Each participating institution will be responsible for monitoring drug supplies. The bottles will be labeled by the unblinded pharmacist as *"CBD or placebo cream"* so that the contents are not discernible to the person administering the treatment. At the time of cross-over, the patient will be given the alternative medication (CBD or placebo), again in a blinded manner.

6.4e3 The unblinded pharmacist will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

7.0 Protocol Treatment

7.1 Treatment Plan:

Patients will be instructed to apply the CBD or placebo cream in a thin layer (approximately 4-5 pumps of product) to affected areas twice daily for 14 days.
CIPN in hands: apply 4-5 pumps to hands twice a day
CIPN in feet: apply 4-5 pumps to feet twice a day
After two weeks of using the designated treatment participants will cross over to the other treatment. The other treatment will be applied as described above, twice daily for another two weeks.

7.2 Breaking Code:

During the study, codes should only be broken in emergency situations, which are not expected in this study. In the event of an emergency, call the MCCC Registration Office at [redacted] to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. Central Time. Alternatively, email the Registration Office [redacted] If the code must be broken after hours, assume the patient was assigned to active treatment and treat accordingly. Place a call to the MCCC Registration Office and leave a message informing them of the need to un-blind a patient. Provide your contact information so that MCCC Registration Office personnel can return the call the next business day.

7.3 After the patient has completed the study and the questionnaires have been completed and sent in, the code can be broken, so that the patient can choose whether to continue to use CBD on their own if they felt it gave them benefit. To do this, the MCCC Registration

Office may [redacted] to find out which study therapy the patient was receiving.

8.0 Dosage Modification Based on Adverse Events

There are no dosage modifications. If patients develop any intolerance or bothersome enough side-effect, they are to stop the study drug/placebo. Ideally, they will still complete the study questionnaires.

9.0 Ancillary Treatment/Supportive Care:

This protocol should not interfere with appropriate supportive care measures unrelated to a patient's CIPN, unless use of CBD is specifically restricted.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

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).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting [redacted]	Mayo Sites – attach to MCCC Electronic SAE Reporting Form [redacted] Will automatically be sent to [redacted] Non Mayo sites – complete and forward to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form: [redacted]	Will automatically be sent to [redacted]
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form [redacted] AND attach MedWatch 3500A: [redacted]	Will automatically be sent to [redacted]
Non-Mayo Clinic Sites	MedWatch 3500A: [redacted]	[redacted]

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. Identify the grade and severity of the event using the CTCAE version 5.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined 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.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.

Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND 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 **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 sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[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

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] or investigational agents or commercial/investigational agents on the same arm.

Non-MCCC Institutions*:* Submit copies to [redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table 10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

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

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.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo

Clinic Cancer Center Expedited Event Report form [redacted] he Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

Non-MCCC Institutions*:*

Submit to your IRB as required by your institutional policies.
Submit copies to [redacted]

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND 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 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 should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. 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.

10.53 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 will 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.

10.54 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 unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

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 Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", 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. Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required Routine Reporting

Neurotoxicity Evaluation to be completed at baseline and each evaluation per NCI-CTCAE v5.0 grading in Appendix VI.

10.61 **Baseline and Adverse Events Evaluations**

Pretreatment symptoms/conditions do not need to be graded.

10.62 All other AEs

All other AEs will be addressed during the weekly phone calls with the research nurse or clinician. Patient questionnaire booklets are not collected until the end of the study, therefore, will not be used to collect & document AEs.

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

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

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

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 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.

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

10.8 Deviation Reporting Instructions

For Non-MCCC institutions All deviations must be reported in the Medidata Rave® EDC system via appropriate Case Report Forms. Mayo Clinic Cancer Center (MCCC) Institutions will report via institutional standards.

11.0 Treatment Evaluation/Measurement of Effect

See statistical details in Section 16.

12.0 Descriptive Factors: Not applicable.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Physicians can use the unblinded study data, for the individual patient, to help determine subsequent therapy for individual patients.

