THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Armodafinil for persistent patient-reported fatigue following radiation therapy for head and neck cancer: a randomized phase II study.
2010-0557

Core Protocol Information

Short Title	Single agent armodafinil
Study Chair:	Gary B. Gunn
Additional Contact:	Angele K. Saleeba Araceli G. Garcia-Gonzalez Toni Williams
Additional Memo Recipients:	**Recipients List** **OPR Recipients** (for OPR use only) Araceli G. Garcia-Gonzalez Loretta A. Williams OPR DSMB PDOL OPR DMC Addl Cont **Study Staff Recipients** None
Department:	Symptom Research
Phone:	713-745-3470
Unit:	1450
Full Title:	Armodafinil for persistent patient-reported fatigue following radiation therapy for head and neck cancer: a randomized phase II study.
Protocol Type:	Standard Protocol
Protocol Phase:	Phase I/Phase II
Version Status:	Activated -- Closed to new patient entry as of 11/09/2017
Version:	17
Document Status:	Saved as "Final"
Submitted by:	Angele K. Saleeba--11/7/2017 10:25:33 AM
OPR Action:	Accepted by: Virginia M Gonzales -- 11/8/2017 10:41:28 AM

Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

The primary objective of this protocol is to evaluate the ability of armodafinil to reduce patient-reported fatigue in patients with treated head and neck cancer.

The secondary objective of this protocol is to explore the effect of armodafinil in reducing symptom severity, symptom interference, patient-reported alertness, work productivity and activity impairment.

2.0 Rationale

Fatigue is one of the most severe symptoms reported by patients at any time point assessed in our M. D. Anderson Symptom Inventory - Head and Neck Module studies (Rosenthal et al, ASCO 2010, Rosenthal et al, ASTRO 2010). Further, fatigue severity peaks for approximately one-fourth of patients after treatment completion, and approximately one-third of patients report moderate to severe fatigue at 8 weeks after completion of radiation therapy or chemoradiation (Rosenthal, ASTRO 2010). This is an important time for fatigue-symptom intervention, because many patients are expecting to return to work or to their usual level of functioning around this time frame.

The agent to be tested in this trial is **armodafinil**. Using a blinded, randomized placebo-controlled trial, we will evaluate armodafinil's ability to reduce patient-reported fatigue in patients with persistent moderate to severe levels of fatigue after completion of radiation therapy and all planned cancer therapy. The target of action for the proposed intervention is armodafinil's alertness-promoting property, which could impact patient-reported fatigue, other associated symptoms, and symptom interference with daily activities.

The significance of this research is that it (1) evaluates a commercially available, low-toxicity symptom therapy, (2) evaluates a therapy that could reduce multiple commonly reported symptoms in patients with head and neck cancer by targeting fatigue (one of the most severe symptoms reported by this patient group), and (3) seeks to establish a simple medical symptom-intervention therapy for head and neck cancer, a disease site for which the patient-reported symptom burden is high and few proven medical symptom intervention strategies exist.

3.0 Background

Cancer was diagnosed in more than 1.4 million people in the United States in 2007 alone — 34,360 with head and neck cancer (HNC) (Jemal et al., 2007). Many of these patients receive aggressive therapy and experience multiple symptoms that cause them significant distress and impair function and rehabilitation. Whereas symptoms are often the result of disease, it is increasingly recognized that pain, fatigue, sleep disturbance, cognitive dysfunction, and affective symptoms can also be caused by cancer treatment. Treatment-related symptoms can directly affect survival if they become so severe that the patient abandons potentially curative therapies (Borden & Parkinson, 1998; Jeremic et al., 2003). Moreover, treatment-related symptoms may persist for weeks, months, or years and may worsen, even if the cancer improves.

3.1 Symptom Management

Better symptom management, in cancer as well as in other diseases, has *been hampered by the lack of a strong clinical-trial evidence base for guiding symptom-management practice.* Several barriers have hindered the development of clinical trials in symptom management. First, the subjective nature of symptoms has limited innovative research into the mechanisms underlying these symptoms and the development of novel ways of treating or preventing them. Special difficulties include the poor fit of current disease models of research for implementing this kind of health-related investigation and lack of statistical models that integrate “rough” self-report data and biologic data (Cleeland, 2001). However, patient-reported outcomes research has recently been promoted by the U.S. Food and Drug Administration (FDA) for more accurate therapeutic agent evaluation, and symptom reduction has been recognized as a primary clinical benefit for drug approval (FDA, 2009).

One approach to symptom-directed treatment could include the more routine use of currently available agents such as stimulants (e.g., **armodafinil**) to modify symptom expression at the central nervous system level.

3.2 Head and Neck Cancer Treatment Side-Effects

All cancer therapies, especially multimodality and multiagent treatment programs, are associated with a spectrum of early and late adverse effects. Although chemoradiotherapy for HNC has consistently been shown to yield clinically relevant improvement in locoregional control and overall survival, these benefits are offset by severe early toxicities (Pignon et al., 2000). One recent analysis noted an almost 500% increase in the number of early toxicity events with chemoradiation as compared with standard radiotherapy for HNC (Trotti et al., 2007). Even so, many patients treated with radiation therapy alone report high symptom burden and functional interference, even after treatment completion. For this reason, and because there is a wide variety of symptoms, ranging in severity, and since they can be transient in nature, physician-reported toxicity data is difficult to evaluate. Thus patient-reported symptom burden may be a better candidate for clinical investigation.

