COVER PAGE

DCP Protocol #: WF-97116

Local Protocol #: WF-97116

A Phase 3 Randomized Placebo Controlled Clinical Trial of Donepezil in Chemotherapy Exposed Breast Cancer Survivors with Cognitive Impairment (REMEMBER)

Research Base Name: **Wake Forest NCORP Research Base**

Name of Research Base Principal Investigator: **Glenn Lesser, MD**
Wake Forest School of Medicine
Department of Internal Medicine,
Section on Hematology and Oncology
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-0891
Fax: (336) 716-6275
E-mail address: glesser@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Protocol Principal Investigator: **Stephen R. Rapp, PhD**
Psychiatry and Behavioral Medicine
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-6995
Fax: (336) 716-6830
E-mail address: srapp@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Co-Investigator: **Heidi Klepin, MD**
Department of Internal Medicine
Section on Hematology and Oncology
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-5772
Fax: (336) 716-5687
E-mail address: hklepin@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Co-Investigator: **Edward G. Shaw, MD, MA**
Department of Internal Medicine
Section of Geriatrics and Gerontology
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 716-1034
Fax: (336) 713-5927
E-mail address: eshaw@wakehealth.edu

Organization: **Wake Forest School of Medicine**
Statistician: **Emily V. Dressler, PhD**
Department of Public Health Sciences
Department of Biostatistical Sciences
Medical Center Boulevard
Winston-Salem, NC 27157
Telephone: (336) 713-0917
Fax: (336) 716-6427
E-mail address: edressle@wakehealth.edu

Grant: 1UG1CA189824
NCI/Division of Cancer Prevention
Community Oncology & Prevention Trials Research Group
9609 Medical Center Drive, Room 5E502
Rockville, MD 20850
(240) 276-7050
IND#: Exempt - 131660
Agent(s)/Supplier: Donepezil: Vensun Pharmaceuticals
Placebo: Catalent Pharma Solutions
Protocol Amendment #: 4
Protocol Version Date: 06/07/2019

Protocol History:

Initial	Version 10/10/2016	Not Activated
Amendment 1	Version 03/23/2017	Activated 05/12/2017
Amendment 2	Version 11/29/2017	Released 02/12/2018
Amendment 3	Version 04/02/2019	Released 05/16/2019

Participating Organizations

WAKE/ Wake Forest NCORP Research Base

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
Regulatory Submission Portal:
(Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for detailed instructions.</td><td>Data will be submitted to the WF NCORP Research Base.

Address:
Wake Forest NCORP Research Base
Wake Forest Baptist Medical Center
Building 525@Vine, 4th Floor
Medical Center Boulevard
Winston-Salem, NC 27157

