MCC-16-12518
NCT04468230

Phase 2 Study of Nicotine for the Treatment of Pain Associated with Chemotherapy-Induced Peripheral Neuropathy

10/21/2022

Virginia Commonwealth University Massey Cancer Center

MCC Protocol #: MCC-16-12518

Phase 2 Study of Nicotine for the Treatment of Pain Associated with Chemotherapy-Induced Peripheral Neuropathy.

Principal Investigator:
Renato Martins, MD

[redacted]

[redacted]

[redacted]

Version #: 2 **Version Date:** 10/21/2022

SCHEMA

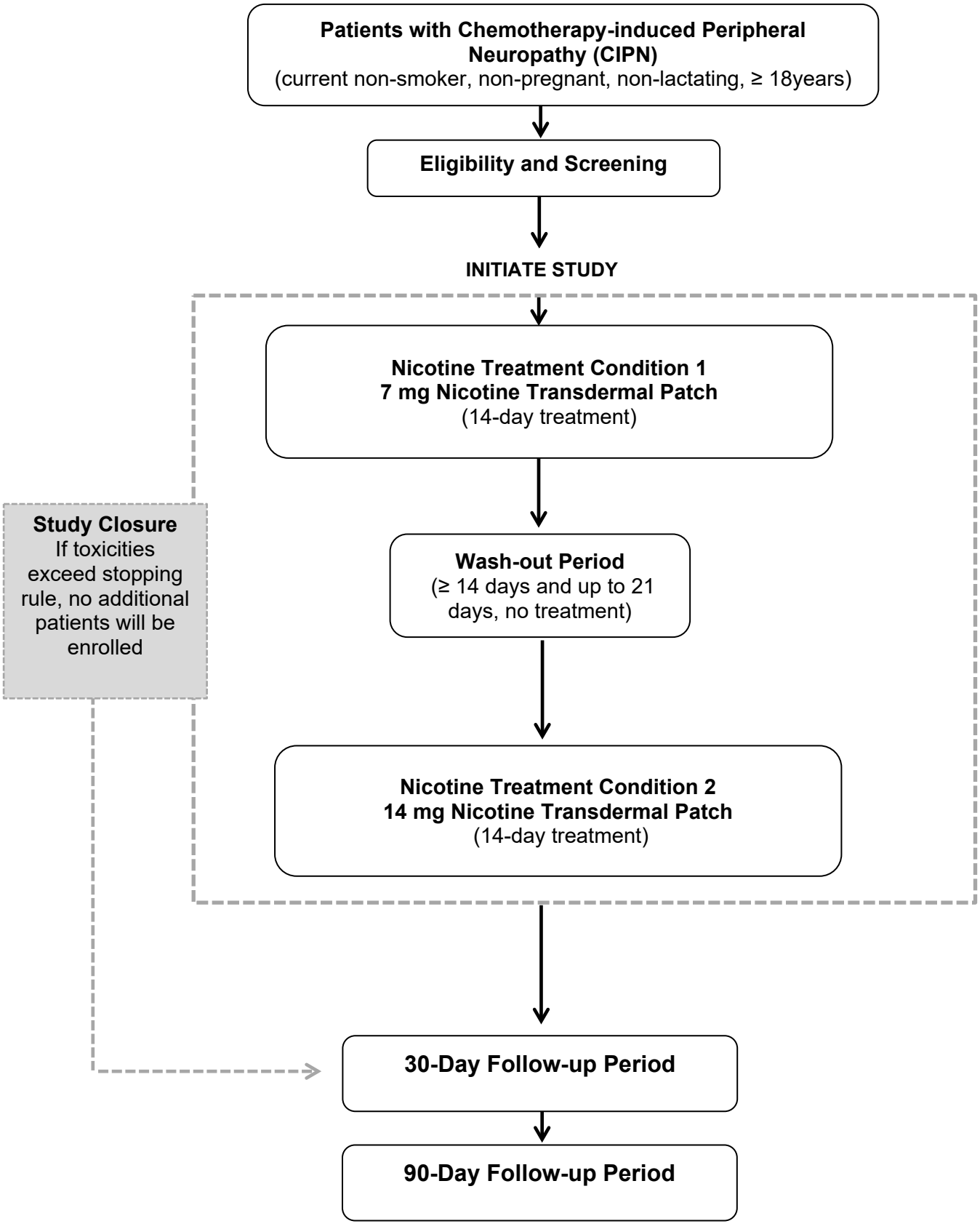

Patients with Chemotherapy-induced Peripheral Neuropathy (CIPN)
(current non-smoker, non-pregnant, non-lactating, ≥ 18years)
Eligibility and Screening
INITIATE STUDY
Nicotine Treatment Condition 1
7 mg Nicotine Transdermal Patch
(14-day treatment)
Wash-out Period
(≥ 14 days and up to 21 days, no treatment)
Nicotine Treatment Condition 2
14 mg Nicotine Transdermal Patch
(14-day treatment)
Study Closure
If toxicities exceed stopping rule, no additional patients will be enrolled
30-Day Follow-up Period
90-Day Follow-up Period

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
BPI-SF	Brief Pain Inventory – Short Form
CIPN	Chemotherapy-induced peripheral neuropathy
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTRL	Clinical and Translational Research Lab
DLT	dose-limiting toxicity
DSMC	Data and Safety Monitoring Committee
EORTC QLQ-CIPN20	European Organization for Research and Treatment of Cancer Quality of Life-CIPN20 Questionnaire
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
IIT	Investigator Initial Trial
IMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IRB	Institutional Review Board
MCC	Massey Cancer Center
nAChR(s)	nicotinic acetylcholine receptor(s)
NYHA	New York Heart Association
OHRP	Office for Human Research Protections
PGIC	Patient Global Impression of Change
PRO	patient-reported outcome
PRMC	Protocol Review and Monitoring Committee
SAE	serious adverse event
SAR	suspected adverse reaction
UP	unanticipated problem
VCU	Virginia Commonwealth University

1 BACKGROUND

1.1 Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect associated with the taxanes and platinum-based compounds, drugs commonly used for the treatment of breast, lung, and ovarian cancer. CIPN results from damage to, or dysfunction of, the peripheral motor, sensory, and autonomic nerves and manifests with a variety of symptoms including mechanical and cold allodynia, numbness and tingling, loss of proprioception, and long-lasting burning pain (1-4). CIPN affects quality of life, and can often result in chemotherapy dose reductions and early treatment discontinuation (5).

Depending on the specific chemotherapy regimen used, the duration of exposure, and method of CIPN assessment, approximately 30% to 70% of multiple-agent, chemotherapy-treated cancer patients are diagnosed with CIPN (6-8). Current CIPN treatment options include duloxetine, tricyclic antidepressants, gabapentin, and topical applications (eg, baclofen and ketamine) (5). However, treatment options to manage CIPN are not consistently effective for the majority of patients. Thus, there is a critical need to identify new agents that can manage the pain associated with CIPN.

This clinical trial is designed to determine if nicotine transdermal patch use can suppress the pain associated with CIPN. Demonstrating that nicotine can suppress such pain would be highly significant on 3 fronts. First, by relieving CIPN-associated pain, suboptimal chemotherapeutic dosing schemes might be adjusted upwards, increasing the probability of effective treatment of the cancer. Second, the use of an FDA-approved, over-the-counter drug with a relatively safe short-term use profile would greatly accelerate the clinical development of this pain management strategy. Third, a demonstration that nicotine can manage the pain associated with CIPN would stimulate the development of targeted agents that interact with subtypes of nicotinic acetylcholine receptors (nAChRs) and which might act with fewer side effects.