14.0 Body Fluid Biospecimens – None**.**

15.0 Drug Information

Placebo and creams will be provided by Nightingale Remedies. This product has been tested by an independent lab for content and has 0% THC (testing attached). The study cream contains CBD isolate; both creams are odorless. 4-5 pumps of product will cover hands/feet and contains approximately 4 mg of CBD isolate. Patients with CIPN only on hands or feet would then get approximately 8 mg of topical CBD per day. Patients with CIPN on both locations would get approximately 16 mg of topical CBD per day. See appendix VII for product ingredients. See investigator brochure for detailed information about drug product and safety issues.

Shipping, handling, and storage

Creams should be stored at room temperature (59°-77°F). Product will be shipped from Nightingale Remedies to participating sites. They will not be blinded to their local pharmacist who must keep all of the other clinical partners blinded to the study product and placebo.

IND number: 157457

15.1 CBD Cream

15.11 Drug procurement:

Nightingale Remedies will supply all drug. Each institution will order the drug from Nightingale Remedies. Submit the Drug Order Form request to:

[redacted]

Outdated or remaining drug is to be destroyed on-site per procedures in place at each institution.

The investigator is responsible to ensure supervision of accurate monitoring of the receipt, storage and allocation of the study product. Copies of all invoices of shipments must be retained. Accurate study product inventory, dispensing and accountability logs must be obtained and stored in the Pharmacy Binder.

15.111 Each participating institution may ship Study Product/Placebo directly to their patients if the site standards allow. All local site procedures should be followed and accurate accountability logs should be maintained.

15.12 Nursing guidelines

Educate patient regarding this protocol and address questions.

1. Instruct patients to report any rash or burning with application
2. Instruct patients to avoid eye contact after applying lotion
3. Agent should be stored at room temperature

16.0 Statistical Considerations and Methodology

16.1 Primary

This is a randomized, two arm, placebo-controlled, double-blind, pilot study of whether CBD can improve CIPN more than a placebo. The purpose of this pilot study is to estimate the treatment effects of CBD compared to the placebo arm. These preliminary efficacy estimates will aid in the design of a large-scale randomized phase III clinical trial.

The primary endpoint is the change in CIPN from baseline to week 2. CIPN will be measured by the sensory subscale of the EORTC QLQ-CIPN20 which is composed of 9 individual items. Secondary endpoints include other measures of neuropathy as measured by the EORTC QLQ CIPN20 motor subscale, the EORTC QLQ CIPN20 autonomic scale, and the CTCAE neuropathy scale. Adverse event profiles will also be assessed using symptom questionnaires and the CTCAE 5.0.

As this is a pilot study, descriptive statistics and statistical plots will be utilized to summarize and estimate the primary and secondary endpoints. Statistical hypothesis testing will be used in an exploratory manner and will be interpreted accordingly.

For the primary analysis, changes in sensory neuropathy from baseline to week 2 will be compared between arms using two-sample, two-sided t-tests. The CBD arm will be compared to the placebo arm. We will construct 95% confidence intervals for the mean difference in sensory neuropathy score between arms. Repeated measures mixed models will be applied to the sensory scores over all time points to determine longitudinal effects and to adjust for confounding factors. Graphical results will include profile plots over time, stream plots of individual changes over time, and forest plots of the 95% confidence intervals by arm.

For logistical and financial reasons, the sample size for this pilot study is set at 40 patients (20 per treatment group). While this is only a descriptive study and is not powered to detect significant differences between arms, the following table provides power analyses for various effect sizes based on a two-sided, two-sample t test at $\alpha = 0.05$ for a fixed sample size of 20 patients per arm.

Effect size, $\Delta = \lvert \mu 1 - \mu 2 \rvert / \sigma$	0.5	0.6	0.7	0.8	0.9	1.0
Power	0.34	0.46	0.58	0.69	0.79	0.87

For example, we will have 79% power to detect an effect size of 0.9 in EORTC QLQ-CIPN20 with a sample size of 40 patients (20 per arm). This effect size is the mean difference divided by the common standard deviation within each arm.

