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A Phase II Double-Blind Feasibility Study of Armodafinil for Brain Radiation-Induced Fatigue

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SCHEMA

A Phase II Double-Blind Feasibility Study of Armodafinil for Brain Radiation-Induced Fatigue

Patients receiving partial or whole-brain radiation therapy (RT) for a primary brain tumor

↓

Baseline data collection

↓

1:1 Randomization

↓

Armodafinil 150mg qd versus Placebo
(Starting as early as possible following the onset of brain RT,
but no later than the 5th fraction)

Primary Endpoint: Feasibility

Secondary Endpoints: Fatigue (FACIT-F and BFI), sleepiness (ESS), quality of life (FACT-Br), and neurocognitive function (Wake Forest Cognitive Function Battery)

Stratification factors: RT alone vs. RT + chemotherapy for primary brain tumor and KPS 60, 70 or 80 vs. 90 or 100

Study Sample: N=54

Estimated Study Duration: 14 months for enrollment, 17 months for completion
(Participants at Wake Forest will be asked to return once ≥ 6 months following completion of brain irradiation for quality of life and cognitive function tests.)

Key: FACT-BR; FACIT-F – fatigue subscale of FACT; BFI – Brief Fatigue Inventory; ESS – Epworth Sleep Scale

TABLE OF CONTENTS

Page

COVER PAGE i
SCHEMA iii

1. OBJECTIVES
1.1 Primary Objectives 1
1.2 Secondary Objectives 1

2. BACKGROUND
2.1 Study Disease 1
2.2 Study Agent 4
2.3 Cognitive Function and Quality of Life Assessments 4
2.4 Rationale 5

3. SUMMARY OF STUDY PLAN
3.1 Study Design 6
3.2 Number of Participants 6
3.3 Study Population 6
3.4 Intervention Plan 6
3.5 Study Assessments 6

4. PARTICIPANT SELECTION
4.1 Inclusion Criteria 6
4.2 Exclusion Criteria 7
4.3 Inclusion of Women and Minorities 8
4.4 Recruitment and Retention Plan 9

5. AGENT ADMINISTRATION
5.1 Dose Regimen and Dose Groups 10
5.2 Armodafinil Administration 10
5.3 Contraindications 10
5.4 Concomitant Medications 10
5.5 Dose Modification 10
5.6 Adherence 10

6. PHARMACEUTICAL INFORMATION
6.1 Study Agent 11
6.2 Reported Adverse Events and Potential Risks 11
6.3 Availability 13
6.4 Agent Ordering and Distribution 13
6.5 Agent Accountability 13
6.6 Packaging and Labeling 14
6.7 Storage and Handling 16
6.8 Registration and Randomization 17
6.9 Unblinding Methods 18

7. CLINICAL EVALUATIONS AND PROCEDURES
7.1 Schedule of Events 19
7.2 Baseline Assessment 19
7.3 Evaluation During Study Brain RT.....19
7.4 Evaluation at Completion of Brain RT 19
7.5 Evaluation 4 Weeks Following Completion of Brain RT.....19
7.6 Certification Requirements and Procedures for Neurocognitive Testing.....20
7.7 Study Parameters Table……21

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION 21
8.1 Primary Endpoint 22
8.2 Secondary Endpoints.....22
8.3 Off Treatment Criteria 22
8.4 Off Study Criteria 22

9. SPECIMEN MANAGEMENT …… N/A

10. REPORTING ADVERSE EVENTS
10.1 Adverse Events ……23
10.2 Serious Adverse Events ……24

11. STUDY MONITORING
11.1 Data Management Schedule 27
11.2 Case Report Forms 27
11.3 Source Documents.....27
11.4 Data and Safety Monitoring Board.....28
11.5 Record Retention 28
11.6 CDUS Reporting…….. 28

12. STATISTICAL CONSIDERATIONS.....28
12.1 Study Design/Endpoints 29
12.2 Sample Size/Accrual Rate.....30
12.3 Randomization and Stratification 30
12.4 Primary Endpoints.....30
12.5 Secondary Endpoints 30
12.6 Reporting and Exclusions.....31
12.7 Evaluation of Toxicity 31
12.8 Evaluation of Response.....31
12.9 Interim Analysis.....32

REFERENCES 33

APPENDICES

APPENDIX 1
Data Submission Checklist .....

APPENDIX 2
Eligibility Checklist……. …..……..

APPENDIX 3
Performance Status..……

APPENDIX 4
Medication Diary …….. ……..

APPENDIX 5
Med Watch ……..

APPENDIX 6
Flow Sheet ..……

APPENDIX 7
Toxicity Assessment Sheet.……

APPENDIX 8
Current Medication Form……..

APPENDIX 9
Baseline Test Booklet……..

APPENDIX 10
End RT Test Booklet ……

APPENDIX 11
4 Week Post RT Test Booklet……

APPENDIX 12
Monoamine Oxidase Inhibiting Drugs ……...

APPENDIX 13
Radiation Therapy Summary ……..

APPENDIX 14
Brief Fatigue Inventory……

APPENDIX 15
Telephone Contact Form ……..

APPENDIX 16
6 Month Post RT Test Booklet……

1. OBJECTIVES

1.1 Primary

1.1.1 To estimate accrual, adherence, retention, and participation of primary brain tumor patients undergoing partial- or whole-brain RT who are randomized to receive armodafinil (150mg/daily), a CNS stimulant, or placebo.

1.1.2 To estimate the variability of fatigue, quality of life, and neurocognitive function in this patient population.

1.2 Secondary

1.2.1 To obtain a preliminary estimate of the effect of armodafinil on fatigue, as primarily measured by the fatigue subscale of the FACIT-F and secondarily by the Brief Fatigue Inventory (BFI), in primary brain tumor patients who have undergone whole or partial brain irradiation.

1.2.2 To estimate the rates of toxicity and adverse events associated with armodafinil.

1.2.3 To obtain preliminary estimates of the effect of armodafinil on sleepiness measured by the Epworth Sleep Scale, overall quality of life and brain-specific quality of life measured by the FACT-G with the brain (Br) subscale, and cognitive function measured by a comprehensive Wake Forest Cognitive Function Battery.

Wake Forest Participants Only:

1.2.4 To obtain preliminary data on Implicit Sequence Learning in patients that have received whole or partial irradiation for a primary brain tumor as measured by the Serial Reactive Tasks (SRT).

2. BACKGROUND

2.1 Study Disease

Each year in the United States, approximately 17,500 primary brain tumors are diagnosed. The most common types of primary brain tumors are the astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas, which can be low-grade or anaplastic. Following surgery, all patients with anaplastic astrocytoma and glioblastoma multiforme and most patients with low-grade gliomas will receive radiation therapy, typically 5000-6000 cGy over 5-6 weeks. The median survival times are 5-10 years for low-grade gliomas, 2-5 years for anaplastic astrocytomas, and 1 year for glioblastoma multiforme (1).

The impact of primary and metastatic brain tumors on QOL and neurocognitive function can be divided into three categories: global effects, left hemisphere effects, and right hemisphere effects. Archibald et al, Scheibel et al, and Taphoorn et al have reviewed these effects (2-4). Global effects of brain tumors include fatigue, drowsiness, decreased motivation, apathy, decreased memory (particularly short term), decreased concentration, depression, and anxiety. Left hemisphere tumors affect speech and language and verbal intellectual function (including verbal learning, memory, and reasoning) as well as right sided dexterity. Right hemisphere tumors affect visual-perceptual skills (including facial recognition) and left-sided dexterity.

The acute side effects of radiation are defined as those occurring during and up to three months following treatment (5). The acute toxicity of brain radiation has been reviewed by Scheibel et al and Kiebert et al, and includes fatigue, malaise, decreased physical functioning and overall well being, and decreases in concentration, (short term) memory, and graphomotor speed (3,6). Eardley reviewed the acute side effects in 39 patients with head and neck cancer receiving

radiation therapy, the treatment fields of which typically encompass the lower quarter to third of the brain in order to adequately cover the lymph nodes in the upper cervical regions and skull base. Symptoms were assessed at baseline, the end of radiation therapy, and 7 weeks after completing RT. The most common side effects were fatigue, reported in two-thirds of patients, and depression, seen in 47%. During the interval between the end of radiation and 7 weeks later, 53% of patients reported that their side effects were worse, 70% reported that side effects were still noticeable, and 70% were not back to baseline activity, mostly because of persistent fatigue. At 7 weeks, 40% of patients still had significant side effects (7).

The Comprehensive Cancer Center of Wake Forest University (CCCWFU) Community Clinical Oncology Program (CCOP) Research Base recently published the results of a Phase III trial in brain tumor patients using methylphenidate (8). Methylphenidate is a mild CNS stimulant approved for use in patients with attention deficit disorder and narcolepsy. It is rapidly absorbed from upper small bowel intestine and rapidly penetrates the blood-brain barrier (9,10). Methylphenidate is also widely used as a therapeutic agent in brain tumor patients. It has been shown in open-label phase 2 studies to decrease fatigue, improve mood, enhance cognitive function, and increase quality of life (QOL)(11,12). In the CCCWFU CCOP study, methylphenidate was given prophylactically to patients, i.e., it was administered at the onset of RT. The study was double-blind and placebo-controlled, randomizing patients with primary or metastatic brain tumors receiving at least 25Gy partial- or whole-brain RT to methylphenidate versus placebo. Between 2002 and 2005, a time when the CCCWFU CCOP Research Base had >50% fewer participating CCOPs, 68 adults were entered on the study and randomized to methylphenidate or placebo twice daily, which was given during radiation (2-3 weeks for metastatic brain tumor patients, 6 weeks for primary brain tumor patients) and for 8 weeks afterwards, followed by a 4 week washout period during which patients were tapered off methylphenidate or placebo. QOL was assessed using the general Functional Assessment of Cancer Therapy (FACT) (13), with the addition of the Brain Subscale (FACT-BR)(14) and the Fatigue Subscale (FACIT-F)(15). Higher scores represent better QOL for the FACT and its subscales. In addition, the Center for Epidemiologic Studies Depression Scale (CESD) was used to assess depressed mood)(lower scores represent less depression)(16). Global cognitive function was measured with the Mini Mental State Exam (MMSE) (higher scores represent higher cognitive functioning) (17). Patients were evaluated at baseline, the end of RT, then 4, 8, and 12 weeks following the end of RT. The primary outcome for this study was fatigue (FACIT-F) with the secondary outcomes being global QOL (FACT), brain-specific QOL (FACT-BR), depression (CESD) and cognitive function (MMSE). Unfortunately, the study closed prematurely due to withdrawal of support from the sponsoring drug company. In summary, there were no significant differences in the mean fatigue subscale score (MFSS) from the FACIT-F between the methylphenidate and placebo treated patients at baseline, end of RT, or at 4 or 8 weeks following the end of RT. The MFSSs were 34.6, 31.0, 29.1, and 31.7, respectively. Despite this being a negative study, the results do provide important information about baseline and RT-induced fatigue in brain tumor patients. First, with a mean baseline MFSS of 34.6, this population of patients can be characterized as fatigued. In the original publication validating the FACIT-F, the MFSS was 36.76 for the study population of fatigued cancer patients (15). Second, MFSS decreased from baseline to end of RT by 3.6 and from baseline to 4 weeks after the end of RT by 5.5, both of which can be considered clinically significant reductions in the MFSS (i.e., clinically significant increases in fatigue)(18). There were no significant differences between treatment arms for any of the secondary outcomes either. Thus, we concluded that the prophylatic use of the CNS stimulant methylphenidate did not improve in QOL in brain tumor patients undergoing RT.