4.0 Background Drug Information

Armodafinil (Nuvigil®, manufactured by Cephalon, Inc) is the R-isomer of racemic modafinil (R-modafinil).

It is indicated for narcolepsy, obstructive sleep apnea, and shift-work sleep disorder, and for improving wakefulness in patients with excessive sleepiness, similar to modafinil.

The usual dosing is 150mg to 250mg per day, given once in the morning or one hour prior to shift work (Prod Info NUVIGIL ™ oral tablets, 2008).

Armodafinil's exact mechanism for wakefulness producing is unknown. In vitro, both armodafinil and modafinil bind to the dopamine transporter and inhibit dopamine reuptake, but have no dopamine receptor agonist activity. The wakefulness-promoting actions of armodafinil are similar to that of sympathomimetic amines, such as amphetamine and methylphenidate, despite differences in their pharmacologic profiles (Prod Info NUVIGIL ™ oral tablets, 2008).

Modafinil has been shown in clinical studies to have a beneficial effect on fatigue in patients with depression (Thase et al., 2006), narcolepsy (Becker et al., 2004), fibromyalgia (Pachas, 2003), multiple sclerosis (Zifko et al., 2002), and HIV (Rabkin et al., 2004). Studies have reported effect sizes (ES) ranging from 0.57 (Zifko et al., 2002) on fatigue in multiple sclerosis to 0.79 in patients with narcolepsy (Becker et al., 2004).

Pharmacokinetic studies have indicated that even though modafinil and armodafinil have similar half-lives, armodafinil exhibits higher plasma concentration late in the day compared with modafinil on a milligram-to-milligram basis. This difference is due to the stereospecific differences in elimination of the two isomers, which may result in fundamentally different durations of action and may potentially increase the activity of armodafinil throughout the dosing period compared with modafinil. These differences between the two medications cannot be made equivalent by increasing the dose of the racemate, modafinil, without introducing potential safety concerns. Therefore, we have decided to use armodafinil as the active agent for our study.

The safety and effectiveness of NUVIGIL in individuals older than 65 years have not been systematically evaluated. One open-label study showed decreased clearance and an increased half-life in volunteers over the age of 65 years. A lower dose of NUVIGIL should be considered in elderly patients because elimination of NUVIGIL and its metabolites may be reduced as a consequence of aging (Darwish et al, 2010).

To our knowledge, there are no published cancer-related studies with armodafinil. Studies of modafinil, however, have shown its beneficial action on cancer symptoms. A randomized, placebo-controlled, double-blind phase III trial showed modafinil was effective in improving fatigue in cancer patients receiving chemotherapy, although only for patients with severe baseline fatigue scores (Jean-Pierre et al, 2010). A pilot study of 30 patients with brain tumors receiving therapy showed reductions in fatigue severity scores at 8 weeks (ES 1.14) and at 12 weeks (ES 1.21) (Kaleita et al., 2006). In studies of noncancer diseases, the effect size of modafinil in reducing fatigue has been reported to be between 0.57 (multiple sclerosis, Zifko et al., 2002) and 2.00 (biliary cirrhosis, Jones & Newton, 2007). Studies have reported its beneficial effect on mood and cognition (MacDonald et al., 2002; Taneja et al., 2007). Compared with placebo, modafinil improved cognitive performance in breast cancer survivors who had shown a favorable response to modafinil in the preceding open-label phase of the same study (Kohli et al., 2007). Modafinil has been used to augment treatment with selective serotonin reuptake inhibitors (SSRIs) or bupropion in patients with major depression accompanied by residual fatigue and sleepiness (DeBattista et al., 2003; Konuk et al., 2006). Modafinil has also been used to combat opioid-induced sedation in patients with chronic pain (Webster et al., 2003).

Armodafinil is commercially available as 50mg, 150mg, and 250mg tablets. We will purchase commercial grade drug and matching placebo to be dispensed by the investigational pharmacy.

4.1 Absolute Contraindications, Cautions, and Warnings about Armodafinil

4.11 Absolute Contraindications

4.111 Pre-existing psychosis or bipolar disorder

4.112 Pre-existing renal impairment; Severe chronic renal failure (CrCl < or = 20 mL/min) increased modafinil acid 9 fold

4.113 Pre-existing cirrhosis or hepatic impairment

4.114 Pre-existing Tourette's syndrome

4.115 Patient should not be breastfeeding, pregnant, or planning to become pregnant while on armodafinil

4.12 Cautions and Warnings

4.121 Avoid in patients with a history of clinically significant cutaneous drug reaction, or a history of clinically significant hypersensitivity reaction, including multiple allergies or drug reactions

4.122 Caution in patients with a history of angina or cardiac ischemia, a recent history of myocardial infarction or left ventricular hypertrophy, or in patients with mitral valve prolapse

4.123 Induces CYP3A, so avoid midazolam and drugs that are substrates for CYP3A4/5, such as cyclosporine, ethinyl estradiol, triazolam, as dose modification would be needed

4.124 Avoid CYP3A4/5 inducers: carbamazepine, Phenobarbital, rifampin; or inhibitors: ketoconazole, erythromycin

4.125 Moderately inhibits CYP2C19, so avoid omeprazole and drugs that are substrates for CYP2C19, such as phenytoin, diazepam, propanolol, chlomipramine and other tricyclic antidepressants