1.2 Rationale and Previous Work

This clinical trial will focus on nicotine, the prototype agonist of nAChRs, as a possible agent for symptom suppression of CIPN. The analgesic properties of nicotine and nicotinic agonists have been established in many animal (9) and human studies (10) including neuropathic pain in humans (11, 12). Animal models have been developed that reiterate many of the neuropathological changes and electro-physiological abnormalities observed in patients with CIPN (13). Nicotine has analgesic properties and has been shown to reduce pain in both animal and human studies ((9-12). Nicotine has the advantage of having a well-established risk profile and is relatively safe for short-term use (16). It is also available over-the-counter as a transdermal patch which greatly simplifies drug delivery. These qualities of nicotine provide a strong rationale for using it to treat CIPN-associated pain. Thus, the primary objective of this trial is to test, in cancer stable/remission patients with diagnosed CIPN, the efficacy of acute nicotine transdermal patch administration in assessing clinically subjective improvements in measures of neuropathic pain, as well as improvements in quality of life CIPN patient-reported outcomes (PROs). This study will serve as a proof-of-principle study that could lead to future studies employing more selective nAChR-targeted drugs that are currently in development by our group.

1.2.1 Preclinical Data

Paclitaxel and cisplatin have been shown to produce a long-lasting, bilateral neuropathy in mice, featuring hypersensitivity to mechanical and cold stimuli (14). Consequently, well-established mouse models of CIPN have been used by our group (15), as well as other laboratories to investigate nAChRs as potential targets for amelioration and/or prevention of CIPN. In a dose-dependent manner, nicotine has been shown to reverse the mechanical and cold allodynia induced in rats treated with oxaliplatin (9) and in mice treated with paclitaxel (Figure 1) (16). The doses of nicotine used generated plasma concentrations (20 to 30 ng/ml at doses of 0.6 and 0.9 mg/kg) of the drug, well within the concentration range of nicotine reported for nicotine transdermal patches users. These results strongly support the potential utility of nicotine in mitigating CIPN.

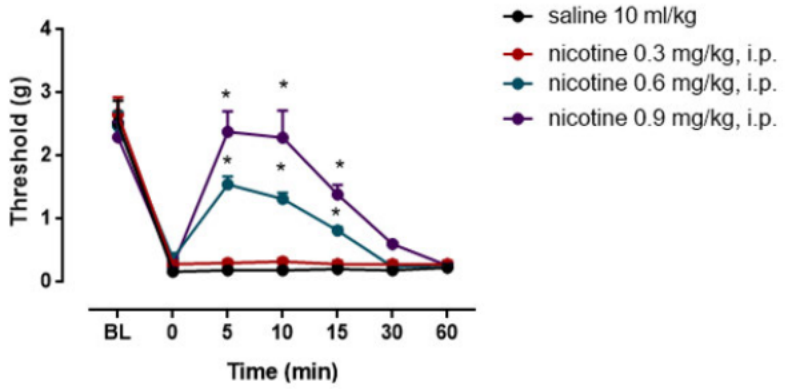


Figure 1. Nicotine reverses paclitaxel-induced mechanical allodynia in mice.

Male C57BL/6J mice received 8 mg/kg paclitaxel via intraperitoneal (i.p.) injection every other day for a total of 4 injections. At 2 weeks post-paclitaxel injections, mice received a single i.p. injection of saline or nicotine. Mechanical threshold was determined via von Frey filament testing on the left and right hind paws. Error bars represent the standard error of the mean for one experiment (n = 6). A two-way ANOVA revealed significant differences; *p < 0.05 vs saline. BL, baseline.

1.3 Study Design

This study will test the efficacy of acute nicotine transdermal patch administration using an open-label, within-subjects clinical trial design with nicotine transdermal patch concentrations of 7 mg and 14 mg. Patients will be recruited via clinician referral and must not have used any nicotine or tobacco products (eg, cigarettes, electronic cigarettes, smokeless tobacco, or other nicotine replacement therapies) within the last 14 days prior to study treatment start date. Each treatment condition will have a duration of 14 days, with a washout period of at least 14 days in between conditions. Patients will be evaluated by the study team once per week during the treatment cycles (2 study visits per treatment cycle). Patients will be evaluated by the study team once during the washout period (1 study visit). Patients will also be evaluated at least once during the 30-day follow-up period (1 study visit). During study visits, patients will be evaluated by the study team for CIPN PROS, pain scale, and Adverse Events (AE). This evaluation schedule will provide complete clinical and research assessments related to pain and neuropathy at baseline, during treatment conditions, and post-treatment.

The primary outcome measure is the change in CIPN-related PRO as measured by the total sensory score of the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-CIPN-20). EORTC QLQ-CIPN-20 is a well-developed 20-item questionnaire, that provides valuable information on CIPN- related symptoms and functional limitations of patients exposed to potentially neurotoxic chemotherapeutic and/or neuroprotective agents (17). It has also been validated clinically by showing very significant association between QLQ-CIPN20 scores and the NIH Common Terminology Criteria for Adverse Events (CTCAE) grades for AEs associated with CIPN symptoms ($p<0.0001$), whereby patients with higher CTCAE grade had worse QLQ-CIPN20 scores (18).

The secondary outcome measures include the following items: 1) the change in average pain based on the well-validated Brief Pain Inventory-Short Form (BPI-SF) average pain severity item; and 2) evaluation of the safety and toxicity of nicotine transdermal patch administration in a population of non-smokers experiencing CIPN.

The BPI-SF contains 4 items assessing average, worst, least, and immediate pain severity in the last 24 hours. Pain severity items are scored using an 11-point numeric rating scale (0, no pain; 10, pain as bad as you can imagine). Seven BPI-SF items will be used to quantify the degree to which pain interferes with daily activities or function (0, does not interfere; 10, completely interferes). The 7 items are summed to obtain a total interference score. The BPI-SF worst pain severity item has been shown to be reliable and valid for use as a single item. We chose average pain severity as an outcome measure based on recommendations from the initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMPACT) and other CIPN studies (19).

Patients will be monitored for nicotine-associated toxicity utilizing CTCAE v5.0. AE assessments will occur at least once per week during treatment conditions.

Exploratory outcome measures include the patient’s assessment of the efficacy of a transdermal nicotine transdermal patch for the treatment of CIPN utilizing the Patient Global Impression of Change and Patient Preference Questionnaire (PGIC) for neuropathy (upper and lower extremity questionnaires). The PGIC is used to assess patients' own impressions of change (20). The questionnaire uses a global scale from “much better”

through “no change” to “much worse” (21, 22). This study will use a version of the PGIC adapted to patients with CIPN that focuses on patients’ self-assessment of their upper and lower extremities. Additional exploratory investigations include: 1) the correlation between serum nicotine levels and efficacy of nicotine transdermal patch administration for the treatment of CIPN in patients whose cancer is stable or in remission; 2) the differences in CIPN PROs and BPI-SF measures between patients that received previous platinum-based chemotherapy versus patients that received previous taxane-based chemotherapy; and 3) the differences in CIPN PROs and BPI-SF measures between never-smokers (nicotine-naïve) and current non-smokers.