Modafinil is a wakefulness promoting drug FDA-approved in the United States for excessive daytime sleepiness associated with narcolepsy in adults. The precise mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions like sympathomimetic agents including amphetamines and methylphenidate, although the

pharmacologic profile is not identical to that of sympathomimetic amines. At pharmacologically relevant concentrations, modafinil does not bind to most potentially relevant receptors for sleep/wake regulation, including those for norepinephrine, serotonin, dopamine, GABA, adenosine, histamine-3, melatonin, or benzodiazepines. Modafinil also does not inhibit the activities of MAO-B or phosphodiesterases II-V. Modafinil is not a direct- or indirect-acting dopamine receptor agonist and is inactive in several in vivo preclinical models capable of detecting enhanced dopaminergic activity. In vitro, modafinil binds to the dopamine reuptake site and causes an increase in extracellular dopamine, but no increase in dopamine release. In a preclinical model, the wakefulness induced by amphetamine, but not modafinil, is antagonized by the dopamine receptor antagonist haloperidol. Modafinil does not appear to be a direct or indirect alpha-adrenergic agonist. Although modafinil-induced wakefulness can be attenuated by the a_1-adrenergic receptor antagonist prazosin, in assay systems known to be responsive to a_1-adrenergic agonists, modafinil has no activity. Modafinil does not display sympathomimetic activity in the rat vas deferens preparations (agonist-stimulated or electrically stimulated) nor does it increase the formation of the adrenergic receptor-mediated second messenger phosphatidyl inositol in *in vitro* models. Unlike sympathomimetic agents, modafinil does not reduce cataplexy in narcoleptic canines and has minimal effects on cardiovascular and hemodynamic parameters. The major route of elimination (~90%) is metabolism, primarily by the liver, with subsequent renal elimination of the metabolites. Urine alkalinization has no effect on the elimination of modafinil. Because modafinil is a reversible inhibitor of the drug-metabolizing enzyme CYP2C19, co-administration of modafinil with drugs such as diazepam, phenytoin, and propranolol, which are largely eliminated via that pathway, may increase the circulating levels of these compounds. In addition, in individuals deficient in the enzyme CYP2D6 (i.e., 7-10% of the Caucasian population; similar or lower in other populations), the levels of CYP2D6 substrates such as tricyclic antidepressants and selective serotonin reuptake inhibitors, which have ancillary routes of elimination through CYP2C19, may be increased by co-administration of modafinil. Coadministration of modafinil with other CNS active drugs such as methylphenidate and dextroamphetamine does not significantly alter the pharmacokinetics of either drug (19).

From a clinical perspective, the effects of modafinil in reducing sleepiness were initially shown in two prospective randomized placebo-controlled clinical trials (20,21). Subsequent clinical trials have shown other effects for modafinil: elevating mood by reducing anxiety in normal volunteers (22), reducing the persistent fatigue and excessive sleepiness associated with major depression (23), and reducing the fatigue associated with multiple sclerosis (24). In cancer patients undergoing chemotherapy with self-reported fatigue, modafinil 200mg/day in a prospective, placebo-controlled clinical trial, significantly reduced fatigue, particularly for patients with severe baseline fatigue (25). In addition, modafinil had a significant beneficial effect for sleepiness (but not depression) in these patients.

There have been two prospective studies of modafinil in primary brain tumor patients, the results of which were recently presented at the November 2008 annual meeting of the Society for Neuro-Oncology by Kaleita et al from UCLA (26, 37, 38). Thirty patients with primary brain tumors who had undergone surgery (100%), radiation therapy (87%) and chemotherapy (70%) were entered on a randomized, double-blind (but not placebo-controlled) study to receive a three-week course of low-dose modafinil (200mg/day) or high-dose modafinil (400mg) in divided doses. Patient characteristics were as follows: 60% AA or GBM, 33% low-grade glioma, 7% other; 47% frontal, 30% temporal, and 13% parietal tumors. Patients had to have self-reported moderate to severe fatigue and/or attention/memory impairment. The following outcome measures were fatigue and depression: Fatigue Severity Scale, Visual Analogue Fatigue Scale, Modified Fatigue Impact Scale, and the Hamilton-Depression Scale (31 items) (HAM-D-31). The outcome measure for global quality of life (QOL) was the Clinical Global Impression (CGI) of Severity (baseline) and the CGI of Change (days 7 and 21). Outcome measures for attention/memory included: Attention Functional Index, Trail Making Test A & B, Oral and Manual Symbol Digit Modalities Test, and

Word Fluency. All outcome measures were assessed at baseline, day 7 (except the HAM-D-31), and day 21. The results were striking. At day 7, all but one of the neurocognitive measures were significantly improved and at day 21, all measures had significantly improved ($p<0.05$). Attention improved 0.41SD at day 7 and 0.6SD at day 21. Sixty-nine percent of patients reported significant improvement in CGI of Change score (of mildly, moderately, or severely impaired baseline global QOL) at day 21, particularly in younger patients and those with frontal lobe tumors. Adverse events were "modest" and included the following: headache (42%), insomnia (26%), dizziness, dry mouth and/or insomnia (23%), depressed consciousness (16%), and nausea (13%), nearly all of which were mild to moderate in severity (26). The authors concluded that "[21 days of] modafinil was essentially uniformly effective at improving neurocognitive abilities, lowering fatigue levels, and decreasing depressive symptoms (37). The second modafinil study performed by UCLA was an open-label extension of the previously reported study which included a 7 day washout period and 56 days of additional treatment. At day 28 (i.e., following 21 days of treatment and the 7 day washout period) all but one of the fatigue measures were significantly improved and at day 84, all measures had significantly improved. The improvement in attention compared to baseline was 0.66SD at day 28 and 0.9 SD at day 84. Eighty-eight percent of patients reported significant improvement in CGI of Change score (of mildly, moderately, or severely impaired baseline global QOL) at day 84, particularly in patients with frontal lobe tumors. The AE profile was identical to that of the 21-day randomized study (38). Neither the 21 day randomized study nor the 84 day open-label study showed any difference between low-dose (200mg/day) and high dose (400mg/day) modafinil.

2.2 Study Agent

Armodafinil, an alpha1-adrenoceptor agonist, the R-enantiomer of modafinil, has a longer half-life than modafinil (15 vs. 3 hours). With the longer half-life, it is theorized that lower doses of armodafinil will promote levels of wakefulness that will be similar to modafinil in terms of early-in-the-day wakefulness and better than modafinil regarding late-in-the day wakefulness. It has been shown that 150 mg armodafinil has a lower maximum plasma concentration (Cmax) than 200 mg modafinil. As such, armodafinil may have fewer side effects and a decreased incidence of CYP-related drug-drug interactions (27). Because of the efficacy-toxicity profile of armodafinil vs. modafinil, Cephalon, Inc., the pharmaceutical sponsor of this investigator-initiated study, will be using armodafinil rather than modafinil in all future Cephalon-supported clinical trials including the proposed study. The dose of armodafinil that will be used on the proposed study is based on three Cephalon sponsored studies (28-30). The primary endpoint of each study was fatigue. The investigators hypothesized that armodafinil would significantly reduce fatigue and excessive sleepiness in patients with obstructive sleep apnea (2 studies) or narcolepsy (1 study). Each study was multinational, randomized, double-blind, and placebo-controlled. The intervention duration was 12 weeks. In two studies, patients were randomized to one of three arms: armodafinil 150 mg/day, armodafinil 250 mg/day or placebo. One of the three studies had a dose escalation built in; patients on the armodafinil arms started at 50mg/day and were rapidly dose escalated to 150mg/day or 250mg/day in 50mg/day increments. Fatigue was evaluated with the Brief Fatigue Inventory (BFI), a 9-item questionnaire that uses an 11-point scale (i.e., 0–10) to assess the severity and impact of fatigue and its effect on daily life. Mild fatigue corresponds to a BFI score of 1-3, moderate fatigue 4-6, and severe fatigue 7-10 (31). Sleepiness was evaluated with the Epworth Sleep Scale (ESS)(31,32). Clinically significant sleepiness corresponds to an ESS score of $\geq$10. All three studies showed a significant reduction in moderate to severe fatigue and clinically significant sleepiness (compared to patients receiving placebo) with both dose the 150 mg/day and 250 mg/day doses of armodafinil (similar to the UCLA modafinil studies in primary brain tumor patients which failed to show any dose response between daily doses of 200 and 400mg). Effects were noted by 4 weeks and maintained over the 12 weeks of the study. Armodafinil was well tolerated with a toxicity profile similar to modafinil. Based on the Cmax and clinical data, the armodafinil dose for the proposed study will be 150 mg/day.