4.126 Avoid other use in combination with other CNS stimulants, such as methylphenidate, dextroamphetamine, and modafinil

4.127 Caution in combination with MAO inhibitors

4.128 Increased monitoring needed for with patients on Coumadin/warfarin

4.129 Clearance may be reduced in the elderly; safety not established for patients over 65

4.130 Avoid in patients with history of CNS stimulant abuse, such as methylphenidate, dextroamphetamine, and modafinil

4.131 Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that armodafinil will not affect their ability to engage in such activities

4.132 Steroidal contraceptive effectiveness may be reduced while on armodafinil and for the following month after discontinuing armodafinil – alternative birth control methods recommended during this period

4.133 Patients should be advised to avoid alcohol

4.2 Armodafinil Common Adverse Reactions
Most commonly reported adverse reactions: headache, nausea, dizziness, and insomnia

4.21 Occurring in greater than >10% of study subjects across randomized studies with armodafinil:

Central nervous system: Headache (14% to 23%)

4.22 Occurring in 1% to 10% of study subjects across randomized studies with armodafinil:

Cardiovascular: Palpitation (2%), increased heart rate (1%)

Central nervous system: Dizziness (5%), insomnia (4% to 6%; dose related), anxiety (4%), depression (1% to 3%; dose related), fatigue (2%), agitation (1%), attention disturbance (1%), depressed mood (1%), migraine (1%), nervousness (1%), pain (1%), pyrexia (1%), tremor (1%)

Dermatologic: Rash (1% to 4%; dose related), contact dermatitis (1%), hyperhidrosis (1%)

Gastrointestinal: Nausea (6% to 9%; dose related), xerostomia (2% to 7%; dose related), diarrhea (4%), abdominal pain (2%), dyspepsia (2%), anorexia (1%), appetite decreased (1%), constipation (1%), loose stools (1%), vomiting (1%)

Genitourinary: Polyuria (1%)

Hepatic: GGT increased (1%)

Neuromuscular & skeletal: Paresthesia (1%)

Respiratory: Dyspnea (1%)

Miscellaneous: Flu-like syndrome (1%), thirst (1%)

4.23 Postmarketing and/or case reports: Anaphylactoid reaction, angioedema, hypersensitivity, liver enzymes increased, pancytopenia, systolic blood pressure increased (see section on Serious adverse events for symptom drug below)

4.3 Armodafinil Monitoring Parameters
Monitoring Parameters: Signs of hypersensitivity, rash, psychiatric symptoms, levels of sleepiness, increased blood pressure and pulse rate, and drug abuse

4.31 Evidence:

Rash: Rash occurred in 2% (n=645) of patients receiving armodafinil (250 mg and 150 mg) compared with 0% of patients receiving placebo (n=445) in clinical trials. Approximately 0.8% of pediatric patients discontinued treatment due to rash, which occurred within a median of 13 days of therapy. Rash appeared to be dose-related in patients taking armodafinil for narcolepsy and shift work sleep disorder. Rash occurred in 4% (n=198) of patients receiving armodafinil 250 mg and in 1% (n=447) of patients receiving armodafinil 150 mg compared with less than 1% of patients receiving placebo in controlled clinical trials (Prod Info NUVIGIL(TM) oral tablets, 2008).

Blood pressure and heart rate: Monitoring of blood pressure may be appropriate, as small but consistent changes in systolic and diastolic blood pressure readings have been seen, ranging from 1.2 to 4.3 mmHg increase. (Prod Info NUVIGIL(TM) oral tablets, 2008). Small but consistent changes in pulse rate have been seen, ranging from 0.9 to 3.5 bpm increase. Prod Info NUVIGIL(TM) oral tablets, 2008).

4.4 Armodafinil (or Modafinil) Drug Interactions

Induces CYP3A, so avoid midazolam and drugs that are substrates for CYP3A4/5, such as cyclosporine, ethinyl estradiol, and triazolam, as dose modification would be needed

Avoid CYP3A4/5 inducers: carbamazepine, Phenobarbital, rifampin, aminoglutethimide, nafcillin, nevirapine, phenytoin; or inihibitors: azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, and verapamil

Moderately inhibits CYP2C19, so avoid omeprazole and drugs that are substrates for CYP2C19, such as phenytoin, diazepam, propanolol, chlomipramine (or other tricylic antidepressants), citalopram, methsuximide, and sertraline

Oral contraceptives: Serum concentrations may be reduced (due to metabolism enzyme induction); contraceptive failure may result; alternative contraceptive measures are recommended during therapy and for 1 month after armodafinil is discontinued

Warfarin: Serum concentrations/effect may be increased by modafinil; would require increased PT/INR monitoring

4.6 Storage Information
Store at 20°C to 25°C (68°F to 77°F)

4.70 Serious Adverse Events for Symptom Drug

Serious and life-threatening rashes have been reported with modafinil and include: Stevens-Johnson Syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms. In clinical trials of modafinil, these rashes were more likely to occur in children; however, in the postmarketing period, serious reactions have occurred in both adults and children. Most cases have been reported within the first 5 weeks of initiating therapy; however, rare cases have occurred after prolonged therapy. No risk factors have been identified to predict occurrence or severity of these reactions (Lexi-Comp online, Lexi-Comp, Inc. 1978-2010).