Phone: (336) 716-0891
Fax: (336) 713-6476
Email:
NCORP@wakehealth.edu

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page of the CTSU Members' Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> contact the Site Coordinator at the Wake Forest NCORP Research Base Protocol Information Office at NCORP@wakehealth.edu or (336)716-0891.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
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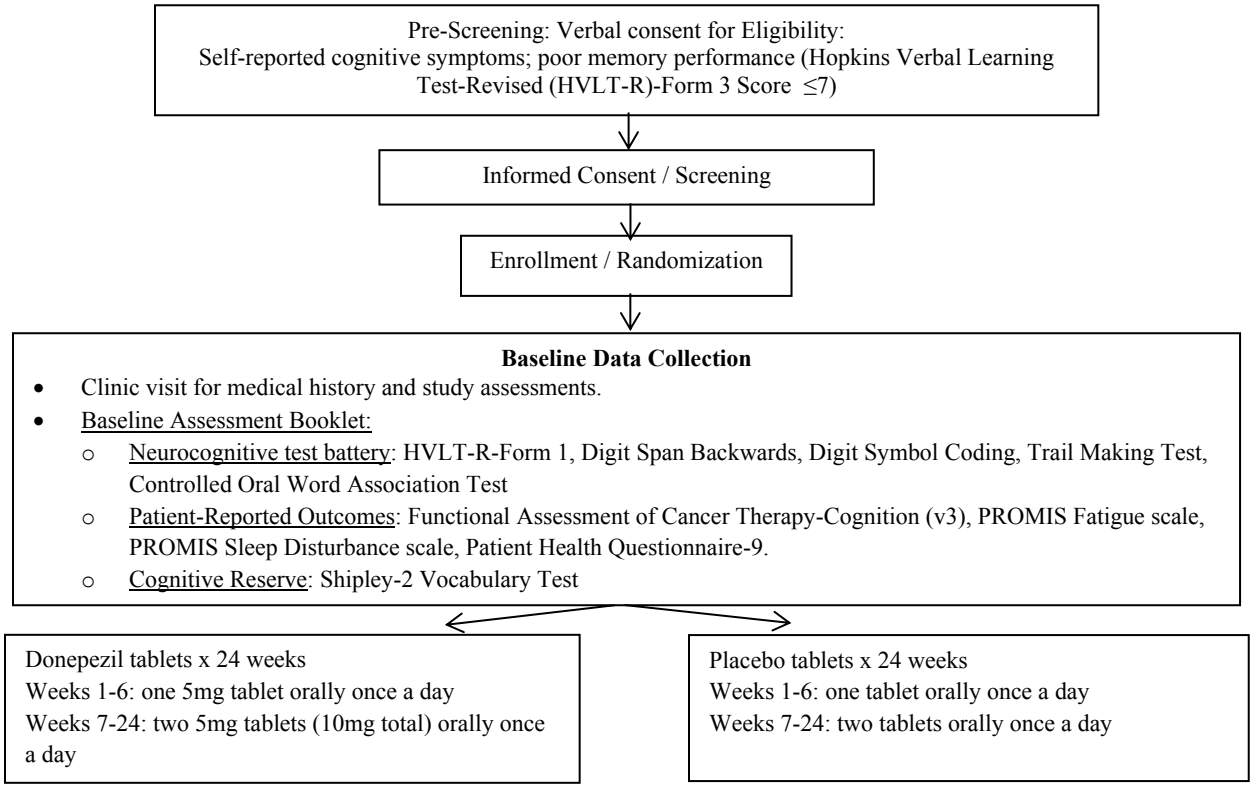
SCHEMA



Intervention*

Week 3:	Phone interview for assessment of toxicities
Week 6:	Phone interview for assessment of toxicities; if indicated, increase dose to two 5mg tablets of donepezil daily or two placebo tablets starting at week 7
Week 12:	Clinic visit for study assessment, Neurocognitive test battery, Patient Reported Outcomes, Toxicity assessment, Verify dosage and continued compliance with study medication
Week 24:	End of drug administration; beginning of wash-out. Clinic visit for study assessment, Neurocognitive test battery, Patient Reported Outcomes, Toxicity assessment
Week 36:	End of wash-out. Clinic visit for study assessment, Neurocognitive test battery, Patient Reported Outcomes, Toxicity assessment

*Select patients will have an ECG or heart rate taken 3-7 days post start of intervention, at the 3 Week study time point, and 3-7 days post study agent dose increase.

Endpoints

Primary:	Memory: HVLT-R Immediate Recall score
Secondary:	Other cognitive domains: Executive function, working memory, processing speed, verbal fluency, global cognitive function, Patient-reported outcomes: cognitive problems Other: toxicities, adverse events.

Stratification: **Age (<50, 50-59, 60-69, ≥70)**
***Study Sample*: N=276 (138 per group)**
***Study Duration*: Approximately 40 months**
Brief Eligibility Criteria: ≥18 years old, female, history of invasive breast cancer, completed adjuvant/neo-adjuvant chemotherapy between 1-5 years prior to enrollment, received ≥ 4 cycles of cytotoxic chemotherapy, self-reported cognitive complaint, documented memory deficit.

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1. OBJECTIVES

1.1 Primary Objective

Aim 1: Determine whether randomization to a 24-week course of treatment with donepezil compared to placebo improves memory performance in women who have received chemotherapy for breast cancer 1 to 5 years previously. Hypothesis: Women randomized to donepezil for 24 weeks will have better memory performance than women receiving placebo.