16.2 Analysis Plan for Secondary Outcome and Translational Endpoint

Analyses for secondary endpoints will also be descriptive in nature. Due to the exploratory nature of this research, we will not adjust for multiple comparisons for the secondary analyses. Analyses of the motor and autonomic subscales will be identical to the analyses of the primary endpoint. Analyses of CTCAE grades and the symptom questionnaire individual items will compare the incidence and maximum (worst) values between arms. Fisher's exact tests will be used to compare incidence rates and Wilcoxon rank-sum tests will be used to compare maximum values between arms.

16.3 Data & Safety Monitoring

16.31 Safety review

The principal investigator(s) and the study statistician will review the study monthly to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least biannually, based on reports provided by the MCCC Statistical Office.

16.32 Adverse Event Stopping Rules

Patients who report > grade 2 rash, pain, allergic reaction, or any other > grade 2 side effects attributed to the study medication will stop study drug/placebo and be monitored. Appropriate local care should be administered by the treating physician.

The PI has the right to discontinue this study at any time for reasonable medical or administrative reasons. The DSMB may also terminate study per early stopping rules.

16.4 Subset Analyses for Minorities

16.41 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.42 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.43 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	18	18	36
Ethnic Category: Total of all subjects	**20**	**20**	**40**
Racial Category			
American Indian or Alaskan Native	1		1
Asian		1	1
Black or African American	2	2	4
Native Hawaiian or other Pacific Islander	1		1
White	16	17	33
Racial Category: Total of all subjects	**20**	**20**	**40**

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.

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 Records and Data Collection Procedures

17.1 Submission Timelines:

Baseline information should be provided within 2 weeks of patient registration, while 2 and 4 week data should be provided within 2 weeks of patient submission of such.

17.2 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.

17.3 Site responsibilities

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

17.4 Overdue items

A member of the Mayo Clinic study team (e.g. Protocol specialist, data manager, PI, etc.) may contact site personnel via email regarding overdue forms and outstanding queries.

18.0 Budget

18.1 Costs charged to patient: routine clinical care

18.2 Tests to be research funded:

CBD cream & placebo will be provided from research funds.

19.0 References

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Appendix I: 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 II: 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 III: 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 IV: Peripheral Neuropathy Question

1. How much of a problem has 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 tingling or pain in fingers and/or toes									Tingling or pain in fingers and/or toes as bad as you can imagine	