The clinical trial will yield several important results. First, using an acute nicotine transdermal patch administration will determine both the potential efficacy and feasibility of using nicotine as a potential treatment for neuropathic pain associated with CIPN. Additionally, if nicotine appears to have a positive treatment effect, as defined by a ≥ 2.7 point decrease in patient’s total sensory score (baseline compared to treatment and post-treatment scores) of the QLQ-CIPN-20 questionnaire (eg, an improvement in the patients quality of life by one grade), future randomized clinical trials comparing nicotine to other commonly prescribed treatments, such as duloxetine, may be warranted. In addition, further studies of subtype receptor selective agents or of patient population subgroups (based on smoking history, gender, chemotherapeutic agents, or receptor expression level) can be designed.

1.4 Potential Risks and Benefits of the Investigational Treatment

1.4.1 Potential Benefits

The analgesic properties of nicotine and nicotinic agonists have been established in many animal and human studies. Acute nicotine transdermal patch administration could improve patient’s CIPN-associated pain, and thus their quality of life. Further, successful management of patients’ CIPN could circumvent chemotherapy dose reduction and early treatment discontinuation. The use of an FDA-approved, over-the-counter drug with a relatively safe short-term use profile would greatly accelerate the clinical development of this as a pain management strategy. Finally, if successful, this study would stimulate the development of targeted agents that interact with subtypes of nAChRs, which might act with fewer side effects.

1.4.2 Potential Risks

One of the challenges with the use of nicotine as a therapeutic agent relates to the potential side effects of nicotine on nicotine-naïve patients (ie, patients with no nicotine use history). Related symptoms experienced by non-smokers being treated with a nicotine transdermal system include nausea, dizziness, vomiting, minor skin irritations, and palpitations (23). There is also a risk for the development of nicotine dependence for current non-smokers and a recurrence of nicotine dependence for previous smokers. Overall, the published side effects for a 15mg or less nicotine transdermal patch were reported as mild and tolerable (24-27). Nonetheless, we will evaluate the safety and toxicity of nicotine transdermal patch administration in a population of non-smokers experiencing CIPN as described in our secondary outcome measures.

2 OBJECTIVES

2.1 Primary Objective

Assess the efficacy of short-term nicotine transdermal patch administration for the treatment of CIPN in cancer stable patients or patients in remission.

2.2 Secondary Objectives

Secondary objectives include:

2.2.1 Assess pain-related functional interference associated with nicotine transdermal patch administration for the treatment of CIPN in patients whose cancer is stable or in remission.

2.2.2 Assess the AEs profile of nicotine transdermal patch administration for the treatment of CIPN in patients whose cancer is stable or in remission.

3 STUDY DESIGN

3.1 General Description

This phase 2 study will test the efficacy of short-term transdermal nicotine transdermal patch administration in patients who have been diagnosed with CIPN. The study will follow an open-label, crossover within-subjects clinical trial design with nicotine transdermal patch concentrations of 7 mg and 14 mg.

3.2 Primary Endpoint

Efficacy of short-term nicotine transdermal patch administration in the treatment of CIPN in patients whose cancer is stable or in remission as defined by a ≥ 2.7 point decrease in the total sensory score of the EORTC QLQ-CIPN-20 (eg, an improvement in the patients quality of life by one grade).

3.3 Secondary Endpoints

Secondary endpoints include:

3.3.1 Efficacy of short-term nicotine transdermal patch administration in the treatment of CIPN in patients whose cancer is stable or in remission by assessing changes in the degree of pain-related functional interference measured by the BPI-SF interference score.

3.3.2 Nicotine transdermal patch safety and tolerability in non-smokers by assessing AEs characterized and graded according to CTCAE v5.0 and PROs related to nausea, dizziness, vomiting, minor skin irritations, and palpitations.

4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible to participate in the study.

4.1.1 Age ≥ 18

4.1.2 CIPN characteristics

4.1.2.1 Clinically diagnosed peripheral sensory neuropathy defined as:

4.1.2.1.1 Greater than Grade 1 peripheral sensory neuropathy using the CTCAE v5.0 grading scale

- **Grade 1** Asymptomatic
- **Grade 2** Moderate symptoms; limiting instrumental activities of daily living (ADL)
- **Grade 3** Severe symptoms; limiting self-care ADL
- **Grade 4** Life-threatening consequences; urgent intervention indicated

AND

4.1.2.2 Have a baseline CIPN PRO total sensory score ≥ 24.3 on a 19 to 76 scale using the EORTC QLQ-CIPN-20 questionnaire

AND

4.1.2.3 Have a CIPN-related neuropathic pain score ≥ 4 on a 0 to 10 scale using the Brief Pain Inventory-Short Form (BPI-SF) item 5

Note: Patients currently being treated for CIPN will not be excluded and are allowed to continue their treatment and current treatment dose while on study.

4.1.3 Will not have used any nicotine or tobacco products (eg, cigarettes, electronic cigarettes, smokeless tobacco, or other nicotine replacement therapies) within 14 days prior to study treatment start date

4.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix 1)

4.1.5 Not currently receiving any chemotherapy

4.1.6 Have previously received platinum- and/or taxane-based chemotherapy treatments and have persistent pain at least 3 months after completion of treatments.

4.1.7 Willing and able to comply with study procedures and visit schedule.

4.1.8 Willing to abstain from all tobacco/nicotine product use during study treatment and 30-day follow-up period.

4.1.9 Ability to self-apply or have the patch applied at home daily.

4.1.10 Ability to understand and the willingness to sign a written informed consent document

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria is ineligible to participate in the study.

4.2.1 History of pre-existing peripheral sensory neuropathies related to the following:

- Autoimmune disease
- B12/folate deficiency
- Diabetes Mellitus
- Human immunodeficiency virus (HIV)
- Hyper/hypothyroidism
- Monoclonal gammopathy of undetermined significance or multiple myeloma

4.2.2 History of receiving other types of neurotoxic chemotherapy drugs (eg, vinca alkaloids, bortezomib, thalidomide)

4.2.3 Current or prior pheochromocytoma

4.2.4 History of or active or clinically significant cardiac disease including any of the following:

- Unstable angina (eg, anginal symptoms at rest) or onset of angina within 3 months prior to initiating study treatment
- Myocardial infarction diagnosed within 6 months prior to initiating study treatment
- Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers

4.2.5 New York Heart Association (NYHA) class III or IV congestive heart failure (see Appendix 2)

4.2.6 Poorly controlled high or low blood pressure defined as:

- SBP ≥ 140; DBP ≥ 90

- SBP ≤ 90; DBP ≤ 60

4.2.7 Regular use of the following medications:

- Varenicline
- Bupropion (ie, bupropion hydrochloride sustained release)

4.2.8 Women will be excluded if they are breastfeeding or are pregnant (by urinalysis) within 14 days prior to the start of nicotine transdermal patch administration.

4.2.9 Medical, psychological, or social condition that, in the opinion of the investigator, may increase the patient's risk or limit the patient's adherence with study requirements

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Pre-Registration Screening Tests and Procedures

Refer to the study calendar in Section 12 for the screening tests and procedures that are required prior to registration.

5.1.2 Study Enrollment

The following documents are required for patient registration:

- Completed registration cover sheet
- Completed, signed, and dated eligibility checklist
- Signed and dated consent form

The registrar will complete the registration process by assigning a study identification (ID) number and forwarding the "Confirmation of Registration" form to the registering study team.

No patient may begin study treatment until the Confirmation of Registration assigning a study ID number has been received from the registrar. The registering study team will enter the patient's initial enrollment data (eg, demographics, consent, eligibility, on study) into the OnCore database within 24 hours following study registration (before treatment begins).