2.3 Cognitive Function and Quality of Life Assessments

The following is a brief description of the cognitive function assessment that will be used for this study which is a subset of the Wake Forest Cognitive Function battery (34) that includes the following tests: Verbal Fluency-Category (Animals), Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Tests Parts A and B (TMT-A and TMT-B), and Digit Span Test-Backwards. The VF-C test (39,40) measures speed of mental processing, verbal fluency, and executive functions. Subjects are asked to name as many words as possible from a specific category (animals) in 1 minute. The score on the VF-C test is the total number of words named minus repetitions. The HVLT-R (41) measures verbal learning and episodic memory. It consists of a 12-item word list which is read to subjects on three successive learning trials. Free recall scores are recorded for each learning trial. After a 20-minute interval during which subjects complete other non-interfering tasks and questionnaires they are asked to recall the target words. Lastly, a yes/no recognition task is then presented in which subjects are asked to identify all target words by responding "yes," and to reject 12 non-target words by responding "no". The HVLT has six equivalent alternate forms (42,43) to reduce practice effects across assessment sessions. Test-retest reliability of the HVLT-R is quite good (0.74). The test is brief, taking only 10 minutes to administer, and it is well-tolerated by compromised (geriatric and dementia) populations. Scores for immediate recall (total of three trials), delayed recall (total number of words recalled after 20 minutes), and recognition (total number of words correctly identified) will be the variables derived from the HVLT. The TMT-A (44) measures attention and concentration and visual motor speed and requires subjects to connect 25 numbered circles in the proper sequence (1-2-3-…) as quickly as possible. TMT-B is similar except subjects are required to connect dots in an alternating numerical and alphabetical sequence (1-A-2-B-…). TMT-B with its added complexity and set shifting requirements is a widely used measure of executive functions. The score for TMT-A and TMT-B is the total time in seconds required to complete the task. Scores can also be generated for number of errors and number of circles correctly connected. The TMT has excellent reliability and validity. The DST-B (45) assesses attention, concentration and working memory. Participants are required to repeat back spans of numbers that gradually increase in length. Seven series of two spans of each length are presented and repeated backwards. A total score is the number of correctly recalled spans.

To assess the effect of the study intervention on quality of life, several assessments will be used in the proposed study. The Functional Assessment of Cancer Therapy-Brain (FACT-Br) scale was developed to provide information about health-related QOL that is specific to brain cancer patients (23). The FACT-Br consists of 27 questions with five domains assessing physical well being (7 items), social/family well-being (7 items), emotional well-being (6 items), and daily functional well-being (7 items)(13). A 19-item brain subscale includes items specific to cancer patients with brain tumors (14) and will be our measure of subjective complaints/symptoms. The FACIT-F fatigue subscale and the Brief Fatigue Inventory (BFI) will be used to assess fatigue. The FACIT-F subscale has 13 fatigue-specific items (46). The BFI (30) is a rapid assessment of fatigue that includes several visual analogue scales as well as questions that assess the impact of the patient's fatigue on a number of aspects of quality of life. The Epworth Sleep Scale (31,32) is a measure of daytime sleepiness in which the patient records their likelihood of dozing or sleeping during a number of routine daily activities. Both the BFI and ESS have been used extensively in Cephalon's modafinil clinical trials, and for continuity, will be used in the proposed study as well.

- In addition to the cognitive testing assessed in this study, participants at Wake Forest will be completing the computer task of the Serial Reaction Time Task (SRT).

  This is a computerized task coded with in E-prime v2.0 software (Psychology Software Tools, Inc. Sharpsburg, PA) by AMP. The task is completed within 15 minutes and was designed based on the serial reaction time (SRT) task developed

by Nissen and Bullemer (1987). The task investigates the implicit learning system, which primarily relies on cortico-striatal networks (for reviews, see Forkstam & Petersson, 2005; Robertson, 2007). Implicit learning has been shown to be impaired in pre-morbid Parkinson's disease (Helmuth et al., 2000) but spared in patients with mild-cognitive impairment (Negash et al., 2007). Preliminary results in a cohort of cancer survivors post-radiotherapy to the head has shown a substantial decrease in implicit memory ability compared to sex, age-matched controls with no history of chemo- or radiotherapy (unpublished results) (48-52).

- Briefly, the SRT task investigates implicit sequence learning by having participants press keys as quickly as they can in response to cues on the screen. In essence, they are playing a 4 note keyboard. The 10 item sequence repeats itself unbeknownst to the participant 5 times per block. Participants are given a self-paced break in between each block. Following 10 blocks, participants are asked if they noticed a repeating song (transfer to explicit memory system) and are asked to "play" it. They are then assessed on an implicit recall test by completing two additional sequence blocks. The first block is the same 10 item sequence which was practiced; while the second is a novel 10 item sequence. If participants demonstrate faster response times and/or more accurate responses to the repeated sequence compared to the novel, implicit learning occurred. Response time and accuracy will serve as the dependent variables assessed in the analysis of implicit learning.

2.4 Rationale

The majority of patients with primary brain tumors will have significant symptoms of their disease and of radiation therapy +/- chemotherapy, especially fatigue that will negatively impact global QOL, neurocognitive function, and mood. Recent studies of the wakefulness-promoting drug modafinil in primary brain tumor patients have shown early and sustained significant objective improvements in QOL and cognition as well as a reduction in depression with modest toxicity using the standard- (i.e., low-) dose (200mg) of the drug. Several recent studies of the R-enantiomer of modafinil, armodafinil, have been conducted showing similar efficacy and toxicity profiles to modafinil but in narcolepsy and sleep-apnea non-cancer patients. Therefore, we propose a randomized, placebo-controlled, double-blind study of 9-11 weeks armodafinil 150mg/day in patients with primary brain tumors. The endpoints will be feasibility (accrual, adherence, and retention), global and brain-specific quality of life (especially fatigue), sleepiness, neurocognitive function, and toxicity/adverse events in patients receiving placebo versus armodafinil.

3. SUMMARY OF STUDY PLAN

3.1 Study Design

This is a feasibility study of armodafinil for brain radiation induced fatigue. Patients will be randomized 1:1 to either armodafinil 150mg/day or placebo.

3.2 Number of Participants

Fifty-four participants will be accrued, approximately half of whom will be randomized to armodafinil and half to placebo. Assuming an accrual rate of approximately 4 participants per month, we expect accrual to be completed in 14 months.

3.3. Study Population

Patients with primary brain tumors undergoing external beam cranial radiation therapy, either partial- or whole-brain radiation, must meet all three of the following criteria: 1) minimum dose 4500cGy; 2) number of fractions ≥25 and 3) minimum dose per fraction 150cGy. Concurrent chemotherapy is allowed. Prior interstitial or intracavitary chemotherapy and/or RT, as well as stereotactic radiosurgery (Gamma Knife, Linac, or Cyberknife) is allowed if ≥4 weeks prior to registration. Planned interstitial or intracavitary chemotherapy and/or RT, as well as stereotactic radiosurgery (Gamma Knife, Linac, or Cyberknife) is allowed if it will take place following the completion of all protocol treatment and followup.

3.4 Intervention Plan

Participants will be randomized 1:1 to armodafinil 150mg/day or placebo. Participants will take the study agent during brain RT (an average duration of 5-7 weeks) and for 4 weeks afterward. Thus, the study duration will be between 9-11 weeks. Participants at Wake Forest will be asked to return once ≥ 6 months following completion of brain irradiation for quality of life and cognitive function tests.

3.5 Study Assessments

After signing informed consent, patients will be screened and undergo baseline assessment with a medical history and physical examination, blood tests (CBC and CMP [including creatinine, total bilirubin, SGOT, and SGPT]), FACT-Br (i.e., FACT-G + brain subscale), FACIT-F (fatigue subscale), ESS, BFI, and cognitive function tests. After randomization to either armodafinil 150mg/day or placebo, patients will undergo daily brain RT for 5-7 weeks. The BFI will be performed weekly during brain RT. At the conclusion of brain RT and 4 weeks after the conclusion of RT, the FACT-Br and FACIT-F, ESS, BFI, and cognitive function tests will be repeated. In addition, patients will be called by the study nurse/coordinator after the completion of RT weekly for three weeks to verify compliance and evaluate adverse events.

Wake Forest participants only will be asked to return once ≥ 6 months following completion of brain irradiation for FACT-Br (i.e., FACT-G + brain subscale), FACIT-F (fatigue subscale), ESS, BFI, and cognitive function tests which will include one additional computer task of the (SRT) Serial Reaction Time Task. Participants who agree and return for this appointment will be given a $20.00 Wal-Mart gift card to assist with travel expenses.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Age ≥18 years.

4.1.2 Histologically confirmed primary brain tumor: glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, low-grade glioma, meningioma, ependymoma, and other primary brain tumor histologies.

4.1.3 Planned course of fractionated external beam cranial radiation therapy (partial or whole brain). **Note: patients can be enrolled on study after starting radiation as long as they begin study drug by their 5th treatment.**

4.1.3.1 Total dose of ≥4500 cGy.

4.1.3.2 Total number of fractions ≥25.

4.1.3.3 Fraction size ≥150 cGy each.

4.1.3.4 Prior interstitial or intracavitary chemotherapy and/or RT, as well as stereotactic radiosurgery (Gamma Knife, Linac, or Cyberknife) is allowed if ≥4 weeks prior to registration. Planned interstitial or intracavitary chemotherapy and/or RT, as well as stereotactic radiosurgery (Gamma Knife, Linac, or Cyberknife) is allowed if it will take place following the completion of all protocol treatment and followup.

4.1.3.5 Concurrent chemotherapy allowed

4.1.4 Karnofsky performance status ≥60

4.1.5 Participants must have normal marrow and organ function as defined by:

4.1.5.1 Hemoglobin ≥ 10.0 g/dL (Note: if patient becomes symptomatically anemic with Hgb<10, use of erythropoietin, and/or transfusion is allowed). Note: a CBC without a differential is allowed. There is no specified minimum WBC or platelet count, though values of WBC/platelets will be recorded.

4.1.5.2 Creatinine ≤2mg/dL.

4.1.5.3 Total bilirubin ≤2x ULN.

4.1.5.4 SGOT and SGPT ≤3x ULN.

4.1.6 Patients with prior malignancies are eligible including those receiving hormonal therapies. (Patients receiving non-hormonal therapies, such as Herceptin and other targeted agents as well as cytotoxic chemotherapy (other than chemotherapy for their primary brain tumor) are not eligible.)

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

4.2 Exclusion Criteria

4.2.1 Prior fractionated external beam cranial RT.

4.2.2 Planned use of modafinil (Provigil), donepezil (Aricept), memantine (Namenda), methylphenidate (Ritalin), amphetamine/dextroamphetamine (Adderall), ginkgo biloba, or any other cognitive function enhancing drugs. For patients who are or have used these any other cognitive enhancing drug, they must discontinue their use 2 weeks prior to registration.