Patients will be advised to discontinue drug at first sign of body rash during this study.

Supplemental NDA 20-717 2 Cephalon, Inc., Provigil® (modafinil) Tablets (C-IV) Version 1.6;
http://www.fda.gov/ohrms/dockets/ac/03/briefing/3979B2_01_Cephalon-Provigil.pdf
http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4325s2_10_Modafinil%20Flowers,%20RPh%20(FDA).pdf

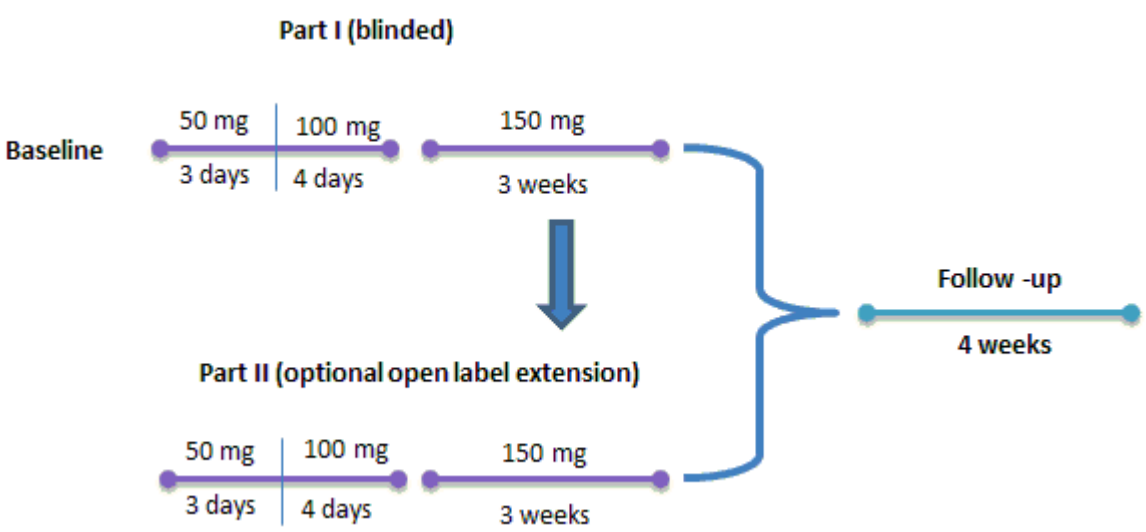
5.0 Study Design

Using a Phase II blinded, randomized placebo-controlled trial, with optional open label extension period, we will evaluate armodafinil's ability to reduce patient-reported fatigue in patients with treated head and neck cancer.This type of trial design is especially important in trials where symptom reduction is the outcome and where knowledge of the treatment arm might bias assessment by the staff or patient. We will purchase commercial grade drug and matching placebo to be dispensed by the investigational pharmacy.

Design: Phase II blinded, randomized placebo-controlled trial, with optional open label extension period

Symptom Intervention Agent: Armodafinil

Study Period: 8-12 weeks depending on participation in the optional open label component : intervention agent daily for 4 weeks (Part I), with continued assessment follow-up period of 4 weeks (Part II). At the end of the 4-week agent intervention, the patient will be given the option to receive open label armodafinil during the 4 weeks follow-up period. If the patient agrees to this option, the follow-up period for these patients will be extended for another 4 weeks.



Primary Symptom Outcome Variable: 4-week (+/- 7 days) area under the curve (AUC) for patient-reported fatigue at its worst (item from the Brief Fatigue Inventory).

Secondary outcomes assessed will include: (1) the 5 most-severe MDASI-HN symptoms at 2-month follow up based on previously collected MDASI-HN data (2) overall MDASI-HN symptom severity, (3) overall MDASI-HN interference, (4) patient-reported alertness (via Epworth Sleepiness Scale), and (5) work productivity and activity impairment questionnaire.

Forty patients will be randomized to either armodafinil or placebo, twenty in each arm. AUC values for patients who drop out of the study after providing 2 weeks of AUC data will be included by carrying their last symptom data forward for the remaining study period under the intent-to-treat rule. The carry-forward method of handling drop-outs will be revisited upon completion of the study to determine if adjustments to these values can be made using longitudinal regression models estimated from patients who completed the entire study.

A list of adverse events (AEs) known to be associated with primary treatment is listed in section 4.0 of the protocol. Study staff will monitor for AEs via telephone contact with the subjects using the Phone Contact Form according to the Assessment Schedule. In addition, study participants will be able to contact study personnel via a telephone hotline, and study participants can be seen by study personnel at MD Anderson if there are any concerns or questions regarding potential side effects. If seen in person by study personnel, clinical monitoring form will be completed. Also, if study subjects are coming to MD Anderson for

routine clinical follow up (visits unrelated to this study), they will be seen by study staff as frequently as weekly during the study period, and the clinical monitoring form will be completed every time.

Patients will be advised to discontinue drug at first sign of body rash during this study and to immediately notify study personnel, who will in turn notify the PI for appropriate medical management.

All grade 3 and 4 toxicities reported by patients in this trial will be evaluated by the principal investigator in consultation with the treating physician, or by another attending physician if the PI is not available, to determine whether the toxicities were possibly caused by the study medication (rather than being effects from previous cancer therapy). The investigators will discriminate between expected dermatitis related to radiation therapy or chemotherapy versus armodafinil hypersensitivity. If 1 or more armodafinil-related grade 3 or 4 toxicities is observed in the patients assigned to armodafinil, the study will be terminated.