5.2 Study Withdrawal

A patient may decide to withdraw from study participation at any time. Patients must be withdrawn from the study when any of the following occurs:

- The patient has withdrawn consent for study treatment and study procedures.
- If, in the investigator's opinion, continuation of the study requirements would be harmful to the patient's well-being.
- The patient is lost to follow-up.

The reason for and date associated with study withdrawal or removal from the study must be documented in the source documents and OnCore database.

6 STUDY TREATMENT

6.1 Baseline Tests and Procedures

Refer to the study calendar in Section 12 for requirements prior to initiation of treatment administration. Initiation of study treatment should begin as soon as possible following study registration. Patients who are eligible and enrolled in the study but do not immediately initiate study treatment are expected to meet eligibility criteria until the time when treatment is initiated.

6.2 Investigational Agent Administration

6.2.1 Nicotine Transdermal Patch Administration and Treatment Schedule:

- Each patient will complete two 14-day treatment conditions, one each for 7 mg and 14 mg nicotine transdermal patch administration with a washout period in between (≥ 14 days and up to 21 days).
- Nicotine transdermal patch administration will begin on Cycle 1, Day 1 (7mg) and Cycle 2, Day 1 (14mg).
- Nicotine transdermal patches will be applied once daily for 14 consecutive days.
- Nicotine transdermal patches will be removed for at least 14 days and up to 21 days at the end of Cycle 1, Day 14.
- Patients will be instructed as follows:
  - Apply the nicotine transdermal patch to dry, clean, hairless skin
  - Patients should apply and remove the nicotine transdermal patch at the same time everyday
  - Patients should wear the nicotine transdermal patch for at least 16 hours per day.

6.2.2 Missed Doses

Patients will be instructed to apply the nicotine transdermal patch on the same day, as soon as they remember, with the following considerations:

- Patients should still remove the missed nicotine transdermal patch at the planned daily removal time.
- Patients should not apply more than one nicotine transdermal patch per day.

6.3 General Concomitant Medication and Supportive Care Guidelines

Nicotine transdermal patch-related symptoms experienced by non-smokers include nausea, dizziness, vomiting, minor skin irritations, and palpitations (23). These common side effects associated with nicotine administration can occur more commonly in patients with no nicotine use history (ie, never-smokers, nicotine naive patients). The published side effects for a 15mg or less nicotine transdermal patch have been reported as mild and tolerable (24-27).

6.3.1 Nausea/Vomiting

Management of nausea and vomiting will include anti-nausea medication to reduce the risk of grade 3 nausea or nicotine transdermal patch discontinuation. Anti-emetics should be prescribed as clinically indicated.

6.4 Duration of Therapy

Treatment will continue until any of the following occurs (also see information regarding study withdrawal in Section 5.2):

- AE that requires discontinuation of study treatment (See Section 7.2.2)
- Pregnancy
- Patient decision to discontinue study treatment or withdraw from the study
- Investigator determination that discontinuation is in the patient's best medical interest
- Patient non-compliance with the required study treatment visits such that the patient has not been present for more than 60% of the visits (≥ 3 out of 5 visits)
- Inability to initiate Cycle 2 within 21 days after completion of Cycle 1

6.5 Follow-Up Period

During the 30-day follow-up period, patients will be evaluated by the study team at least once. They will be assessed for nicotine serum levels, pain (BPI-SF), global impression of change, CIPN PROs, and AEs.

6.6 Extended (90-day) Follow-Up Period

The extended (90-day) follow-up period will begin at the end of Cycle 2, Day 14 after the last nicotine transdermal patch is removed. The 90-day follow-up will consist of a phone call to patients once at the end of the 90-day follow-up period. Patients will be asked if they have continued to use the nicotine transdermal patch to lessen their CIPN symptoms and if they have developed a dependence to nicotine in any form (eg, cigarettes, electronic cigarettes, smokeless tobacco, or other nicotine-containing products).

6.7 Monitoring Patient Compliance

Patients will be instructed to record the time of their daily self-administration and removal of the nicotine transdermal patch in the study drug diary that will be provided. This record will also document the number of nicotine transdermal patches used during each treatment cycle. Patients will be instructed to bring their diary and any unused drug supply to each visit with the study team.

Patient reports of self-administration and review of the study drug diary will be used to assess the patient's compliance with the nicotine transdermal patch study treatment regimen.

7 MISSED DOSES

Dose reductions or dose omissions will not occur.

7.1 Recording Missed Doses

All missed doses will be recorded in the source documents and captured in the OnCore database.

7.2 General Instructions and Guidelines

7.2.1 Missed Doses

- If a nicotine transdermal patch is missed for an entire 24-hour period, the transdermal patch is omitted, not made up.
- If a nicotine transdermal patch is missed for less than a 24-hour period, the transdermal patch is applied for the remaining hours of the 24-hour period, if possible.

7.2.2 Required Discontinuation of Study Treatment

Nicotine transdermal patch administration will be discontinued if clinically significant toxicities or qualifying toxicities that are related to nicotine transdermal patch therapy occur (See Section 8.1.6 for Qualifying Toxicities).

8 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.1.2 Suspected Adverse Reaction (SAR)

Any AE for which there is a reasonable possibility that the drug caused the AE. “Reasonable possibility” means that there is evidence to suggest a causal relationship between the drug and the AE.

An AE with an attribution of possible, probable, or definite (see Section 8.1.9 below) is a SAR.

8.1.3 Serious AE (SAE) or Serious SAR (SSAR)

An AE or SAR is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE (An AE or SAR is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.),
- inpatient hospitalization or prolongation of existing hospitalization,

  Planned inpatient hospitalizations are exempt from SAE reporting. Events that prolong hospitalization beyond the expected period of time and otherwise meet reporting criteria are, however, subject to SAE reporting requirements.
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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.

8.1.4 Unexpected SAR

A SAR is considered “unexpected” if

- it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed;

- or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

  "Unexpected" as used in this definition, also refers to SARs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.5 Unanticipated Problem (UP)

UPs include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, 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;

- related or possibly related to participation in the research (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

- 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.

8.1.6 Qualifying Toxicities

The following nicotine-related toxicities listed below are considered qualifying toxicities and will be used to ensure patient safety and tolerability. The following toxic event as defined per CTCAE v5.0 will be counted toward the stopping rules (See Section 13.3).

- Grade 3 nausea

- Grade 3 vomiting

- Grade 3 dizziness

- Grade 3 pruritus

- Grade 3 headache

- Grade 2 heart palpitations

8.1.7 AE Description and Grade

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

8.1.8 AE Expectedness

AEs can be 'Unexpected' or 'Expected'.

Expected AEs are listed in Section 8.2 below.

Unexpected AEs are those AEs occurring in one or more subjects participating in the research protocol, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

8.1.9 AE Attribution

- Definite – The AE *is clearly related* to the study treatment.

- Probable – The AE *is likely related* to the study treatment.

- Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.

- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Known AEs List

The expected AEs for a nicotine transdermal patch can be found in Section 9.1.9

8.3 Time Period and Grade of AE Capture

All AE's regardless of grade or attribution will be recorded from the beginning of study treatment (Cycle 1, Day 1 of nicotine transdermal patch administration) through the 30-day follow-up period. AE assessment may be shortened if the patient goes off study.