Appendix Va: Symptom Experience Diary –Baseline

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

1. 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

2. Do you have any skin rash on your hands or feet:

0	1	2	3	4	5	6	7	8	9	10
None										As bad as it can be

Appendix Vb: Symptom Experience Diary —During Treatment

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

1. 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

2. Do you have any skin rash on your hands or feet:

0	1	2	3	4	5	6	7	8	9	10
None										As bad as it can be

3. How many doses of the study medication do you think that you missed over the past week? (Circle one answer)

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

4. Did you have any skin side effects from the study product?

____ No

____ Yes, if so, please describe the symptom(s) and severity:

_____
_____
_____

5. Did you have any other side effects from the study product?

____ No

____ Yes, if so, please describe the symptom(s) and severity:

_____
_____
_____

Appendix VI: CTCAE Criteria

Neurotoxicity Evaluation

Grade	I	II	III	IV
NCI-CTCAE v5.0	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Questions	Sample answers for each toxicity grade			
Do you have problems tying your shoe laces, buttoning your shirts, fastening buckles or pulling up zippers?	"No, I might feel some tingling in my hands, but I have no problems tying laces, buttoning shirts, fastening buckles or pulling up zippers"	"It is a bit harder than before, but I can still tie laces, button shirts, fasten buckles or pull up zippers"	"I have severe difficulties tying shoe laces, buttoning shirts, fastening buckles or pulling up zippers" or "I cannot tie laces, button shirts, fasten buckles or pull up zippers anymore"	"I haven't been able to tie laces, button shirts, fasten buckles or pull up zippers for weeks"
Do you have problems writing?	"No, I might feel some tingling in my hands, but I have no problems writing"	"It is a bit harder than before, but I can still write"	"I have severe difficulties writing" or "I cannot write anymore"	"I haven't been able to write for weeks"
Do you have problems putting on your jewelry or your watch?	"No, I might feel some tingling in my hands, but I have no problems putting on my jewelry or my watch"	"It is a bit harder than before, but I can still put on my jewelry or my watch"	"I have severe difficulties putting on my jewelry or my watch" or "I cannot put on my jewelry or my watch anymore"	"I haven't been able to put on my jewelry or my watch for weeks"
Do your have problems walking?	"No, I might feel some tingling in my feet, but I have no problems walking"	"It is a bit harder than before, but I can still walk"	"I have severe difficulties walking" or "I cannot walk anymore"	"I haven't been able to walk for weeks

Appendix VII: PRODUCT AND PLACEBO INFORMATION

I. Source of Hemp: The source of the Hemp is USA grown from pesticide-free farms.
Manufacturer: Nightingale Remedies, Portland OR

II. Method of CBD extraction: CBD isolate is extracted using Super Critical C02 Extraction method. This process is described below:

An extractor chamber is filled with ground cannabis/hemp material (called trim). A pump forces pressurized carbon dioxide gas at the optimum temperature (ScCO2) into the extractor chamber. The supercritical carbon dioxide interacts with the cannabis, dissolving the cannabinoid compounds it contains. The supercritical CO2 carries the cannabis oil particles past a pressure release valve to a cyclonic separator. In the separator, the pressure is lower and the carbon dioxide and cannabis oil separates. The carbon dioxide rises and is routed back to the CO2 tank for reuse in the case of a closed loop system. The cannabis oil, waxes and resins descend in the separator where they are captured by a collection vessel. The resulting substance is processed further into various products, such as CBD-rich "cannabis oil", free of any solvents.

III. Manufacturing Process: The manufacturing process is in a certified facility (see attachments). All ingredients are pre-screened with COA's for each ingredient. Production standards of cGMP are followed in every step of the process. The manufacturing process is a controlled environment and FDA / cGMP certified.

IV. Ingredients

Placebo:
Water, Organic Coconut Oil, Grapeseed Oil, Emulsifying Wax, Stearic Acid, Glycerin, Xanthan Gum, Phenoxyethanol, Tetrasodium Glutamate Diacetate, isopropyl palmitate, caprylic/capric triglyceride, propylene glycol, ceteareth-20, cetearyl alcohol, glyceryl stearate, PEG-100 stearate, dimethicone, octyldodecanol, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, lecithin, phenoxyethanol, ethylhexylglycerin, trolamine.

Experimental Cream:
Water, CBD Isolate* (Hemp Extract), Organic Coconut Oil, Grapeseed Oil, Emulsifying Wax, Stearic Acid, Glycerin, Xanthan Gum, Phenoxyethanol, Tetrasodium Glutamate Diacetate, isopropyl palmitate, caprylic/capric triglyceride, propylene glycol, ceteareth-20, cetearyl alcohol, glyceryl stearate, PEG-100 stearate, dimethicone, octyldodecanol, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, lecithin, phenoxyethanol, ethylhexylglycerin, trolamine.
***Active Product: Added CBD isolate to placebo base, 250 mg per 1.7 oz**

V. Certificate of Analysis: COA showing full panel test results is included in the current Investigator's brochure. The COA shows that there is 0% THC in the final CBD Isolate product.

VI. Study Product: The study product is being manufactured specifically for this study. It contains the ingredients listed above and will not have the herbals that are contained in the

marketed Nightingale Remedies product “CBD Relief Cream”. COA for the study product is included in the current Investigator’s Brochure.