The interaction screening will be the responsibility of the research staff. Study exclusion criteria of known drug interactions and drugs that would require additional monitoring if given in conjunction with armodafinil will also be in place for patient safety. The research staff will review any current or new patient medications prior to initiating treatment, and will document all medications patients have used or will use during the trial. During the trial, the research staff will capture any potential drug interactions that could cause an AE on the Adverse Event forms. Medication sheets will be provided to both patients and treating physicians to inform them of the possibility that the patients may be receiving armodafinil (see Appendix EEE and EE).

6.0 Administration of Pharmacologic Agent

Armodafinil or placebo will begin after enrollment and will continue daily for a total of 4 weeks.

Patients will pick up the assigned study medication at one of the outpatient pharmacy stations in MD Anderson. At pickup, patients will receive instruction on how to take study medications (Appendix EEE). If the patient is unable to pick up the study medication, the investigational pharmacy will mail the study medication to the patient home, overnight.

The participants will take study medication enterally, once daily, in the morning, starting after study entry and continuing for 28 days (4 weeks). The dosing schedule for the symptom intervention agent is described in the table below.

Study medication use will be reviewed at the end of week 4 by study staff. Patients will be asked to bring their study medication to the clinic if they are coming in for a routine visit, at which time study staff will perform a medication count. If the patient is not coming to the clinic at study completion, the medication review will be completed by telephone. Results of the count will be recorded on the Study Medication Accountability form (Appendix K).

During the end of week 4 assessment, the study staff will also offer the participant the option to receive open label armodafinil, at the same dosing schedule described in the table below. If the patient agrees to the optional open label extension, they will either pick-up armodafinil during their routinely scheduled follow-up visit or the pharmacy will mail it to them. A 5-day window will be allowed between the end of Part I and the start of the optional open label extension.

Symptom Intervention Agent	**Dosage Forms**	**Total daily dose: starting day 1 of week 1**
Armodafinil or matching placebo	50mg and 100mg capsules or tablets	50 mg the first 3 days, 100 mg the next 4 days, and 150 mg for the remaining treatment period.*

*capsules or tablets, one every morning, may be given without regard to meals. This dosing schedule is to be followed during the 4-week symptom intervention and the optional open label extension.

Patients who are satisfied with the study medication and express interest in continuing will be able to consult with their physicians about the risks and benefits of continuing the armodafinil; if they elect to continue, further clinical monitoring will be provided by the patient's treating physician. Patients with persistent moderate to severe levels of fatigue will be offered further evaluation. MD Anderson patients will be referred at the MD Anderson Fatigue Clinic. Patient's final disposition will be collected on the Patient Disposition Form (Appendix V).

7.0 Data Collection Tools

7.1 <u>Symptom Measurement</u> Patient-reported symptom data will be collected using the: (1) **Brief Fatigue Inventory** (**BFI**); (2) **MDASI-HN** module of the M. D. Anderson Symptom Inventory (Appendix F and E) and (3) **Epworth Sleepiness Scale** (**ESS**) (Appendix G). These and other patient-reported outcome questionnaires will be completed face-to-face in the clinic at the time of enrollment. Subsequent assessments during the study period will be collected either face to face in the clinic, through phone calls by field coordinators or study staff, by Interactive Voice Response (IVR) system, or by regular mail, as outlined in the Assessment Schedule (Appendix X).

Interactive Voice Response (IVR) system combines the use of touch-tone telephones with computers and the Internet to follow patients who have symptoms like pain that need to be monitored closely while away from the hospital. Using the telephone keypad, of a touch-tone telephone, a patient rates his/her pain at its worst in the past 24 hours from 0 (no pain) to 10 (pain as bad as you can imagine). Even when the patient responds using the keypad, these systems are referred to as interactive voice response (IVR) systems. An IVR system should be especially helpful for assessing symptoms such as pain, fatigue, distress, or sleep disturbance that patients may be reluctant to report to their treatment team. The IVRS is programmed to contact patients at their preferred times on specified dates. Once a contact is made, the symptom assessment script runs. Patient responses to the symptom and interference questions are deposited into a web-based database with real-time updates. Brochure describing how to report symptoms through the IVRS will be provided to patients who choose to use it (Appendix HH).

7.2 Measure of Quality of Life The EuroQol (EQ)-5D is a standardized instrument for use as a measure of health outcome (Appendix L). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The EQ-5D was originally designed to complement other instruments but is now increasingly used as a standalone measure. The EQ-5D descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems" (level 1), "moderate health problems" (level 2), and "extreme health problems" (level 3). A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Each unique health state described by the instrument has an associated 5-digit descriptor ranging from 11111 for perfect health to 33333 for the worst possible state. The resulting descriptive system defines 243 health states. In addition, "unconscious" and "immediate death" are included in the EQ-5D valuation process but are not a part of the descriptive system.

7.3 Measure of Global Quality of Life The Global Quality of Life (GQL) is a single item asking patients to rate their quality of life on a 0 to 10 scale over the past week (Appendix M).

7.4 Measure of Patient Satisfaction with Study Medication The Study Medication Satisfaction Scale is a short questionnaire that asks patients about several areas of satisfaction (Appendix N). The scale includes questions about ease or difficulty of taking the medication in general and in its current form, the convenience of taking the study medication as instructed, and patient confidence that the study medication is of benefit.