4.2.3 Baseline headaches (i.e., headaches occurring in the week prior to baseline assessment) of Grade 4 severity are an exclusion criterion. Baseline Grade 1-3 headaches are acceptable. The following definitions of headache severity will be used:

- Grade 1 headaches – mild headaches, not requiring analgesics, not interfering with function or activities of daily living (ADLs)
- Grade 2 headaches – moderate headaches, requiring analgesics, not interfering with function or ADLs
- Grade 3 headaches – severe but not disabling headaches, requiring analgesics, interfering with but not preventing function or ADLs
- Grade 4 headaches – severe and disabling headaches, requiring analgesics, interfering with and preventing function or ADLs

4.2.4 Current or planned concurrent use of erythropoietin and/or transfusion (if patient becomes symptomatically anemic with Hgb<10, use of erythropoietin and/or transfusion is allowed).

4.2.5 History of allergic reaction attributed to modafinil or armodafinil.

4.2.6 Uncontrolled intercurrent illness that may cause fatigue, interfere with drug absorption, distribution, metabolism, or excretion, or limit compliance with study requirements including, but not limited to: ongoing or active infection, chronic renal insufficiency, psychiatric illness (psychosis, psychotic disorder, history of suicide attempt, or actively suicidal), or extreme social situations (e.g., transportation issues that would prevent compliance with protocol).

4.2.7 Patients with a history of cardiac issues (symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia) should,not use Armodafinil as it may cause chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG.

4.2.8 Anticipated or planned excessive consumption of coffee, tea, and/or caffeine containing beverages averaging more that 600 mg of caffeine/day (approximately 6 cups of coffee/day, 12 cups of hot tea/day, or 12 cans of cola/day).

4.2.9 Use of monoamine oxidase inhibitor (MAOIs) within the past 30 days.

4.2.10 Use of investigational drug within the past 30 days.

4.2.11 Pregnant women are excluded from this study.

4.2.12 Breastfeeding mothers are excluded from this study. There is an unknown potential risk of adverse events in nursing infants secondary to treatment of the mother with armodafinil.

4.2.13 Current Use of Plavix

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial. The anticipated number of racial/ethnic minorities is based on accrual to prior Research Base clinical trials and brain tumor symptom management protocols. In addition, primary brain tumors are uncommon in Blacks (1).

Race/Ethnicity

Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	23	3	1	0	0	27
Female	23	3	1	0	0	27
Total	46	6	2	0	0	54

4.4 Recruitment and Retention Plan

4.4.1 Recruitment

Patients will be recruited from the CCOP and non-CCOP participants in the Comprehensive Cancer Center of Wake Forest University CCOP Research Base. At present, the Research Base has 25 participating CCOPs and 5 participating non-CCOPs which together comprise over 100 community cancer centers in 12 states in the Midwest, Northeast, and Southeast U.S. Feasibility can best be assessed by examining current accrual to an ongoing research base protocol, CCCWFU 91105, Phase III Double Blind, Placebo Controlled Study of Donepezil in Irradiated Brain Tumor Patients ("Donepezil Study"). As with the proposed study, A Feasibility Study of Armodafinil for Brain Radiation-Induced Fatigue ("Armodafinil Study"), the Donepezil Study requires several assessments of quality of life, including the FACT, brain subscale, and cognitive function battery. Research nurses at participating sites must be certified to administer the cognitive function battery. In its first year of accrual, the Donepezil Study has enrolled 3 patients per month. Currently (near the end of year 2), the Donepezil study is accruing 7 patients monthly. Since the Donepezil Study is for 6 month or longer survivors of brain RT, a larger pool of patients should be eligible for the proposed Armodafinil Study, since any patient with a newly diagnosed primary brain tumor meeting the other eligibility criteria would be a potential participant (i.e., the number of newly diagnosed primary brain tumor patients is much larger than the number of 6+ month brain tumor survivors). Thus, we have conservatively estimated accrual of 4 patients per month on the proposed Armodafinil Study. With a sample size of 54 patients, accrual should be complete in 14 months. Patients will be followed for 4 weeks following the completion of a 5-7 week course of brain RT plus daily armodafinil or placebo. After the 4 week post-RT visit, the patient is no longer followed and data is no longer collected except for Wake Forest patients who agree to return for an additional quality of life assessment and cognitive function battery $\geq$ 6 months after completion of brain irradiation.

4.4.2 Adherence and Retention

During study recruitment, patients will be thoroughly advised of the importance of taking their study pills once a day. Patients will be counseled to take their study pills in the morning and/or when they take other daily medications. Once the patient has been enrolled on the protocol and has begun the intervention, the patients will be asked to mark on a weekly medication diary whether they took the medication each morning as recommended. A comment field is also available for patients to indicate what side effects, if any, they observed as a result of the study medication.

During RT, patients will be asked to bring their weekly medication diary to the clinic when they have RT, so that the form may be reviewed by the clinic nurse/study coordinator. Patients will be asked if they encountered any difficulties in taking the daily study pills, and study coordinators will work with patients to resolve any issues they may have in taking the study pills each day. After the completion of RT until the 4 week post-RT study assessment, study participants will be called at weekly intervals by the study nurse/coordinator to record their medication adherence and encourage their ongoing participation in the trial. One of the main reasons for the weekly patient contact during the course of the study is to encourage adherence and retention. Weekly contact will alert a study coordinator regarding barriers to full adherence and retention, and place them in a better position to work with patients and their families to resolve any participation issues. This is particularly important for patients who do not tolerate the study pills, and stop that portion of the study requirements, but for whom

we would still like to complete their study questionnaires and cognitive assessment tests at the prescribed intervals.

At the study assessment 4 weeks post-RT completion, the patients will be asked to bring completed medication diaries to the clinic, as well as the remaining bottle(s) of study pills. A pill count will be performed to verify the patient-recorded information in their medication diary.

5. AGENT ADMINISTRATION

5.1 Dose Regimen and Dose Groups

Patients will be 1:1 randomized to receive the study agent, either armodafinil 150mg/day (taken as three 50mg pills) or three placebo pills/day. Either agent will be taken once each morning, 7 days per week, on an outpatient basis, beginning as early as possible following the onset of brain RT (but no later than the 5th fraction of brain RT) and ending 4 weeks after the last day of RT. Since patients will receive between 5-7 weeks of brain RT, they will take the study agent for approximately 9-11 weeks.

5.2 Armodafinil Administration

The Armodafinil pills used for this study will be 50mg each. Matching placebo pills will be provided. The once daily morning dose by mouth before 8:00 am and 30 minutes prior to breakfast will be three pills of either Armodafinil or placebo, as described in Section 5.1.

5.3 Contraindications

Excessive caffeine intakedefined as follows: Anticipated or planned consumption of coffee, tea, and/or caffeine containing beverages averaging more than 600 mg of caffeine/day (approximately 6 cups of coffee/day, 12 cups of hot tea/day, or 12 cans of cola/day) is a contraindication,.

Patients taking Plavix (clopidogrel) should not use this study drug. Plavix is a pro-drug that needs to be metabolized by 2C19 to its active form. If patients take Plavix with Armadafinil (a CYP2C19 inhibitor) then the efficacy of the Plavix is compromised. CYP2C19 Inhibitors may decrease serum concentrations of the active metabolite(s) of Clopidogrel. Combination should be avoided..

5.4 Concomitant Medications

Patients currently using Decadron must have dose documented on flow sheet weekly.

Beyond the concomitant medication disallowed in the study exclusion criteria (Section 4.2), the only other contraindication is excessive caffeine intake. All medications (prescription and over-the-counter), vitamin, mineral, herb, and any other botanical / natural product supplements taken by the participant will be documented in the current medication form.

Administration of Armodafinil may result in moderate induction of CYP3A activity and moderate inhibition of CYP2C19 activity. A dose reduction of drugs that are substrates for CYP3A (Ie: cyclosporine, ethinyl estradiol, midazolam, phenobarbital and triazolam) or CYP2C19 (Ie: omeprazole, diazepam, phenytoin, clomipramine, warfarin and propanolol) may be necessary for patients treated with Armodafinil [47]**.** Grapefruit juice may also be a potent CYP3A4 inhibitor. This list is not exhaustive. Patient's medications should be reviewed carefully.

Armodafinil may decrease the effectiveness of hormonal contraceptives such as birth control pills, patches, rings, implants, injections and IUDs. It is recommended that patients use non-

hormonal contraceptives, in addition to or in place of hormonal contraceptives, during and for one month following treatment with Armodafinil.

5.5 Dose Modification

There are no dose modifications. If patients do not tolerate the study agent, they will be taken "off treatment" but remain on study to continue providing data. Missed doses do not need to be made up however they should be recorded in the medication diary. Patients who miss doses, regardless of the number of missed doses, will remain on study.

5.6 Adherence

5.6.1 Adherence will be estimated as: 1) the proportion of pills taken while on treatment and 2) the proportion of the total number of pills that could be taken if the participant completed the study. We will calculate and report the mean adherence across all individuals as well as the proportion of patients who were 75% adherent (using both definitions of adherence). The primary analyses will include all randomized participants, regardless of adherence. Secondary analyses will be done using participants who were at least 75% adherent, separately using each definition.

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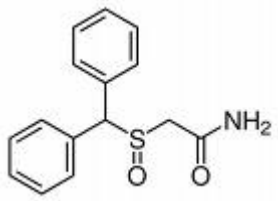
5.6.2 To determine patients' adherence with the study agent, a medication diary will be utilized. In addition, at the completion of the study, remaining bottle(s) of study agent will be collected from the patient and a pill count will be performed to verify the patient-recorded information in their medication diary.

6. PHARMACEUTICAL INFORMATION

Note: the information in this section has been abstracted from the Armodafinil Investigator's Brochure (34). Background information on Armodafinil is provided in Section 2.2.

6.1 Armodafinil

Armodafinil (also referred to as CEP-10953 and R-modafinil, Chemical Abstract Service number 112111-43-0) is the levorotatory (R) enantiomer of the racemic compound modafinil. It is a white to off-white crystalline powder. Armodafinil film-coated tablets contain 50mg of armodafinil and six inactive ingredients. The tablet coating contains three inactive ingredients and a colorant. The chemical structure of armodafinil is shown below:



Like modafinil, armodafinil is a wakefulness-promoting agent. Modafinil tablets are marketed worldwide for a number of indications under various brand names; armodafinil is not yet marketed. In the U.S., modafinil and armodafinil are approved to improve wakefulness in patients with excessive sleepiness associated with obstructive sleep apnea/ hypopnea syndrome, narcolepsy, and shift work sleep disorder; for patients with obstructive sleep apnea, modafinil and armodafinil are indicated as adjunctive treatment to standard therapy for the underlying obstruction. Armodafinil is readily absorbed after oral administration. Peak plasma concentrations are attained at approximately 2 hours in the fasted state. Elimination is slow, with a mean apparent terminal half-life of approximately 15 hours. The apparent steady state of armodafinil is reached within 7 days. Armodafinil is metabolized via multiple pathways. The

most rapid is not related to the cytochrome P450 system. As a result, it is unlikely that concomitant medications will have a substantive effect on the overall pharmacokinetic profile of armodafinil due to cytochrome p450 inhibition. The efficacy of armodafinil has been established in multiple phase I, II, and III clinical trials in patients with excessive sleepiness associated with obstructive sleep apnea/ hypopnea syndrome, narcolepsy, and shift work sleep disorder.