Qualifying toxicities will be captured and recorded from the beginning of study treatment (Cycle 1, Day 1 of nicotine transdermal patch administration) through the 30-day follow-up Day 8 - Day 15 study visit. Qualifying toxicity assessment may be shortened if the patient goes off study.

8.4 Procedures for Recording Events

All AEs, SAEs, UPs, and qualifying toxicities will be recorded in MCC's OnCore Clinical Trials Management System. In most cases, it is acceptable to record in OnCore only the highest grade of a toxicity occurring during a particular study segment when an event has serial fluctuations in grade over time.

- Refer to the study calendar in Section 12 for the AE assessment schedule.
- AEs will be recorded using the OnCore AE eCRF.
- SAE's will be entered into the OnCore SAE domain. For all SAEs, a corresponding entry should be made in the routine AE record to match the event entries in the SAE domain.
- UPs will be entered into the OnCore Deviations domain.

  Note: An SAE that is both an SAE and a UP will be entered in both domains

8.5 Expedited Reporting Procedures for SAEs, SSARs, UPs, and Qualifying Toxicities

Refer to Table 1 for expedited reporting requirement and instructions.

Table 1. Expedited Reporting Requirements (Events, Report Recipients, and Time Frames)

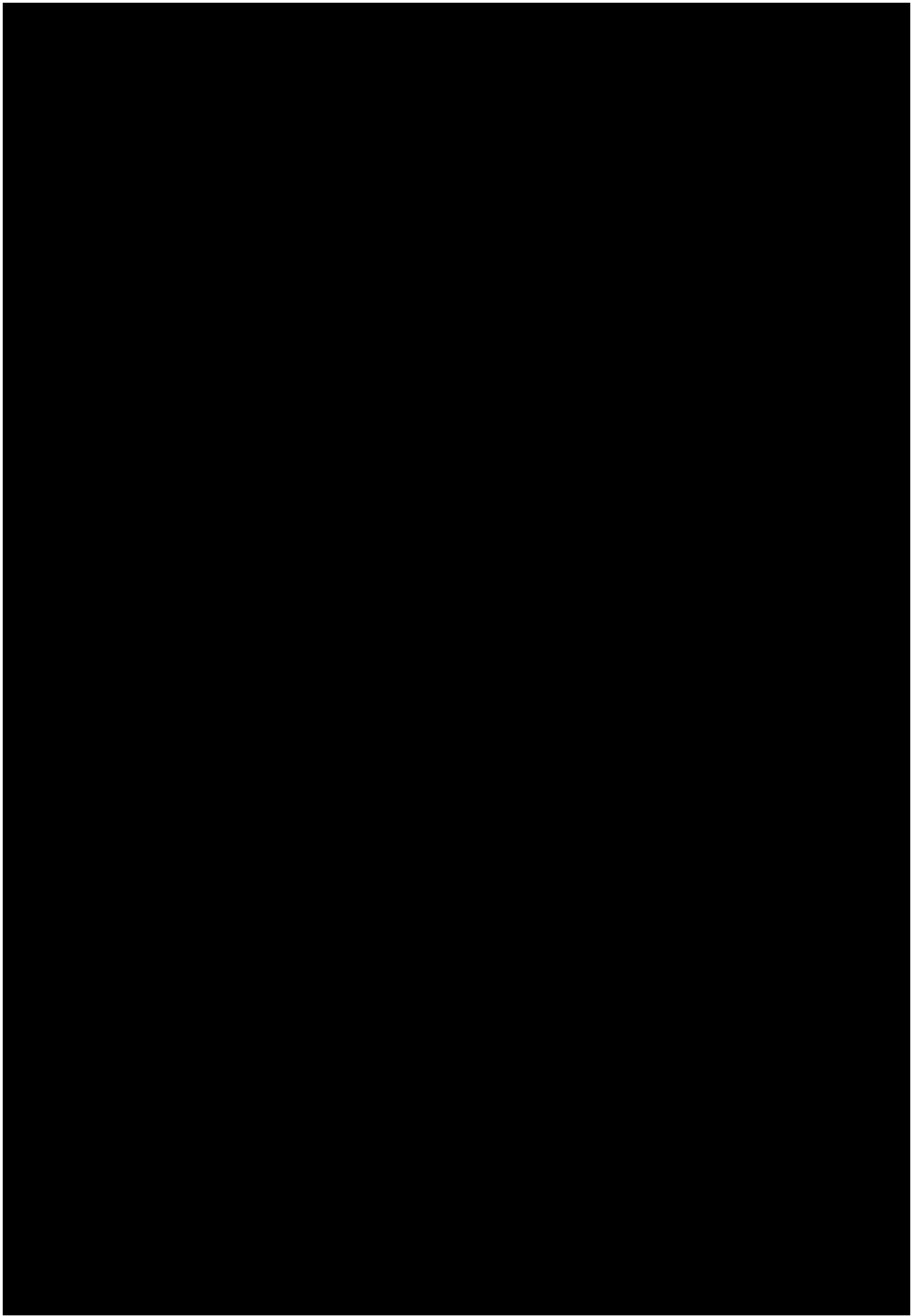
SAEs[1]	UPs[2]	SSARs[1]	Qualifying Toxicities[3]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]		

1. Report event within 1 business days of becoming aware of the occurrence. A PDF of a de-identified OnCore SAE may be used for expedited event reporting purposes.

2. Report event within 1 business days of becoming aware of the occurrence. A PDF of a de-identified OnCore SAE and/or deviation record may be used for expedited event reporting purposes.

3. Report event by email within 1 business day. See Section 8.1.6 and 13.3.

4. Each UP must be reported to the VCU IRB within 5 business days of becoming aware of the occurrence.



9.1.9 Adverse Events

Nicotine transdermal patches can cause the following side effects:

9.1.9.1 Common side effects:

- Dizziness
- Headache
- Itching
- Nausea
- Rapid heartbeat
- Skin irritation

9.1.9.2 Less common side effects:

- Constipation
- Drowsiness
- Stomach cramps

9.1.9.3 Uncommon/rare side effects:

- Atrial Fibrillation
- Hives
- Seizures
- Trouble breathing

10 MEASUREMENT OF EFFECT

10.1 Evaluation of Transdermal Nicotine Patch Efficacy

CIPN PROs will be measured using the EORTC QLQ-CIPN20 sensory subscale score. The QLQ-CIPN20 numerical score has a range of 19-76, in which lower scores indicate less symptoms and a better quality of life. The scores can also be converted to a scale of 0 to 100, in which higher scores indicate less symptoms and better quality of life. A recently published study provides validity and guidance as to how to interpret QLQ-CIPN20 scores (18). Utilizing this study's reported numerical relationship between QLQ-CIPN20 scores and peripheral sensory neuropathy CTCAE grades (initially reported using CTCAE grade v4.0) as a hypothetical guide (See Table 2), we can estimate how many QLQ-CIPN20 score points are needed to decrease the CTCAE score by 1 grade. Using the 19-76 numerical scale for QLQ-CIPN20, a minimum decrease of 2.7 points (range of 2.7-5.6 points) would be required to improve a patient's quality of life by one grade (grade 2 to grade 1).

Table 2. Reported/Suggested Numerical Relationship Between CTCAE v4.0/v5.0 and EORTC QLQ-CIPN-20 Scores.