7.5 Work Productivity and Activity Impairment Questionnaire (WPAI) (Appendix H)

7.6 Head and Neck Treatment Summary Form (Appendix O)

7.7 Patient Contact Form (Appendix P)

7.8 Demographic Form The Demographic Form includes patient birth date, gender, marital status, race, ethnicity, education, and employment status (Appendix Q). The Demographic Form will be completed at baseline.

7.9 Charlson Comorbidity Index The Charlson Comorbidity Index yields a comorbidity score, to control for serious concurrent chronic disease conditions (Charlson et al., 1994) (Appendix R).

7.10 On-Study Form The On-Study Form contains data about disease, previous treatment, whether a patient is on concurrent protocols (Appendix S). This form will be completed at baseline.

7.11 Clinical Monitoring Form The Clinical Monitoring Form contains clinical data, including Body Mass Index (BMI), blood pressure, pulse rate, performance status, symptom treatment, and CTC toxicity scores (Appendix T).

7.12 Medication Form The Medication Form contains data about types of medications patients have been prescribed. Medication types include pain medications, antiemetics, and psychotropics among others. There is also a general section for other types of medications patients may be taking. (See Appendix U).

7.13 Patient Disposition Form Patient's final disposition will be collected on the Patient Disposition Form. Patients who are satisfied with the study medication and express interest in continuing will be able to discuss continuing armodafinil as part of physician-patient decision based on a risk-benefit scenario, with further clinical monitoring to continue under the care of the patient's treating physician. Subjects with persistent moderate to severe levels of fatigue will be offered further evaluation and referral to the MD Anderson Fatigue Clinic (Appendix V).

7.14 Study Medication Accountability Form This form contains study medication data, including the number of tablets dispensed to the patient at the last visit to the outpatient pharmacy, how many tablets were returned from the last visit, and the number of days the tablets were taken (Appendix K).

7.15 Laboratory Data Form No study-specific labs are planned; however, any blood-analysis values obtained for clinical reasons will be captured on the Laboratory Data Form, including C-reactive protein (CRP), serum chemistry (albumin, calcium, phosphorous, glucose, BUN, creatinine, total bilirubin, and total protein), electrolytes (sodium, potassium, chloride, carbon dioxide, magnesium), and complete blood count (CBC). These values will be recorded if they are available in the patient medical record from a blood draw performed for clinical purposes within previous 2 weeks. Note: Liver function tests are required at baseline. If they were not performed within the past 2 weeks prior to starting treatment with the symptom drug/ placebo, they will be drawn for eligibility purposes.
(Appendix W).

7.16 Treatment Summary Form The Treatment Summary Form contains data about previous radiation therapy and cancer treatment (Appendix O).

7.17 Final Study Status Form The Final Study Status Form contains data about patient disposition at the end of the study (i.e., completed study, withdrew, vital status, tumor status) (Appendix Y).

8.0 Patient Eligibility

8.1 Inclusion Criteria

8.11 Patients who were treated with either definitive or postoperative radiation or chemoradiation therapy for HNC with moderate to severe levels of patient reported fatigue, at 6 or more weeks after completing all planned cancer therapy.

Patients who rated their fatigue level at 5 or greater on a 0 to 10 scale during any follow-up clinic visits at MD Anderson.

8.12 Male and female patients ≥ 18 years old.

8.13 Patients who speak English (due to the novel research and its complexity, we are only accruing English-speaking patients to the protocol).

8.14 Patients must agree to discontinue any current herbal supplement use, and refrain from taking any herbal supplement while on protocol.

8.15 Patients must be willing and able to review and understand informed consent documents and to provide written consent.

8.16 Women of childbearing potential (women who are not postmenopausal for at least 1 year and are not surgically sterile) must have a negative urine pregnancy test.

8.17 Sexually active males and females must agree to use effective birth control or to be abstinent for the duration of the study period.

8.18 Women currently taking birth control pills or planning to start birth control pills must agree to an additional method of birth control (either abstinence or a barrier method) while on the study medication and for 1 additional month after study completion.

8.2 Exclusion Criteria

8.21 Patients who rated their fatigue level at 4 or less over the past 24 hours based on the fatigue at its worst item of the BFI.

8.22 Patients with clinical evidence of active persistent cancer or progressive disease after completing planned cancer therapy, or with active recurrent cancer.

8.23 Patients with potential medical or other underlying causes of fatigue, as determined by the treating physician or PI.

8.24 Patients with Hb <10.5 g/dL within previous 2 weeks.

8.25 Patients with untreated or uncontrolled hypothyroidism, or TSH > ULN or free T4< lower level of normal within previous 2 weeks.

8.26 Patients with underlying cardiac or pulmonary disease resulting in dyspnea, hypoxia, or hypercapnea.

8.27 Patients with a Karnofsky performance status <70

8.28 Patients less than 18 years old

8.29 Patients who are enrolled and receiving active treatment in other symptom intervention trials or who are in the treatment phase of another clinical trial

8.210 Patients with pre-existing psychosis or bipolar disorder

8.211 Patients with pre-existing renal impairment, as evidenced by serum creatinine > ULN on the most recent blood work, done at least within the previous 2 weeks.