6.2 Reported Adverse Events and Potential Risks

Animal studies have shown that armodafinil is generally well tolerated and does not consistently produce any specific target-organ toxicity. Armodafinil has been used in six Phase III studies with 60% of patients receiving at least 12 months of drug and 40% at least 6 months. The total exposure to armodafinil in these studies is ~1000 patient-treatment years. Most adverse events seen with armodafinil in these Phase III studies were mild to moderate in severity, self-limiting, and required no action in regard to study drug administration. Toxicities reported in at least 5% of patients included:

- Headache – 24%
- Insomnia – 13%
- Nasopharyngitis – 11%
- Nausea – 10%
- Anxiety – 8%
- URI – 8%
- Dizziness – 7%
- Sinusitis – 6%
- Arthralgia – 6%
- Flu-like symptoms, diarrhea, dry mouth, back pain, rash and hypertension – 5% each

Note: headache, insomnia, nausea, and anxiety were the most likely toxicities to be reported in the first month of armodafinil treatment.

In total, 13% of patients had at least one SAE. Headache was reported as severe in 2% of patients; all other SAEs occurred in less than 1% of patients. The most common treatment-related AEs were:

- Headaches – 19% (severe in 1%)
- Insomnia – 11%
- Nausea – 7%
- Dizziness – 6%
- Anxiety – 6%
- Dry mouth – 5%

Rare but Serious: (<2%)

- Severe Headaches
- Severe Allergic Reaction
- Swelling
- Increased risk of suicidal thoughts
- Habit-forming
- Stevens-Johnson Syndrome:

Stevens-Johnson syndrome is a rare, serious disorder in which your skin and mucous membranes react severely to a medication or infection. Often, Stevens-Johnson syndrome begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters, eventually causing the top layer of your skin to die and shed. Stevens-Johnson syndrome is an emergency medical condition that usually requires hospitalization. Recovery after Stevens-Johnson syndrome can take weeks to months, depending on the severity of your condition. If you develop Stevens-Johnson syndrome and your doctor determines that it might have been caused by the study medication, you'll need to discontinue it.

Overall, 15% of patients discontinued armodafinil due to AEs, three-quarters of which were considered treatment-related. The most frequent AEs leading to discontinuation were headache (2%), anxiety (1%), nausea (1%), and insomnia (1%). All other AEs leading to discontinuation occurred in <1% of patients.

Changes in blood pressure and serum chemistries were minimal and clinically insignificant in armodafinil treated patients.

Although Armodafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking or motor skills. Patients should be cautioned about operating an automobile or other hazardous machinery until reasonably certain that Armodafinil therapy will not adversely affect their ability to engage in such activities.

6.3 Availability

Armodafinil (and matching placebo) pills will be manufactured and supplied by Cephalon, Inc., Frazer, PA. The study agent will be directly supplied to Biologics, Inc., Cary, NC, who will distribute to participating sites located within North Carolina. Cephalon, Inc. will maintain a supply of armodafinil and placebo for dispense to patients registered to the study outside of North Carolina as described in Section 6.6.

6.4 Agent Ordering and Distribution

Cephalon, Inc. will provide Biologics, Inc with armodafinil 50mg pills and matching placebo free of charge. Biologics, Inc will distribute study drug/placebo directly to participating sites located in North Carolina following randomization of study patients. The contact at Biologics, Inc is:

Kathleen Reitzel , CPh.T.
Clinical Trial Project Manager
Clinical Trial Services
Biologics, Inc.
120 Weston Oaks Court
Cary, NC 27513

T • 800.693.4906

D • 919.459.4993
F • 919.256.0794

Cephalon, Inc. will distribute study drug/placebo directly to participating sites located outside of North Carolina following randomization of study patients. The contact at Cephalon, Inc is:

Coleen Myers
Clinical Research Manager
Cephalon Inc.
Medical Affairs, Oncology
(P) 610-738-6686
(F) 610-883-5566

6.5 Agent Accountability

Each participating CCOP site will maintain a careful record of the inventory and disposition of the study agents received (armodafinil or placebo pills) using the NCI Drug Accountability Record Form (DARF). This will include adequate records of receipt, dispensing, quantities, dates and final disposition of study agent. Participating sites outside the state of N.C. must also complete patient information on the study drug label upon receipt. A confirmation of completion of this process must be sent to Biologics at 919-256-0794 and maintained in the study records.

6.6 Packaging and Labels

The Armodafinil and placebo pills will be shipped from Cephalon, Inc. and Biologics, Inc. directly to participating CCOP sites. The study intervention is provided to participants at no cost.

6.6.1 Summary

The study will remain open approximately 17 months or until all 54 patients have been accrued and complete the study. Biologics, Inc. and Cephlon will send, to the participating site, the 11 week supply for each patient randomized to the study .

6.6.2 Packaging

- **Patients Registered WITHIN North Carolina**
  Biologics, Inc. will be providing study drug to all patients who are registered <u>within</u> the state of North Carolina. Biologics will prepare and ship study drug for each of the patients randomized directly-to-site for dispensing. Drug supply will be sent in 3 shipments. Biologics will follow up with each site before each subsequent shipment to confirm the treatment and clarify shipping information. Bottles are prepared as follows:

  - **Bottle #1: 30 day supply (90pills)**
  - **Bottle #2: 30 day supply (90 pills)**
  - **Bottle #3: 17 day supply (51 pills)**

  For easy identification at the site, Biologics will place a patient-specific label including:

  - Protocol Number
  - Patient's name/initials
  - Doctor's name
  - Administration instructions/signatures
  - Kit Number
  - Dispense date
  - Expiration date
  - RX Number
  - Storage instructions

- **Patients Registered OUTSIDE of North Carolina**
  Cephalon will be providing study drug to all patients who are registered <u>outside</u> of the state of North Carolina. Cephalon will prepare and ship the entire supply of study drug

for each of these patients randomized. Drug supply will be sent in 4 bottles and be shipped direct-to-site for dispensing. Biologics will follow up with each site before each shipment to confirm the treatment and arrange the shipment. Bottles are prepared as follows:

- **4 Bottles, 60-ct Pills to cover entire treatment**

For easy identification at the site, Cephalon will place a patient-specific label including:

- Protocol #/ brief name
- Patient's name/initials *(left blank - site to complete upon receipt)*
- Doctor's name *(left blank - site to complete upon dispense to patient.)*
- Investigator's Name *(left blank - site to complete upon dispense to patient.)*
- Administration instructions/signatures
- Kit Number *(left blank - site to complete upon dispense to patient.)*
- Dispense date
- Expiration date
- Storage instructions

Documentation sent with the study drug will indicate the Patient for which the study drug is dispensed.

6.6.3 Enrollment and Processing (Patient Kit Preparation)

When a new patient is enrolled to the study, Biologics, Inc will receive an email notification of the enrollment and randomization.

- For Patients enrolled **WITHIN North Carolina,** the enrolling site will fax the signed prescription for 90 pill with 2 refills to Biologics, Inc. at 919-256-0794. If the patient is registered **within** North Carolina, Biologics will contact the site to confirm that the registration was received, the prescription was received, obtain patient specific information, and arrange the shipment date.

  Biologics prepares and ships a "Patient Kit" that includes:
  - **Bottle #1:** 30 day supply (90 pills)
    At day 15, Biologics will contact site and arrange a second shipment of the following:
  - **Bottle #2:** 30 day supply (90 pills)
    At day 45, Biologics will contact site and arrange a second shipment of the following, to complete treatment:
  - **Bottle #3:** 17 day supply (51pills)

  Upon each receipt of study drug, the site will complete and fax a confirmation of receipt to Biologics, Inc.

  A clinical pharmacist/research coordinator checks off package for accuracy of contents. 21 CFR Part 11 accountability records including date of dispense, lot number, unique patient identifier, quantity dispensed and remaining inventory balance are completed with each order. All accountability records are stored in a secured area throughout the duration of study.

- If the patient is registered **outside** of North Carolina, Biologics will contact the site to confirm that the registration was received, obtain patient specific information, and arrange the shipment date.

  During registration please fax the following items to Cephalon at (610) 883-5566 in order to receive study drug.
  1. DEA License of Patient's Physician
  2. Pharmacy License (if pharmacy will be receiving Armodafinil)
  3. CCOP Shipping Information (Include: name, address, department, phone number etc)
  4. Curriculum Vitae or Biosketch of Patient's Physician

  Biologics then creates a Drug Request Form and sends to Cephalon for study drug dispense. The Drug Request Form will contain the site shipping address, patient specific information, and 'Patient Kit Number' to be dispensed.

  Cephalon will pull the requested "Patient Kit" that includes the entire supply of study drug (or placebo) and ship with the Biologics provided packing slip, direct to site. Upon receipt, the site will complete the patient specific label to include the patient's name, doctor's name, kit number and dispensing date. The site will fax a confirmation of this process to Biologics, Inc. **919-256-0794**

6.6.4 Expedited Delivery and Logistic Services

Biologics ships study drug "same day" for orders received before 2:00 p.m. EST Monday through Thursday. Orders received after 2:00 p.m. Monday through Thursday will be processed the next business morning. All shipments are sent via Federal Express Second Day Delivery. Biologics distribution team monitors packages throughout duration of transit via Federal Express website.

Study materials shipped from Cephalon, Inc will be sent via Overnight Delivery for orders received before 2:00 p.m. EST Monday through Thursday. Orders received after 2:00 p.m. Monday through Thursday will be processed the next business morning. All shipments are sent via Overnight Delivery.

6.6.5 Communications

Upon notification of a new patient registration, Biologics places an outbound call to the site contact confirming their shipment is being processed, while providing the courier, date and time of anticipated delivery. Throughout the course of the study, a 24/7/365 clinical hotline support, staffed with clinical pharmacists, is made available in the event an investigator or site coordinator has a question or emergency unblinding is required. Unblinding methods are provided in section 6.9.