Peripheral Sensory Neuropathy CTCAE v5.0	EORTC QLQ-CIPN20 (Scale 19-76)
Grade 0	21.6
Grade 1	24.3
Grade 2	29.9
Grade 3	33.6

11 SERUM NICOTINE ANALYSIS

11.1 Participation in Serum Nicotine Analysis

A blood sample collected for the analysis of serum nicotine levels will be used to confirm that patients meet eligibility and screening criteria. Blood samples will also be collected once during Cycle 1, once at the beginning of Cycle 2 before nicotine transdermal patch administration, once during Cycle 2, and once during the 30-day follow-up period to measure serum nicotine levels throughout the study (a total of 5 blood samples). Participation in serum nicotine studies using blood samples is mandatory.

11.2 Collection, Processing, and Distribution of Samples

The study team will coordinate collection and de-identification of all blood samples.

11.2.1 Collection Time Points

Blood samples will be collected at the following time points:

- Eligibility/Baseline (during eligibility screening)
- Cycle 1, Treatment Condition 1, Day 8 or within 5 days
- Cycle 2, Treatment Condition 2, before nicotine transdermal patch administration
- Cycle 2, Treatment Condition 2, Day 8 or within 5 days
- 30-day follow-up period, Day 8-15 or within 7 days

11.2.2 Blood Sample Collection Instructions

At least 2.0 mL of blood will be collected at each of the time points listed in Section 11.2.1. Blood collection will follow VCU Toxicology Laboratory specimen specifications.

11.2.3 Labeling for all Blood Samples

- Study number
- Patient study identification number
- Date of sample collection
- Time of sample collection
- Study time point

11.2.4 Tracking for all Blood Samples

Collection and distribution of all blood samples will be logged by the study team in OnCore.

12 STUDY CALENDAR

Table 3. Study Caledar – Eligibility/Screening Through Washout Period

	Eligibility and Screening	**Cycle 1 Treatment Condition 1 7mg Nicotine Transdermal Patch[A]**			**Washout Period No Nicotine Transdermal Patch[B]**
	Within 14 Days	D1	D2	D8[C]	
Informed Consent[D]	X				
Demographics	X				
Vital Signs (BP, HR)[E]	X	X		X	
Baseline Conditions/Symptoms	X				
Medical/Surgical History	X				
Exam[F]	X[G]			X	
Concurrent Medications[H]	X	X		X	
Urine Pregnancy Test	X				
Serum Nicotine Level	X			X	
Assessment of AEs		X		X	
BPI-SF	X			X	
QLQ-CIPN 20	X			X	
PGIC Neuropathy (upper and lower)				X	
AE Assessment Phone Call			X		X[I]

Table 3 Footnotes:

A. Each Treatment Condition Cycle is 14 days.

B. Washout period may occur for ≥ 14 days and up to 21 days after the removal of the nicotine transdermal patch on Cycle 1

C. Cycle 1, Day 8 study visit may occur within 5 days.

D. If registration is delayed to more than 14 days after the informed consent form is signed, a new signed consent form is not required unless the IRB has approved a newer version.

E. Include ECOG performance status.

F. Exam will also include a neurological exam: sensory, motor, reflex, Romberg, and gait.

G. If the neurological exam cannot be completed on the day of screening, it can be completed on Cycle 1, Day 1, but does not need to be completed for both screening and Cycle, Day 1.

H. Include over-the-counter medications.

I. The AE assessment phone call during the washout period will include notation of the date the last nicotine transdermal patch was removed in Cycle 1.

Table 4. Study Calendar – Treatment Condition 2 Through the 90-Day Follow-up Period

	Cycle 2 Treatment Condition 2 14mg Nicotine Transdermal Patch[0,]			**30-Day Follow-up Period**		**90-Day Follow-up Period[B]**
	D1[C]	D2	D8[D]	D1	D8 - D15[E]	
Vital Signs (BP, HR)[F]	X		X		X	
Exam[G]	X		X		X	
Concurrent Medications[H]	X		X		X	
Serum Nicotine Level	X[I]		X		X	
Assessment of AEs	X[I]		X		X	
BPI-SF	X[I]		X		X	
PGIC Neuropathy (upper and lower)	X[I]		X		X	
QLQ-CIPN 20	X[I]		X		X	
AE Assessment Phone Call		X		X[J]		
Follow-up Phone Call						X[B, K]

Table 4 Footnotes:

A. Each Treatment Condition Cycle is 14 days.

B. The 90-day follow-up period will begin at the end of Cycle 2, after the last nicotine transdermal patch is removed. The 90-day follow-up phone call may occur ± 14 days.

C. Cycle 2, Day 1 may occur ≥ 14 days and up to 21 days after the removal of the nicotine transdermal patch in Cycle 1.

D. Cycle 2, Day 8 study visit may occur within 5 days.

E. 30-day follow-up, Day 8 - Day 15 study visit may occur within 7 days.

F. Include ECOG performance status.

G. Exam will also include a neurological exam: sensory, motor, reflex, Romberg, and gait.

H. Include over-the-counter medications.

I. Must occur before 14 mg nicotine transdermal patch is administered.

J. 30-day follow-up, the AE assessment phone call will include notation of the date the last nicotine transdermal patch was removed in Cycle 2.

K. 90-day follow-up, the phone call will assess whether patients have continued to use the nicotine transdermal patch to lessen their CIPN symptoms and if they have developed a dependence to nicotine in any form (eg, cigarettes, electronic cigarettes, smokeless tobacco, or other nicotine-containing products).

13 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a phase 2 study that will test the efficacy of acute nicotine transdermal patch administration using an open-label, crossover within-subjects clinical trial design with nicotine transdermal patch concentrations of 7 mg and 14 mg. Patients will be evaluated for nicotine-associated toxicity and undergo assessments of pain and neuropathy administered by the study team, which will provide subjective and clinical measurements at baseline, during treatment conditions, and post-treatment. The primary endpoint is to assess the efficacy of short-term nicotine transdermal patch administration in the treatment of CIPN in patients whose cancer is stable or in remission by assessing decreases in neuropathic pain symptoms measured by the total sensory score of the EORTC QLQ-CIPN-20.

13.1 Sample Size and Accrual

Using the 19-76 numerical scale for QLQ-CIPN220, a minimum decrease of 2.7 points (range of 2.7 – 5.6 points) would be required to improve the patient's quality of life by one grade (grade 2 to grade 1). A sample size of 47 would provide a power of at least 95% to detect a minimum change of 2.7 EORTC QLQ-CIPN20 scale points, assuming a moderately sized effect (ie, effect size 0.54) and 5% level of significance. Assuming 10% dropout or non-compliance, this will bring the total size to 52 patients. Recruitment ends when the required number of evaluable patients to complete the study is reached. A patient is evaluable if pain scores are available for the patient with each dose level. This still might have missing values due to non-compliance. All of the patients will be included in the final analysis and subjects with missing values will be included based on imputation-based method provided the amount of missing values is not excessive. If final data contains patients with more than 50% missing observations, we will use a pattern mixture model for imputation of missing data followed by longitudinal data.

13.2 Statistical Analysis

13.2.1 Analysis of Primary Endpoint

The primary endpoint of the study is the decrease in neuropathic pain symptoms for CIPN patients using a short-term nicotine transdermal patch. CIPN PROs will be measured using the EORTC QLQ-CIPN20 sensory subscale score. The QLQ-CIPN20 numerical score has a range of 19-76, in which lower scores indicate less symptoms and a better quality of life. Patient QLQ-CIPN20 scores at baseline, during treatments, and post- treatment will be analyzed by a one-sided test of the hypothesis using a matched paired t-test using 5% level of significance. Data will be tested for compliance with normality assumption and simple transformations would be used if required to restore normality of the data.