1.2 Secondary Objectives

Aim 2: Determine whether a 24-week course of treatment with donepezil compared to placebo improves executive functions (working memory, verbal fluency, set shifting), processing speed and global cognitive performance in women who have received chemotherapy for breast cancer 1 to 5 years previously. Hypothesis: Women randomized to donepezil for 24 weeks will have better executive function, processing speed and global cognitive performance than women receiving placebo.

Aim 3: Determine if a 24-week course of treatment with donepezil reduces self-reported cognitive problems in women who have received chemotherapy for breast cancer 1 to 5 years previously compared to placebo. Hypothesis: Women randomized to donepezil for 24 weeks will report fewer cognitive problems than women receiving placebo.

Aim 4: To determine the effect of a 24-week course of treatment with donepezil on toxicities and adverse events. Hypothesis: No group difference.

1.3 Tertiary (Exploratory) Objectives

Aim 5: Determine whether APOE genotype (1 or 2, ε4 alleles v none) is associated with poorer pre-randomization cognitive performance and more cognitive complaints in women who have received chemotherapy for breast cancer 1 to 5 years previously and to determine if APOE predicts who will respond to treatment. Hypothesis: Women who are carriers of the APOE ε4 alleles will have poorer pre-randomization cognitive performance, more cognitive complaints, and respond better to donepezil than women without the ε4 alleles.

Aim 6: Determine whether low cognitive reserve (CR) is associated with poorer pre-randomization cognitive performance and more cognitive complaints in women who have received chemotherapy for breast cancer 1 to 5 years previously and determine if cognitive reserve predicts who will respond to treatment. Hypothesis: Women with lower CR will have poorer pre-randomization cognitive performance, more cognitive complaints, and respond better to donepezil than women high in CR.

2. BACKGROUND

2.1 Study Disease

Cancer-related cognitive dysfunction (CRCD) frequently occurs in breast cancer survivors following cytotoxic adjuvant or neo-adjuvant chemotherapy and will be the focus of this study.

2.2 Study Agent

Donepezil hydrochloride (Aricept®) is a reversible inhibitor of the enzyme acetyl cholinesterase. It is currently FDA approved for use in the treatment of mild to moderate dementia of the Alzheimer's type.

Donepezil hydrochloride is available for oral administration in 5 or 10mg film-coated tablets. The donepezil are not dispersible tablets as such, the donepezil and placebo are over encapsulated and must be swallowed. Donepezil was initially manufactured and marketed by Eisai Inc., Teaneck NJ and distributed by Roerig Division of Pfizer Inc., New York, NY. Generic donepezil is now available and will be purchased from Vensun Pharmaceuticals, Inc., Cranbury, NJ. Drug and matching placebo will be purchased in bulk and provided at no cost for participants participating in this study. Drug/placebo will be packaged and distributed by RxCrossroads by McKesson Inc., Irving, Texas.

IND Status: We have conducted several controlled trials involving cancer patients using the proposed dosages of donepezil and consistently found a very low risk profile. In a feasibility study for this proposal with 62 female breast cancer survivors enrolled between 7/24/2012 and 1/24/2013 and randomly assigned to receive the same dosages as proposed in this study (5mg x 6 weeks increased to 10mg x 18 weeks) or placebo, we had excellent compliance (98% in the donepezil group), few withdrawals from the study due to toxicities (4 in the donepezil group), and only four adverse events (3 in the Control arm and 1 in the Donepezil arm). All were unrelated to the study treatment (Lawrence et al., 2015). In other published studies we reported a similar profile of few toxicities with this agent. In a phase 3 RCT with 198 brain tumor survivors ≥6 months post brain irradiation treatment who were randomized to the same dosage of donepezil (5mg x 6 weeks increased to 10mg x 18 weeks) or placebo, only 14 donepezil participants discontinued treatment due to toxicity compared to 5 control participants ($p = .030$) and 19 SAEs were reported (10 for the donepezil arm and 9 for the control arm); only two of the donepezil events and one control were coded as possibly or probably related to the study drug. Toxicities were queried at 6, 12 and 24 weeks. Fatigue was the most common complaint, experienced to some degree by 58% of the donepezil participants and 67% of the control participants ($p = .241$). Anorexia occurred in 21% and 15% of the donepezil and control group, respectively ($p = .301$), nausea in 14% and 21% ($p = .171$), and diarrhea in 25% and 9% ($p = .005$)(Rapp, Case, Peiffer, Naughton, & Shaw, 2013). A very similar toxicity profile was reported in a pilot study with brain tumor survivors following brain irradiation randomized to donepezil or placebo (Shaw et al., 2006). Thus the risk profiles associated with the proposed dosages of donepezil when used with cancer patients including breast cancer survivors following chemotherapy is minimal and supports not requiring an IND. The study will be submitted to the FDA for IND exemption request as described in the DCP memo dated January 14, 2013.