6.6.6 Drug Destruction/Disposal

At the conclusion of the study, clinical sites will document remaining drug and destroy remaining study agent on-site using their site's institutional guidelines. Biologics will return any remaining study agent to Cephalon, Inc. or destroy it per their own guidelines. Destruction of study agent should be documented using the NCI DARF (see Section 6.5).

6.7 Storage and Handling

Armodafinil pills for sites within N.C. are supplied as 50mg pills in 90, 90 and 51 count bottles. Armodafinil pills for sites outside of N.C. are supplied as 50mg pills in (4) 60 count bottles. They should be stored at 20 to 25°C (between 68 and 77°F).

6.8 Registration/Randomization

6.8.1 Registration Process

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office, Attn: Site Coordinator, prior to patient registration. The fax number is (336)716-6275.

Fill out Appendix 2, "Eligibility Checklist/ Registration Form". Use this to complete the on-line registration.

Online Registration Log on to the Comprehensive Cancer Center of Wake Forest University (CCCWFU) Research Base registration web site at <http://www.phsapps.wfubmc.edu/CCRBIS/Login/defaultlogin.cfm>. Enter your user name and password (which may be obtained by contacting June Fletcher-Steede at jsteede@wakehealth.edu.) In the 'Patient Registration and Protocol Information' table, click the 'Register Patient/Patient Info', with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the drop down boxes. If further information is needed by Biologics or Data Management, they will contact you. Once the patient information has been entered online, print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. Print the confirmation sheet for your records. The CCCWFU On-line Protocol Registration/Eligibility form, initial flow sheet, signed consent, histology reports, scan reports and lab reports (as required in protocol) should be faxed to 336-713-6476 or mailed to the Research Base Data Management Center:

Research Base Data Management Center
Department of Radiation Oncology
1st Floor Outpatient Comprehensive Cancer Center
Wake Forest University Baptist Medical Center
Medical Center Boulevard Winston-Salem, NC 27157

These forms should be retained in the patient's study file. These forms will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base Data Management Center between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-3172 or 713-6507.

Attention Sites Outside of NC:
For sites outside of NC, *during registration* please fax the following items to Cephalon at (610) 883-5566 in order to receive study drug.

1. DEA License of Patient's Physician
2. Pharmacy License (if pharmacy will be receiving Armodafinil)
3. CCOP Shipping Information (Include: name, address, department, etc)
4. Curriculum Vitae or Biosketch of Patient's Physician

6.8.2 Randomization Process

Described in Section 12.3.

6.9 Unblinding Methods

6.9.1 Unblinding During Study

In the event a patient on this study develops a toxicity (adverse event or severe adverse event) for which the patient's physician or other health care professional feels that it is in the patient's best interest to know what drug they are taking (armodafinil or placebo), the following procedure should be followed:

- Step 1: the patient's physician or a designated health care professional should call the Wake Forest University Baptist Medical Center Physician Access Line (PAL) at (336) 716-7654 and ask that Dr. Ed Shaw, Principal Investigator of the CCCWFU CCOP Research Base, be contacted immediately either in his office, by pager, or at home. In the event Dr. Shaw cannot be reached, the PAL operator should contact Dr. Glenn Lesser, Research Base Co-PI in his office, by pager, or at home. If neither Dr. Shaw nor Dr. Lesser can be reached, the PAL operator should contact Gina Enevold, GNP, Research Base Administrator, either in her office, by pager, or at home.

- Step 2: Once contact has been made; the patient's physician or health care professional should explain the reason for the request to unblind the treatment arm that the patient is on. If the Research Base representative feels that the toxicity (AE/SAE) is possibly, probably or definitely related to the study drug, then the next step will be followed.

- Step 3: The responsible Research Base representative will call the pharmacist @ Biologics, Inc. at (800) 850-4306. There is an "on-call" service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The Biologics pharmacist may contact the patients' physician and/or health care professional directly with the unblinding information. Written documentations of the unblinding process will be sent to the Research Base Principal Investigator by Biologics, Inc.

- Step 4: In the event that the patient's treatment is unblinded, that patient will be taken off study with no further study follow-up. Appropriate procedures for grading toxicities, assigning causality, and reporting adverse events and severe adverse events (if applicable) should be followed. The event will be reviewed by the CCCWFU Clinical Research Oversight Committee and Data Safety and Monitoring Board.

6.9.2 Unblinding At Study Completion

Study Participants may be unblinded at the end of their study completion or at the conclusion of the study if **all** patient specific data for the requesting site are completed and submitted to the DMC.

Site members can obtain unblinding information by sending an email request to the CCCWFU CCOP Administrator or Data Management Supervisor with a list of PID #s.

After confirming with the DMC that patient specific data for a participant/ all participants at a single site have been received and are complete, Biologics, Inc will be notified. An email from Biologics, Inc containing the unblinding information will be sent directly to the requesting site.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

At each participating Research Base site, medical charts will be screened to determine potential eligibility by physicians (including residents or fellows, if applicable), research nurses, or clinical research associates. Patients identified as potentially eligible will then be asked to consider joining the study. Patients meeting initial eligibility criteria and who agree to participate in the study will sign informed consent and then undergo a baseline history and physical exam, laboratory tests, quality of life tests, and the neurocognitive testing. Patients will be instructed in the self-administration of the study agent, which will be taken beginning as early as possible following the onset of brain RT (but no later than the 5th fraction of brain RT), continuing throughout brain RT, and ending 4 weeks after the last day of brain RT. Patients will take three pills daily, preferably in the morning. Potential side effects and risks are described in Section 6.2. Adverse event reporting is described in Section 10. Study outcomes will be assessed at baseline, prior to the onset of brain RT + study agent (quality of life and neurocognitive tests), weekly during brain RT (Brief Fatigue Index only), and at the end of brain RT and 4 weeks afterward (quality of life and neurocognitive tests).

Patients will be called by the study nurse/coordinator after the completion of RT weekly for three weeks to verify compliance and evaluate adverse events.

Participants at Wake Forest will be contacted by research staff and asked to voluntarily return for one additional quality of life and neurocognitive test battery $\geq$ 6 months following completion of brain irradiation.

7.2 Baseline Assessment

7.2.1 History, physical exam, complete blood count ,Hgb, WBC, platelets; (differential not required) and complete metabolic panel (must include creatinine, total bilirubin, SGOT and SGPT)

7.2.2 Baseline Quality of Life Testing

- Karnofsky Performance Status (KPS)
- FACT-Br (i.e., FACT-G + brain subscale)
- FACIT-F (fatigue subscale)
- Brief Fatigue Inventory(BFI)
- Epworth Sleep Scale (ESS)

7.2.3 Baseline Neurocognitive Testing

- Verbal Fluency – Category(Animals) (VF)
- Hopkins Verbal Learning Test (HVLT)
- Trail Making Test, Parts A and B (TMT-A and TMT-B)
- Digit Span Test - Backwards (DST)

7.3 Evaluations During Study Brain RT

- KPS
- BFI

7.4 Evaluations at Completion of Brain RT

- Quality of life testing – same as baseline, see Section 7.2.2
- Neurocognitive testing – same as baseline, see Section 7.2.3

7.5 Evaluation 4 Weeks Following Completion of Brain RT

- Quality of life testing – same as baseline, see Section 7.2.2
- Neurocognitive testing – same as baseline, see Section 7.2.3

7.5.1 Wake Forest patients only:

Evaluation ≥ 6 Months Following Completion of Brain RT

- Quality of life testing – same as baseline, see Section 7.2.2
- Neurocognitive testing – same as baseline, see Section 7.2.3
- Serial Reaction Time Task – described in section 2.3

7.6 Certification Requirements and Procedures for Neurocognitive Testing

All neurocognitive assessments will be conducted by trained and certified research personnel. Training and certification procedures must be completed by research staff prior to patient enrollment. Certification for administration of the neurocognitive battery will include viewing of a training video on the Wake Forest University Health Sciences website, reviewing the content of the protocol-specific test booklets including all aspects of administration and scoring, a didactic presentation of each test and questionnaire to be administered, and role-playing of administrations with Q&A and feedback. All training will be supervised by experienced test administrators (Dr. Stephen Rapp, psychologist and co-PI of this study, June Fletcher-Steede, trained/certified administrator and CCCWFU CCOP Research Base Site Coordinator, and other trained/certified administrators designated by the CCCWFU CCOP Research Base.) There are 4 ways to become certified: 1) Any research staff already trained and certified for CCCWFU Protocol 91105 (Donepezil Study) will automatically be considered certified for this study; 2) Training and certification on-site by June Fletcher-Steede (contact Ms. Steede at 336-716-6733 to schedule a training/certification visit); 3) Training and certification at the annual meeting of the CCCWFU CCOP Research Base, held each fall (contact Lisa Hawkins, Research Base Administrative Secretary at 336-716-0891) for date of next meeting.

7.7 Study Parameters Table

Baseline evaluations and labs are required within 4 weeks of registration.

Evaluation/ Procedure	Registration / Baseline	Weekly during radiation	Last week of radiation	Weeks 1, 2, 3 Post-RT	4 Weeks after end radiation	Wake Forest Patients Only > 6 months Post-RT
Informed Consent	X					
Medical History (1)	X					
Physical Exam (1)	X					
KPS	X	X	X		X	X
CBC (2)	X					
Creatinine, total bilirubin, SGOT and SGPT	X					
Serum BHCG (3)	X					
Toxicity Assessment Sheet	X	X	X	X	X	
Flow Sheet	X	X	X		X	X
Current Med Form	X	X	X		X	X
Brief Fatigue Inventory (BFI) (4) (5)	X	X	X		X	X
FACT-Br (5)	X		X		X	X
FACIT-F (5)	X		X		X	X
Epworth Sleep Scale (ESS) (5)	X		X		X	X
Cognitive Function Tests	X		X		X	X
Serail Reaction Tasks (SRT)						X
Radiation Therapy Summary			X			
Medication Diary	X	X	X	X	X	
Telephone Contact (6)				X		
Pill count (Unused Study Agent)					X	
Decadron Dose (7)	X	X	X	X	X	X

(1) Can be performed by MD, RN, NP or PA
(2) Includes hemoglobin, WBC, platelets (differential not required)
(3) Negative serum pregnancy test required within 10 days prior to registration for women of child-bearing potential.
(4) **Weekly during RT** and included in Cognitive Function test booklets.
(5) Included in Cognitive Function test booklets.
(6) Patients will be called by the study nurse/coordinator after the completion of RT weekly for three weeks to verify compliance and evaluate adverse events.
(7) For patients taking Decadron , doses are to be documented on the flow sheet weekly.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoints

The primary endpoints for this study are measures of feasibility – accrual, retention, adherence, patient availability, and agreement to participate.