8.212 Patients with pre-existing cirrhosis or hepatic impairment or with abnormal liver function test as evidenced by total bilirubin >1.5 x ULN or 2 times the upper limit of normal of alkaline phosphatase (ALP), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) on the most recent blood work, done at least within the previous 2 weeks.

8.213 Patients with pre-existing Tourette's syndrome

8.214 Patients who have used monoamine oxidase (MAO inhibitors) within the past 14 days

8.215 Patients undergoing abrupt discontinuation of ethanol or sedatives (including benzodiazepines)

8.216 Patients currently taking, or having taken within the previous 1 month, armodafinil, modafinil, amphetamine, or methylphenidate

8.217 Patients on anticoagulants (i.e. warfarin, coumadin, or heparin) or clopidogrel

8.218 Patients with a history of clinically significant cutaneous drug reaction, or a history of clinically significant hypersensitivity reaction, including multiple allergies or drug reactions

8.219 Patients with a history of angina or cardiac ischemia, a recent history of myocardial infarction (within the past 1 year) or left ventricular hypertrophy, or patients with mitral valve prolapse

8.220 Patients with uncontrolled hypertension or tachycardia, as determined by treating physician

8.221 Patients who are pregnant, breastfeeding, or planning to become pregnant during the study period and for 1 month after stopping the study drug.

8.222 Female patients who are currently on birth control pills as primary means of contraception, but are not willing to seek an additional effective method of contraception (such as barrier method) during the study period and for 1 month after stopping the study drug.

8.223 Patients with a history of CNS stimulant abuse, such as methylphenidate, dextroamphetamine, or modafinil.

8.224 Patients with major depressive disorder or severe depression (a score of 13 or greater on the BDI Fast Screen (BDI-FS) will be excluded. If this is the case, we will notify their treating physician for appropriate management or referral.

8.225 Patients with current or a history of suicidal ideation.

8.226 Patients currently taking midazolam, cyclosporine, ethinyl estradiol, or triazolam

8.227 Patients currently taking carbamazepine, phenobarbital, rifampin, aminoglutethimide, nafcillin, nevirapine, phenytoin, azole antifungals, clarithromycin, diclofenac, doxycycline, erythromycin, imatinib, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin, or verapamil

8.228 Patients currently taking omeprazole, diazepam, propanolol, chlomipramine (or other tricylic antidepressants), citalopram, methsuximide, or sertraline.

9.0 Patient Enrollment and Registration

Patient Enrollment

Patients will be screened for eligibility and recruited for enrollment in the outpatient Head and Neck Cancer Clinic in the Department of Radiation Oncology at MD Anderson, 6 or more weeks after completing planned cancer therapy (this time line will generally coincide with the first follow up appointment for most patients with HNC treated with radiation therapy). By this time, most patients should have had significant improvement in their radiation therapy-related mucositis, dermatitis, and pain. Recruitment brochures will be available to give to the patients in the clinic (Appendices ZZ and ZZZ).

Patients with major depressive disorder or severe depression (a score of 13 or greater on the BDI Fast Screen (BDI-FS) will be excluded. If this is the case, we will notify their treating physician for appropriate management or referral. The first disease/treatment response assessment is made around this time period as well.

Women of child-bearing potential who want to participate will be told that we will perform a mandatory pregnancy screening test through a urine sample at baseline. Study staff will provide the pregnancy kits to these women and make sure the results are known and recorded in the follow-up notes in Clinic Station before study drug prescription are filled by the Investigational Pharmacy. If the pregnancy test is positive the patient will be excluded from the study.

Research staff will maintain a log of all patients screened, and the reasons that patients do not enter the study will be documented.

Eligible patients who agree to enroll in the study will provide written informed consent/authorization.

At enrollment, patients will be informed that they will receive a $40 stipend for participating in the pilot study. The stipend will be distributed in $20 increments twice during the study, at enrollment and at study completion.

Enrolled patients will be registered into the Clinical Oncology Research System (CORe), the MD Anderson institutional patient data management system.

Patient Randomization and Assignment to Treatment Arm

The study will accrue 40 patients who will be randomized into 2 arms (armodafinil and placebo), with 20 patients each (see Section 5.0 Study Design). Prior to accruing the first patient, a randomization list will be generated by our biostatistician collaborator from the Department of Biostatistics for all 40 patients, stating to which group a patient was randomized. This list containing the accrual number and treatment group information will be given to Investigational Pharmacy. A sealed backup list will be kept by the assigned data analyst in the Department of Symptom Research. This list will be opened only if unblinding is needed.

Once a patient is enrolled, study staff will inform the Investigational Pharmacy of the patient's accrual number and patient ID. Once a patient is randomized to a treatment arm, the Investigational Pharmacy will retrieve the randomized treatment arm information from the generated randomization list and will relay that information to the dispensing Pharmacy. The patient may visit the most convenient outpatient pharmacy to pick up the study medication assigned.

10.0 Assessment Schedule

Please see Appendix X for an expanded study assessment/evaluation schedule.

Data Confidentiality Plan

All patient-reported outcome, laboratory, and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

When all analysis has been completed and all study results have been reported, the electronic and paper files will be stored in a password-protected MD Anderson secure server. This stored data may be made available to MD Anderson research and

clinical faculty for research purposes, with appropriate validation and access controls, so it can facilitate research cross-fertilization and speed insight discovery. Patient data also will be stored and accessible in the MD Anderson Translational Research Accelerator database (TRA; PI: A. Futreal).