13.2.2 Analysis of Secondary Endpoints

The secondary endpoints include the following:

13.2.2.1 Changes in the degree of pain-related functional interference measured by the BPI-SF interference score.

13.2.2.2 This trial will use change in average pain severity as an outcome measure based on recommendations from the initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMPACT) and other CIPN or pain studies (16). Specifically, a previously published study investigating the effects of transdermal nicotine transdermal patches on post-operative pain observed an average of 1 point reduction in numerical pain scores in the nicotine group (28). Patient BPI-SF scores at baseline, during treatments, and post- treatment will be analyzed by a one-sided test of the hypothesis using a matched paired t-test. Nicotine transdermal patch safety and tolerability in non-smokers will be assessed using CTCAE v5.0 and PROs related to nausea, dizziness, vomiting, minor skin irritations, and palpitations.

Incidence and severity of AEs will be listed and summary descriptive statistics will be calculated.

13.3 Qualifying Toxicities for Early Stopping Rule

Early stopping criteria based on nicotine-related toxicities listed below will be used to ensure patient safety and tolerability. The stopping rule is based on a 30% maximum rate of toxic events. For all the toxic events the assumed null proportion of subjects with any dose-limiting toxicity is 30% for each of the 6 toxicities listed below.

The following toxic event as defined per CTCAE v5.0 will be counted toward the stopping rules in Table 5.

- Grade 3 nausea
- Grade 3 vomiting
- Grade 3 dizziness
- Grade 3 pruritus
- Grade 3 headache
- Grade 2 heart palpitations

Table 5. Number of Subjects With Observed Toxic Events Needed to Stop Trial Given Accrued Sample Size.

	Patient Number								
Accrued Sample Size	10	15	20	25	30	35	40	45	50
Toxic Event Stopping Rule	6	8	10	12	14	16	18	20	21

13.4 Evaluability for Qualifying Toxicity and Efficacy

13.4.1 Qualifying Toxicity Evaluability

A patient is evaluable for nicotine-related toxicity if the patient has received any study treatment.

13.4.2 Efficacy Evaluability

All blood samples collected for an individual patient will need to be analyzed for serum nicotine levels to determine if an individual patient is evaluable for efficacy. A nicotine serum value of > 2.0 ng/mL and a cotinine serum value of > 2.0-20 ng/mL via LC-MS/MS analysis is consistent with the use of nicotine. A nicotine or cotinine serum value of > 10-20 ng/mL via immunoassay analysis is consistent with the use of nicotine. Evaluability may not be determined until the patient has completed the study treatment and is off study and serum nicotine analysis has been for all blood samples.

A patient is evaluable for efficacy if **ALL** of the following study requirements have been fulfilled:

- Attended at least 60% of the visits (≥ 3 out of 5 visits).
- Maintained a therapeutic level of serum nicotine for at least 60% of the serum nicotine analysis time points (≥ 3 out of 5 blood samples).
- Completed at least 60% of the survey/questionnaire data collection points (≥ 3 out of 5 data collection points; and 2 out of 4 for the PGIC). Each data collection point will include an EORTC QLQ-CIPN-20 questionnaire and BPI-SF questionnaire. The neuropathy upper and lower extremity PGIC questionnaires will only be collected at 4 points throughout the study.

14 DATA AND SAFETY MONITORING PLAN (DSMP)

14.1 Study Team

While patients are on treatment, the principal investigator, the study team members (research nurses, and clinical research associates) will meet at least monthly to review study status. The biostatistician will review data with the principal investigator and study team members at least quarterly. This review will include, but not be limited to, reportable events and an update of the ongoing study summary that describes study progress in terms of the study schema. All meetings, including attendance, are documented.

14.2 Monitoring and Auditing

14.2.1 MCC Compliance Office

Compliance specialists in the MCC Compliance Office will provide monitoring and auditing for this study.

14.2.2 Data Safety and Monitoring Committee (DSMC)

The study will be reviewed by the MCC DSMC initially according to the risk level specified by the MCC Protocol Review and Monitoring Committee (PRMC) and then according to a schedule based on study status and quality indicators. The DSMC will review reports provided by the principal investigator/study team and the MCC Compliance Office focusing on data integrity and patient safety.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with the clinical trial protocol and with federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Patients/Informed Consent); 21 CFR 56 (Institutional Review Boards); 21 CFR 312 (IND Application); and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children).

15.3 Institutional Review Board

The VCU IRB, which is registered with the Office for Human Research Protections (OHRP), must review and approve the protocol, the associated informed consent document, and recruitment material (if any). Any amendments to the protocol or consent form must also be approved.

15.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion of risks and possible benefits of this therapy will be provided to patients and their families. Consent forms describing the study interventions, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to patients for their records; the original consent form will be maintained in the research records. The rights and welfare of patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.5 Patient Confidentiality and Access to Source Documents/Data

Patient confidentiality is strictly held in trust by the principal investigator, participating investigators, and any staff. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of principal investigator

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

16 DATA COLLECTION AND MANAGEMENT

16.1 Data Management Responsibilities

The principal investigator is responsible for: (i) the overall conduct of the investigation; (ii) ongoing review of trial data including all safety reports; and (iii) apprising participating sites of any UPs.

16.2 Case Report Forms and Data Collection

MCC will provide standard electronic case report forms (eCRFs) and create study-specific eCRFs to be able to capture all information required by the protocol. The eCRFs will be approved by the study team to ensure the most effective data acquisition.

The investigator(s) and study coordinator(s) must maintain source documents for each patient in the study. All information on eCRFs will be traceable to the source documents which are generally maintained in the patient's file.

All eCRFs should be completed and available for collection within a timely manner, preferably no more than 14 days after the patient's visit.

16.1 OnCore Data Entry

Data will be entered into MCC's OnCore database on an ongoing basis by the study team. The study team is responsible for updating data to allow for data compilation and review. The electronic data submissions will be reviewed periodically for data timeliness and accuracy.

16.2 Study Record Retention

As applicable, study records will be maintained a minimum of 5 years beyond: (i) the publication of any abstract or manuscript reporting the results of the protocol; (2) the submission of any sponsored research final report; or (iii) submission of a final report to clinicaltrials.gov.

17 REFERENCES

1. Cata JP, Weng HR, Lee BN, Reuben JM, Dougherty PM. Clinical and Experimental Findings in Humans and Animals with Chemotherapy-Induced Peripheral Neuropathy. *Minerva Anestesiol*. 2006; 72(3):151-169. PMID: 16493391.

2. Polomano RC, Mannes AJ, Clark US, Bennett GJ. A Painful Peripheral Neuropathy in the Rat Produced by the Chemotherapeutic Drug, Paclitaxel. *Pain*. 2001; 94(3):293-304. PMID: 11731066.

3. Windebank AJ, Grisold W. Chemotherapy-Induced Neuropathy. *J Peripher Nerv Syst*. 2008; 13(1):27-46. PMID: 18346229.

4. Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-Induced Peripheral Neuropathy: Prevention and Treatment Strategies. *Eur J Cancer*. 2008; 44(11):1507-1515. PMID: 18571399.

5. Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL, American Society of Clinical Oncology. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2014; 32(18):1941-1967. PMID: 24733808.

6. Cavaletti G, Marmiroli P. Chemotherapy-Induced Peripheral Neurotoxicity. *Nat Rev Neurol*. 2010; 6(12):657-666. PMID: 21060341.