1) Accrual – number of patients accrued divided by the number of months the study was open.

2) Retention – proportion of participants who complete the 4-week post-RT assessments.

3) Adherence – a) as the proportion of pills taken while on treatment; and b) as the proportion of the total number of pills that could be taken if the participant completed the study. We will calculate and report the mean adherence across all individuals as well as the proportion of patients who were 75% adherent (using both definitions of adherence).

4) Patient availability – number of patients seen at each site with primary brain tumors receiving partial or whole-brain radiation and the number of those who met the eligibility criteria. For those not meeting the eligibility criteria, reasons will be noted so that eligibility criteria can be refined in the subsequent trial.

5) Agreement to participate – proportion of eligible patients who are randomized.

6) Variability of outcome measures – variability of each outcome measure will be estimated using an ANCOVA model which includes the treatment arm and each stratification factor.

8.2 Secondary Endpoints

1) Toxicity – using the CTCAE v4.0.

2) Fatigue – quantified primarily by the fatigue subscale of the FACIT-F and secondarily by the Brief Fatigue Inventory.

3) Overall quality of life - measured by the FACT-Br.

4) Sleepiness – measured by the Epworth Sleep Scale.

5) Cognitive function – assessed using the battery of tests shown in 7.2.3.
   Wake Forest participants who agree and return $\geq$ 6 months after completion of brain irradiation will also be assessed with a computer task of the SRT (Serial Reaction Time Task).

The assessment schedule for these outcome measures is shown in section 7.7.

8.3 Off Treatment Criteria

Participants may go “off-treatment” and stop taking armodafinil for the following reasons: AE or SAE associated with intolerance of study intervention, inadequate agent supply, noncompliance, use of unacceptable concomitant medications, development of a medical contraindication, or medically necessary unblinding of study agent (see section 4.2). Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Participants who drop out before providing 4-week post RT data will be replaced. Participants who decide to discontinue treatment but agree to provide outcome data will not be replaced.

8.4 Off Study Criteria

Participants may go “off-study” for the following reasons: completed the study and any study-required follow-up, AE or SAE associated with intolerance of the study intervention, lost to follow-up, use of unacceptable concomitant medications, development of a medical contraindication, or

medically necessary unblinding of study agent (see section 4.2), withdrawal of consent, death, or other reasons as discussed/approved by study principal investigator.

9. SPECIMEN MANAGEMENT - N/A

10. REPORTING ADVERSE EVENTS

DEFINITION: An adverse event (AE) is any untoward medical occurrence in a study participant. An AE does not necessarily have a causal relationship with the treatment or study participant. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study. A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6.2.

10.1 Adverse Events (AE)

10.1.1 Reportable Adverse Events

All adverse events that occur after the informed consent is signed (including run-in) must be recorded on the adverse event CRF (paper and/or electronic) whether or not related to study agent.

Wake Forest participants who agree to return ≥ 6 months after irradiation will not have AE's and SAE's collected that occur more than 30 days after completion of study medication.

10.1.2 Adverse Event (AE) Data Elements

- AE reported date
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study agent
- Outcome of the event
- Comments

10.1.3 Severity of AEs

The CTCAE v4.0 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
4	Life threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

Activities of Daily Living (ADL) *** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.** **** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.**

10.1.4 Assessment of relationship of AE to treatment
The possibility that the adverse event is related to study drug will be classified as one of the following: not related, unlikely, possible, probable, definite.

10.1.5 Follow-up of AEs
All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

10.2 Serious Adverse Events (SAE)

10.2.1 DEFINITION: ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997 define serious adverse events as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

10.2.2 Reporting Serious Adverse Events
Adverse Event reporting begins after the patient is registered to the study. Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

1. The protocol Principal Investigator will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require notification within 24 hours of discovery.

3. Any medical event which precipitates hospitalization or prolongation of existing hospitalization must be reported regardless of attribution or whether the adverse event is expected or unexpected.

4. A written report, including all relevant clinical information and all data collection forms due up to and including the date of the event will be sent by mail or FAX to the RB DMC within 10 calendar days unless specified otherwise within the protocol. The material must be labeled:

Attention: Adverse Event Reporting

5. The Research Base Grant PI, Clinical Research Oversight Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

6. Serious adverse events will be communicated by phone and MedWatch as soon as identified to the CCCWFU Research Base Data Management Center (DMC) at (336) 713-3172. The DMC is responsible for communicating with the FDA, WFU IRB, and other regulatory agencies, as well as reporting all SAE's grade 4 or 5 to the Clinical Research Oversight Committee (CROC).

   Each participating site must report the following AEs/SAEs directly to the site IRB and to Cephalon via MedWatch form 3500A within 1 business day:

   - All SAEs in Sections 10.1 and 10.2, regardless of causality
   - All expedited AEs/SAEs of interest (e.g., serious skin rash and other hypersensitivity AEs/SAEs in adults)
   - Any exposure of a pregnant study patient to the study drug within 30 days of exposure
   - A female partner of a male study participant becoming pregnant within 30 days of exposure.
   - Any medical event which may reasonably be believed to impair the integrity, validity or ongoing variability of the study.

7. In the event that a site IRB requests additional safety information, Cephalon should be notified of the request within 1 business day.

8. Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies and to Cephalon per instruction #6 above.

9. When submitting AE, SAE reports and supporting documentation, the study number and the case number (PID #) must be recorded on the FDA Form 3500 (MedWatch) so that the case may be associated with the appropriate study file.

10.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the MedWatch form in the appropriate format. Follow-up information should be sent to the RB Data Management Center as soon as available.

SAEs for this protocol should be followed until resolved, especially for those related to the study agent.

AE Reporting Table

Reporting requirements for Adverse Events (AEs) and Serious Adverse Events (SAEs). Adverse Events occurring within 30 days of study completion must be reported via MedWatch

	MILD				MODERATE				SEVERE			
	1		1		2		2		3		3	
	Unexpected		Expected		Unexpected		Expected		Unexpected		Expected	
	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization	*With Hospitalization	Without Hospitalization
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required
Possible Probable Definite	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required

	LIFE-THREATENING/DISABLING				DEATH			
	4		4		5		5	
	Unexpected		Expected		Unexpected		Expected	
	*With Hospitalization	*Without Hospitalization	*With Hospitalization	*Without Hospitalization	*With Hospitalization	*Without Hospitalization	*With Hospitalization	*Without Hospitalization
Unrelated Unlikely	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days
Possible Probable Definite	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days

* See Section 10.2.1 for SAE Definition

CTEP, NCI Guidelines 2004

11. STUDY MONITORING

11.1 Data Management Schedule

The Eligibility checklist/Registration Form should be completed on-line prior to placing the patient on study. Data forms will be submitted to the CCCWFU CCOP Research Base. See address above or faxed to (336) 713-6476 according to the timetable below:

Form	Submission Schedule
Registration Form	At registration
Baseline Labs	Baseline
Flow Sheet	Baseline; wkly during RT; last wk RT; 4 wks after end RT
Adverse Events (SAEs and AEs)	Baseline; wkly during RT; last wk RT; wks 1, 2 and 3 Post RT, 4 wks after end RT
Current Medication List	Baseline; wkly during RT; last wk RT; 4 wks after end RT
Brief Fatigue Inventory	Baseline; wkly during RT; last wk RT; 4 wks after end RT
Baseline Assessment Booklet	Baseline
End of RT Assessment Booklet	At end of last wk of RT
4 Weeks Post-RT Assessment Booklet	4 wks after end RT
Medication Diary	Week 4, last wk RT; 4 wks after end RT
Pill count	4 weeks after end of RT
Telephone Contact	Weeks 1, 2, and 3 Post RT
Wake Forest Only: > 6 Months Post-RT Assessment Booklet	≥ 6 months after end of RT

11.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRFs).

11.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

11.4 Data and Safety Monitoring Board

The CCCWFU Data Safety Monitoring Board meets every six months to review all randomized phase II and III protocols, including those of the CCCWFU CCOP Research Base. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the statistician. Areas of review may include the following: Patient Accrual – observed vs expected; Patient Status and Retention – observed vs expected; Study Status; Last Contact Status; Patient Adherence; Patient Characteristics; Observed Toxicities/Adverse Events - Date, Event briefly described, Relationship to Drug, Arm assigned; Data quality – percent of data received and processed and missingness; Summary of Primary and Secondary Measures.

11.5 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, and NCI/DCP requirements unless the standard at the site is more stringent.

Record retention should be 2 years after the study is discontinued for studies without an IND (21 CFR 312.62).

11.6 CDUS Reporting

The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS).

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a randomized, placebo controlled, Phase II study assessing the feasibility of using armodafinil (150mg/daily), a CNS stimulant, to reduce fatigue in primary brain tumor patients undergoing whole or partial brain radiation. Patients will be stratified by Karnofsky performance status and whether or not they receive chemotherapy during brain RT and assigned with equal probability to armodafinil or placebo using random permuted block randomization. The primary objectives for this trial are: 1) to estimate accrual, adherence, retention, and participation rates and 2) to estimate the variability of fatigue, quality of life, sleep problems, and cognitive function. The secondary objectives are: 1) to obtain a preliminary estimate of the effect of armodafinil on fatigue, 2) to estimate the rates of toxicity and adverse events associated with armodafinil, and 3) to obtain preliminary estimates of the effect of armodafinil on sleep problems, overall and brain-specific quality of life, and cognitive function. Estimates of treatment efficacy will be obtained using the 'intent to treat' approach. That is, all randomized participants will be used in the analyses, regardless of whether the participants were treated according to protocol.

12.2 Sample Size/Accrual Rate

The majority of our outcome measures are estimates – estimates of accrual, retention, adherence, variability, and treatment efficacy. Increasing the sample size means we can achieve tighter estimates. However, as these are preliminary estimates that are to be used in designing a more definitive trial, it is not crucial that the estimates be exceedingly tight. Table 12.2.1 below summarizes the precision we can achieve in our estimates as a function of the sample size.