VII. Product Safety: No formal PK studies have been done on this particular product however the literature supports safety of topical cannabis creams. The dose of CBD isolate is approximately 4 mg BID, and a very small amount may be systemically absorbed. Similar creams have been used with no reported adverse effects. The CBD product that we propose using is currently available commercially (with additional added herbal products) without need for a prescription from a health care provider. In a case series of 26 patients who had tried a variety of topical cannabis creams for CIPN (D’Andre, submitted to Integrative Cancer Therapies, 2021) there was not any toxicity that could be clearly attributed to the topical CBD therapy. One patient had a transient increase in CIPN symptoms, so the topical CBD was stopped and the symptoms subsequently returned to baseline. It is not clear to us whether the worsening CIPN symptoms were a result of the CBD cream of just a case of CIPN symptoms waxing and waning, as is frequently observed in clinical practice. In the literature, there are no reports of toxicity in patients using topical cannabinoids similar to what we are proposing to use in the currently proposed trial. This includes a trial from Xu et al, whereby CBD 250 mg/3fl oz/emu oil was studied; no adverse events were noted (1). Maida et al. reported three patients that used topical cannabis for pyoderma gangrenosum. These patients reported less pain, and there were no side effects noted. The dose used was 5-7 mg THC, 6-9 mg CBD (2). Maida et al also reported two more case series using a CBD based cream for non-healing ulcers in 2 patients and 14 patients, noting improved wound healing and pain control. In patients with open wounds, the systemic absorption of topicals is enhanced, and even in this situation there were no side effects noted (3,4). Three patients self-initiated use of CBD oil for the treatment of pediatric epidermolysis bullosa. All patients reported improved skin condition, less pain, and no adverse effects were noted (5). Additionally, 50 patients with inflammatory skin diseases were treated with a cream that contained cannabis, macadamia, and rosa moschata seed oils. Thirty had complete healing in 12 weeks and 20 had partial healing. The authors were trying to substitute this cream instead of using chronic steroid creams. One patient with radiation induced dermatitis, had complete healing. No side effects were noted (6). Another 11 patients were treated with a 3% seed extract CBD cream for acne and had decreased erythema and sebum production, compared to a base cream; no side effects were noted (7). Lastly, in a study of 35 patients with alopecia, a high dose (108 mg/2 oz) of a topical CBD cream was used to promote hair growth for six months; there were no reported adverse effects (8).

STATE OF CALIFORNIA

DEPARTMENT OF PUBLIC HEALTH
FOOD AND DRUG BRANCH

COSMETIC MANUFACTURING REGISTRATION

DHD Global Inc.
902 Columbia Ave.
Riverside, CA 92507

REGISTRATION NUMBER: 99914
EXPIRATION DATE: 8/13/2021

The person named herein is registered to manufacture cosmetics through the expiration date of this license. This annual license is issued in accordance with the provisions of Division 104, Chapter 7, Article 4 of the California Health and Safety Code and is not transferable to any other person or place. The registrant is required by law to immediately notify the California Department of Public Health of any change in the information reported in the application.

Food and Drug Branch, 1500 Capitol Avenue, MS 7602, PO Box 997435, Sacramento, CA 95899-7435 (916) 650-6500

Printed: 6/30/2020

OSP 07 102308

Appendix VIII ECOG Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group,
Robert Comis M.D., Group Chair.

[redacted]

Appendix IX: Patient Suicidal Thoughts Assessment and Evaluation for Skin Toxicity

Nurse/clinician Phone Call Questions to address regarding suicidal thoughts and potential skin toxicity.

Patients will be asked at the end of each week.

1. Given an abundance of precaution, we want to ask you about whether you have had any thoughts of suicide since starting this protocol?

    - If the answer is 'no', please record.
    - If the answer is 'yes', please record then physician contact is required, and appropriate intervention is to be provided.

2. Do you have skin irritation on your hands and/or feet in the location of the cream application?
3. Do you have any rash, blisters, or open areas of skin in the location of the cream application?

    - Please record responses.
    - If the answer is 'yes' to any of the above two questions, the patient will be asked to come in to be seen by a provider for a skin examination.

Additionally:

4. At the end of weeks 2 and 4, please remind patients to mail in or bring in their questionnaires from the prior 2 weeks.
5. Please note any other pertinent information that the patient provides.