7. Cavaletti G, Cornblath DR, Merkies IS, Postma TJ, Rossi E, Frigeni B, Alberti P, Bruna J, Velasco R, Argyriou AA, Kalofonos HP, Psimaras D, Ricard D, Pace A, Galie E, Briani C, Dalla Torre C, Faber CG, Lalisang RI, Boogerd W, Brandsma D, Koeppen S, Hense J, Storey D, Kerrigan S, Schenone A, Fabbri S, Valsecchi MG, C. I-PeriNomS Group. The Chemotherapy-Induced Peripheral Neuropathy Outcome Measures Standardization Study: From Consensus to the First Validity and Reliability Findings. *Ann Oncol*. 2013; 24(2):454-462. PMID: 22910842.

8. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, Colvin LA, Fallon M. Incidence, Prevalence, and Predictors of Chemotherapy-Induced Peripheral Neuropathy: A Systematic Review and Meta-Analysis. *Pain*. 2014; 155(12):2461-2470. PMID: 25261162.

9. Di Cesare Mannelli L, Zanardelli M, Ghelardini C. Nicotine Is a Pain Reliever in Trauma- and Chemotherapy-Induced Neuropathy Models. *Eur J Pharmacol*. 2013; 711(1-3):87-94. PMID: 23648560.

10. Flood P, Damaj MI. Nicotine Is Out: Nicotinic Agonists May Have Utility as Analgesics. *Anesth Analg*. 2014; 119(2):232-233. PMID: 25046780.

11. Richardson EJ, Ness TJ, Redden DT, Stewart CC, Richards JS. Effects of Nicotine on Spinal Cord Injury Pain Vary among Subtypes of Pain and Smoking Status: Results from a Randomized, Controlled Experiment. *J Pain*. 2012; 13(12):1206-1214. PMID: 23107508.

12. Rowbotham MC, Duan WR, Thomas J, Nothaft W, Backonja MM. A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Abt-594 in Patients with Diabetic Peripheral Neuropathic Pain. *Pain*. 2009; 146(3):245-252. PMID: 19632048.

13. Authier N, Balayssac D, Marchand F, Ling B, Zangarelli A, Descoeur J, Coudore F, Bourinet E, Eschalier A. Animal Models of Chemotherapy-Evoked Painful Peripheral Neuropathies. *Neurotherapeutics*. 2009; 6(4):620-629. PMID: 19789067.

14. Hoke A. Animal Models of Peripheral Neuropathies. *Neurotherapeutics*. 2012; 9(2):262-269. PMID: 22415319.

15. Toma W, Kyte SL, Bagdas D, Alkhlaif Y, Alsharari SD, Lichtman AH, Chen ZJ, Del Fabbro E, Bigbee JW, Gewirtz DA, Damaj MI. Effects of Paclitaxel on the Development of Neuropathy and Affective Behaviors in the Mouse. *Neuropharmacology*. 2017; 117:305-315. PMID: 28237807.

16. Kyte SL, Toma W, Bagdas D, Meade JA, Schurman LD, Lichtman AH, Chen ZJ, Del Fabbro E, Fang X, Bigbee JW, Damaj MI, Gewirtz DA. Nicotine Prevents and Reverses Paclitaxel-Induced Mechanical Allodynia in a Mouse Model of Cipn. *J Pharmacol Exp Ther*. 2018; 364(1):110-119. PMID: 29042416.

17. Postma TJ, Aaronson NK, Heimans JJ, Muller MJ, Hildebrand JG, Delattre JY, Hoang-Xuan K, Lanteri-Minet M, Grant R, Huddart R, Moynihan C, Maher J, Lucey R, Group EQoL. The Development of an Eortc Quality of Life Questionnaire to Assess Chemotherapy-Induced Peripheral Neuropathy: The Qlq-Cipn20. *Eur J Cancer*. 2005; 41(8):1135-1139. PMID: 15911236.

18. Le-Rademacher J, Kanwar R, Seisler D, Pachman DR, Qin R, Abyzov A, Ruddy KJ, Banck MS, Lavoie Smith EM, Dorsey SG, Aaronson NK, Sloan J, Loprinzi CL, Beutler AS. Patient-Reported (Eortc Qlq-Cipn20) Versus Physician-Reported (Ctcae) Quantification of Oxaliplatin- and Paclitaxel/Carboplatin-Induced Peripheral Neuropathy in Ncctg/Alliance Clinical Trials. *Support Care Cancer*. 2017; 25(11):3537-3544. PMID: 28634656.

19. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, Chappell A, Chartier K, Cleeland CS, Costello A, Cowan P, Dimitrova R, Ellenberg S, Farrar JT, French JA, Gilron I, Hertz S, Jadad AR, Jay GW, Kalliomaki J, Katz NP, Kerns RD, Manning DC, McDermott MP, McGrath PJ, Narayana A, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Reeve BB, Rhodes T, Sampaio C, Simpson DM, Stauffer JW, Stucki G, Tobias J, White RE, Witter J. Research Design Considerations for Confirmatory Chronic Pain Clinical Trials: Immpact Recommendations. *Pain*. 2010; 149(2):177-193. PMID: 20207481.

20. Hurst H, Bolton J. Assessing the Clinical Significance of Change Scores Recorded on Subjective Outcome Measures. *J Manipulative Physiol Ther*. 2004; 27(1):26-35. PMID: 14739871.

21. US Department of Health E, and Welfare Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration. Cdeu Assessment Manual for Psychopharmacology. Rockville, MD 1976.

22. Patient Global Impression of Change (Pgic) Questionnaire, Distributed by Mapi Research Trust.

23. Barr RS, Culhane MA, Jubelt LE, Mufti RS, Dyer MA, Weiss AP, Deckersbach T, Kelly JF, Freudenreich O, Goff DC, Evins AE. The Effects of Transdermal Nicotine on Cognition in Nonsmokers with Schizophrenia and Nonpsychiatric Controls. *Neuropsychopharmacology*. 2008; 33(3):480-490. PMID: 17443126.

24. Mishriky BM, Habib AS. Nicotine for Postoperative Analgesia: A Systematic Review and Meta-Analysis. *Anesth Analg*. 2014; 119(2):268-275. PMID: 24384863.

25. Srivastava ED, Russell MA, Feyerabend C, Masterson JG, Rhodes J. Sensitivity and Tolerance to Nicotine in Smokers and Nonsmokers. *Psychopharmacology (Berl)*. 1991; 105(1):63-68. PMID: 1745713.

26. Levin ED, Conners CK, Sparrow E, Hinton SC, Erhardt D, Meck WH, Rose JE, March J. Nicotine Effects on Adults with Attention-Deficit/Hyperactivity Disorder. *Psychopharmacology (Berl)*. 1996; 123(1):55-63. PMID: 8741955.

27. Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE. A Single Dose of Nicotine Enhances Reward Responsiveness in Nonsmokers: Implications for Development of Dependence. *Biol Psychiatry*. 2008; 63(11):1061-1065. PMID: 17976537.

28. Hong D, Conell-Price J, Cheng S, Flood P. Transdermal Nicotine Patch for Postoperative Pain Management: A Pilot Dose-Ranging Study. *Anesth Analg*. 2008; 107(3):1005-1010. PMID: 18713921.

18 APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self; unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about > 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

19 APPENDIX 2. NEW YORK HEART ASSOCIATION CLASSIFICATION

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.