Table 12.2.1. Precision of outcomes and detectable differences as a function of the sample size

Total Sample Size	95% CI for Accrual #	95% CI for Adherence	95% CI for Retention*	Inflation Factor**	Length of 95% CI for Difference in Outcomes between Arms ***	Detectable Difference***
20	12.2-30.9	± .22	± .19	1.177	0.88	1.16
25	16.2-36.9	± .20	± .17	1.132	0.78	1.03
30	20.2-42.8	± .18	± .15	1.105	0.72	0.93
35	24.4-48.7	± .17	± .14	1.087	0.66	0.86
40	28.6-54.5	± .16	± .13	1.075	0.62	0.80
45	32.8-60.2	± .15	± .13	1.065	0.58	0.75
50	37.1-65.9	± .14	± .12	1.058	0.55	0.71

\# Exact Poisson CI; divide by number of months of accrual to get CI for monthly accrual rate.

* The CI's for retention are smaller than those for adherence because the denominator includes those patients who drop out (which are not included in the adherence estimate).

** See reference 36. This is the number by which we will need to inflate our variance estimates in designing a subsequent trial to account for the fact that we'd be using a variance estimate to calculate the sample size (assuming the subsequent trial will be designed with 90% power at the 5% two-sided level of significance).

*** In standard deviation units (assuming 80% power at the 5% one-sided level of significance).

For this trial we will accrue 40 evaluable patients. Assuming accrual lasts 14 months, the exact 95% confidence interval for the monthly accrual rate of evaluable patients based on the Poisson distribution will be 2.0 to 3.9. A sample size of 40 valuable patients will allow us to estimate retention and adherence to within ± .13 and ± .16 with 95% confidence, respectively. In addition, that number will provide estimates of the variances for our outcome measures that would only need to be inflated by 7.5% in the subsequent design of a randomized comparative trial (assuming the trial would be designed with 90% power at the 5% two-sided level of significance) (36). Furthermore, with a total of 40 evaluable patients, we can estimate the treatment effect to within ± .62 standard deviations and can detect a .80 standard deviation difference in outcomes between the treatment arms with 80% power at the 5% one-sided level of significance. For example, in the methylphenidate study described in Section 2.1, the mean fatigue score at baseline among patients with primary brain tumors was 34.0 and the standard deviation of post-RT fatigue was 5.95 (obtained using an ANCOVA model on the average of the two fatigue scores obtained immediately post-RT and four weeks after the end of RT) adjusting for baseline fatigue, age, sex, performance status). Assuming similar numbers in this trial, with a total of 40 evaluable patients, the 95% CI for the difference in fatigue between the two arms will be ± 3.7and the detectable difference will be 4.8(an approximate 14% relative difference).

We will make a concerted effort to retain participants until the end of the study. Retention will be stressed throughout the trial, and patients who refuse further therapy will be encouraged to remain in the study to provide outcome data. Assuming that 25% of these patients will be lost, we will need to accrue a total of 54 patients to this study. We anticipate that we can accrue 4 patients per month to this trial, meaning that accrual would be completed within 14 months and the entire trial would be completed within 17 months.

12.3 Randomization and Stratification

Patients will be stratified by Karnofsky performance status (60, 70, 80 vs 90, 100) and whether or not they receive chemotherapy during brain RT (Yes vs No) (4 strata in all) and assigned with equal probability to armodafinil or placebo using random permuted block randomization. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous assignments. Analyses will not be done separately by strata.

12.4 Primary Endpoints

The primary endpoints for this study are measures of feasibility – accrual, retention, adherence, patient availability, and agreement to participate – as described in Section 8.1. Accrual will be estimated as the number of patients accrued divided by the number of months of accrual. An exact 95% confidence interval for the monthly accrual rate will be calculated based on the Poisson distribution. Retention will be primarily defined as the proportion of patients who provide data 4-weeks post-RT. That is, participants who discontinue the study drug but remain in the study and complete the outcome assessments will be counted in the numerator for calculating retention. (Their adherence will be low, however.) Retention estimates will be calculated overall and by treatment arm. A Fisher exact test will be used to assess the difference in retention between the two arms. In addition, since participants drop out at varying times throughout the study, Kaplan-Meier methods will be used to estimate the time to drop-out, and a logrank test will be used to assess the difference in these distributions between treatment arms.

Adherence will be calculated 1) as the number of pills taken divided by the ideal number of pills that could have been taken while on study, and; 2) as the number of pills taken divided by the number of pills that could be taken if the participant completed the study. We will calculate and report the mean adherence across all individuals as well as the proportion of patients who were 75% adherent (using both definitions of adherence). Neither definition of adherence is perfect. The first gives a measure of the adherence while the patient is engaged in the study. The second gives a measure of the amount of ideal drug taken overall and penalizes those who drop out. The first measure of adherence, together with the retention estimates, probably provides the most accurate description of the study. For example, participants are 80% adherent while on study but only 80% complete the study. ANCOVA will be used to assess the difference in mean adherence between the two arms and a chi-square test will be used to compare the proportion of patients who were at least 75% compliant in the two arms.

Patient Availability and Participation Rate: Each site will keep a list of the number of patients seen with primary brain tumors receiving partial or whole-brain radiation and the number of those who meet the eligibility criteria. For those not meeting the eligibility criteria, reasons will be noted. These data will be important in determining if patient numbers exist to make a subsequent phase III trial feasible and if changes need to be made in the eligibility criteria to improve accrual. The number of patients who are randomized divided by the number eligible will provide an estimate of the rate of participation. This rate will be calculated separately by site to see if we can learn what does and does not work in getting patients to participate.

12.5 Secondary Endpoints

The outcome measures have been described previously in Section 7 and 8. Briefly, these include fatigue as quantified primarily by the fatigue subscale of the FACIT-F and secondarily by the Brief Fatigue Index, overall quality of life as quantified by the FACT-Br, sleepiness as quantified by the Epworth Sleep Scale, and cognitive function as assessed using the battery of tests shown in 7.2.3. These measures, for the most part, will be assessed at baseline, the last week of RT, and 4 weeks post-RT. Descriptive statistics (means, standard deviations, frequencies, etc.) will be presented for each of these outcome measures at baseline and at each follow-up point stratified by treatment arm.

ANCOVA models will be used to obtain estimates of the treatment effect for each outcome, to test for treatment differences, and to obtain adjusted estimates of the variability of these outcomes post-RT and 4 weeks post-RT. The primary ANCOVA model will include the treatment arm and the stratification factors, the latter included as covariates in the model to ensure that the analysis matches the design. Least squares means and 95% confidence intervals will be provided for each outcome, stratified by treatment arm, and for the difference between the treatment arms. Subsequent ANCOVA models will be used that include additional covariates such as age, BMI, gender, etc. These additional covariates will be included to correct for chance imbalances in important prognostic variables and account for that part of the variability in the outcome measures that is due to the covariates, thus improving the precision of the treatment effect. Regression diagnostics and residual plots will be used to find appropriate transformations for the variables in the model to ensure that the models satisfy the 1) linearity assumption, 2) homogeneity of variances assumption, and 3) normality assumption.

A repeated measures model for longitudinal data will then be used to assess the difference in the mean of the two post-randomization measures for each outcome (following RT and 4 weeks post-RT) between treatment groups assuming equal variance at each time. For this analysis, baseline fatigue will be a covariate, time and treatment will be fixed class variables, and the actual outcome measures following RT and 4 weeks subsequent to RT will be the repeated measures. With no missing data, this model is equivalent to the usual ANCOVA model of the mean of the two post-randomization outcome measurements. Least squares means and treatment differences, along with 95% confidence intervals, will be estimated at each time and for the average of the two times based on the fitted model.

Wake Forest patients will have additional measures taken ≥ 6 months post-RT. These assessments will be included in separate RM models for this subgroup of patients to assess the longer term changes over time and to assess the effect of treatment on those changes (realizing this test will have low power). Additionally, we will collect data on implicit sequence learning only at the latter time point. The outcomes will be response and accuracy measures from the Serial Reaction Tasks, and we will use these data to estimate means and standard deviations for use in designing subsequent trials using these outcomes. We will also use regression models to assess the association between implicit sequence learning and the cognitive and quality of life measures.

12.6 Reporting and Exclusions

Adherence, as defined in 12.4, is one of the primary outcomes that we will be monitoring in this study. The primary analyses estimating treatment efficacy will include all randomized patients, regardless of adherence. Drop-outs are a more difficult problem, one that is more satisfactorily handled proactively rather than retrospectively. We will make a concerted effort to minimize the number of drop-outs, beginning with the patients that are accrued. If a patient seems unwilling to participate or indicates that he may not be able to be compliant, we will not press him to participate. In addition, patients who refuse treatment at some point during the course of therapy will be encouraged to stay in the study and provide outcome data. Despite the best of efforts, some data will be missing due to missed visits, deaths, or patients refusing further participation. The primary analyses are based on maximum likelihood methods and assume patients are missing at random, that is the missingness can depend on covariates and observed outcomes but not the missing outcomes. This assumption that the missingness does not depend on the missing data cannot be tested completely since the data needed to test the assumption is missing. Exploratory analyses using multiple imputation will assess the impact of various assumptions regarding the missingness on the estimates of treatment effect.

12.7 Evaluation of Toxicity

Toxicities will be determined using the CTCAE v4.0 for Toxicity and Adverse Event Reporting, and will be evaluable for toxicity from the time of their first dose of armodafinil or placebo. It is posted on

the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

12.8 Evaluation of Response

All participants included in the study will have their outcomes assessed according to the schedule outlined in Section 7.7. Efforts will be made to collect these data even if patients refuse further treatment. Data should only be missing for those who expire or withdraw consent. As noted above, all randomized participants will be included in the primary analyses of treatment efficacy on the outcomes described above. The preliminary estimates of treatment effect and the estimates of variability that will be used in the design of a subsequent comparative trial will be based on the analyses of all the randomized patients. Secondary analyses will be performed on the participants who completed the study with good adherence, perhaps providing us with an upper bound estimate of treatment efficacy should all patients remain in the study and be adherent. This estimate is likely biased, however, and will be interpreted with caution. The reasons for excluding participants from any analysis will be clearly reported.

12.9 Interim Analysis

No interim analysis is planned for this Phase II study. However, all Research Base randomized phase II and III studies are monitored by the CCCWFU DSMB twice yearly for accrual, retention, adherence, data quality, and safety (see Section 11.4). In addition, all grade 3+ toxicities are reviewed by the Wake Forest University Comprehensive Cancer Center's Clinical Research Oversight Committee, which meets monthly.

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