11.0 Adverse Event Reporting

11.1 Adverse Events (AE) (Appendix I)

Telephone monitoring will be conducted by study staff weekly over the entire study period. Patients can contact study staff at any time during study period through the study hotline with questions or concerns regarding potential side effects of study medication. In addition, patients can be seen by either the treating physician or the PI as needed.

Treatment-related toxicities (NCI Common Terminology Criteria for Adverse Events, version 4) will be monitored by both clinic and research staff weekly either by phone or during any regular clinical appointments as described above. Other clinical variables will be collected as described in the Assessment Schedule. (Appendix X - AE Form).

Expected (due to previous cancer treatment or symptom treatment) or unrelated grade 1 or 2 toxicities will not be reported. AEs that are grade 3 and above that are definite, probable, or possible and related will be reported. AEs will be tabulated and reported as a summary on the continuing review report. All grade 3 and 4 toxicities will be evaluated by the PI and treating physician to determine if the toxicities were due to study medication.

11.2 Serious Adverse Events (SAE) (Appendix J)

A serious adverse event is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death.

- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization.

- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions.

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the PI or the IND Sponsor, The University of Texas MD Anderson Cancer Center Institutional Review Board system (UTMDACC IRB) .

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to UTMDACC IRB, regardless of attribution (within **5 working days** of knowledge of the event).

All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, require a written report to be submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in UTMDACC IRB .

The MD Anderson "Internal SAE Report Form for Prompt Reporting" will be used for reporting to UTMDACC IRB .

SAEs will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory test have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any SAE that occurs after the 30-day time period and that is related to the study treatment must be reported to UTMDACC IRB. This may include the development of a secondary malignancy.

It is the responsibility of the PI and the research team to ensure that SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12.0 Criteria for Removal from the Study

12.1 Patients will be taken off study if these values are met or exceeded:

12.11 Alkaline phosphatase (ALP) is 2 times the upper limit of normal

12.12 Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is 2 times the upper limit of normal

12.13 Total bilirubin >1.5 x ULN

12.14 Signs and symptoms of severe rash (CTC version 4 ≥ grade 3) or hypersensitivity

12.15 Pregnancy during the study period

12.16 INR > 1.5. Treating physician notified so that medical management occurs.

12.17 Development of psychosis.

12.18 Development of symptomatic tachycardia or palpitations or uncontrolled hypertension.

13.0 Statistical Analysis Plan

13.1 Sample Size and Randomization

Forty patients will be randomized equally to the 2 treatment arms - armodafinil and placebo. With 20 patients per treatment arm, we will be able to detect a 0.70 SD effect size on the BFI AUC between the 2 treatments with 70% power and one-sided 5% significance test. A 0.70 effect size for the BFI is about **1.7 points (change in terms of AUC)** on a 0 to 10 scale. Because this is a small Phase II study with the intent of providing effect size estimates to inform a large clinical trial in the future, we chose a modest statistical power.

13.2 Analysis Plan

We will test armodafinil in its ability to reduce values of patient- reported fatigue scores. Our emphasis is to test the efficacy of armodafinil as a potential agent in reducing patient-reported symptoms in patients with HNC after planned cancer therapy. The proposed phase II clinical trial for screening this potentially effective symptom-intervention agent will provide moderate power in detecting modest intervention effect. If the treatment has a more pronounced effect, it will be detected with higher power.

This study will allow us to obtain estimates of treatment effect and the variability of these estimates. Estimates of treatment effect will be obtained using standard linear regression techniques in which AUC values *(hn(i))* are regressed on indicator variables that represent treatment received. Estimates of treatment effect and between-subject variability will then be used to design a more comprehensive study in future clinical trials.

In addition to the formal evaluation of treatment effects on the primary outcome, we will also examine the prognostic effects of disease stage, type of cancer treatment, ECOG status, age and gender in predicting the outcome variable. We will compare the percentages of patients who were satisfied with the study drug against those who were taking the placebo. We will include an indicator variable in our model to determine whether patients who had a full dose of armodafinil differ from those who had a run-in period. Standard exploratory data analysis techniques and descriptive statistics will be used.

Assuming that patients accrue at the rate of 4 per month, we anticipate that this pilot study will require approximately 14 months to complete.

Intent to treat
We will need at least 2 weeks of BFI data for the patient to calculate AUC. Any patient who drops out prior to this will be replaced.

13.21 Primary Outcome Variable

The primary outcome variable will be the combined AUC for the “fatigue at its worst” item of the BFI. The value of this variable for patient *i* is denoted *bfi(i)* and is comprised of the BFI scores collected during the 8 weeks of the study period.

13.22 Secondary Outcome

We will use linear mixed models determine whether the placebo and the armodafinil groups differ on our secondary outcomes: the 5 most-severe symptoms, symptom interference, work productivity, and sleepiness.

We are also interested in exploring predictors of survival. Univariate Cox proportional hazards models will be used to screen for potential predictors (symptoms, demographic and clinical variables) of overall survival. Standard model fitting diagnostics will be performed. Finally, Kaplan-Meier survival curves will be plotted.

13.23 Non-Compliance with Study Agent

Patients who do not comply with study agent dosing requirements will remain in the study under the intent-to-treat rule.

14.0 References

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