The recommended dosage for patients with dementia is donepezil 5mg/day for 6 weeks escalated to donepezil 10mg/day if well-tolerated. Participants will be randomized 1:1 to either one tablet of donepezil 5mg or one tablet of matching placebo orally once a day for 6 weeks followed by an escalation to two 5mg tablets (10mg total) or two tablets of matching placebo orally once a day for 18 weeks. This dose and schedule has been used in our previous phase 2 and phase 3 studies of donepezil and is similar to regimens used in the treatment of cognitive impairment associated with neurodegenerative disease. A 12-week wash-out phase will occur immediately following the 24 week active intervention phase.

We recently completed a phase II, placebo-controlled, double-blind feasibility study comparing a standard dose of oral donepezil (5mg for 6 weeks followed by 10mg daily for 18 weeks) to placebo in breast cancer survivors who had completed adjuvant chemotherapy 1-5 years prior to enrollment and who reported cognitive dysfunction (WF NCORP Research Base study #97211). The study was open at 16 sites within the WF NCORP Research Base. We enrolled 62 women between 7/24/11 and 1/24/12 for an excellent accrual rate of 10.2 subjects per month. Of the women who completed study (76% of those enrolled), self-reported compliance to study drug was 98% and completion of all assessments was 98%. Participant toxicities were minimal (mostly Grade 1 and 2; $p>.05$).

In addition, the identical dosage and regimen was used successfully in a phase 2 study (WF NCORP Research Base study #97100) (N=35 of brain tumor patients who had completed a course of ≥30 Gray of brain radiotherapy at least 6 months prior to enrollment as well as in a subsequent phase 3 study (WF

NCORP Research Base study #91105) (N=198) with the same patient population. In both studies tolerance of donepezil was quite good and self-reported adherence was >90%.

2.3 Rationale

There are 2.5 million breast cancer survivors in the United States today,[1] and the number is increasing as treatments increase life expectancy. Some of the most important late effects of cancer treatment to patients are the negative impact on cognition, energy and mood which result in decreased quality of life [2].

Chemotherapeutic agents lack tissue selectivity resulting in damage to non-targeted organs. Despite the protection offered by the blood-brain barrier, some agents penetrate the central nervous system and adversely affect brain tissue resulting in cognitive dysfunction for a substantial number of patients. CRCD can range from mild to severe, often is chronic and affects social and occupational functioning and life quality [3-6].

The specific phenotype and course of CRCD remain unclear. 70% of longitudinal studies of non-CNS cancer patients treated with chemotherapy show some cognitive deficits with point estimates ranging from 17% to 70% [7]. CRCD is often reported by patients long after chemotherapy has ended [5, 8-12]. For example, among breast cancer patients treated with chemotherapy 21% exhibited CRCD before chemotherapy, 65% exhibited cognitive changes during or shortly after treatment, and 61% showed decline approximately 1 year after treatment ended with approximately 2/3 of these patients showing deficits that were not previously detected[13]. Breast cancer survivors who were assessed between 1 to 5 years following a course of chemotherapy showed significantly poorer learning and memory performance compared with women who were treated with local therapy (surgery and radiation)[10]. Late CRCD effects including poorer memory, processing speed and executive functioning in breast cancer survivors have been observed up to 21 years following treatment[14]. In our recently completed phase II feasibility study (#97211) conducted through the Wake Forest CCOP Research Base, we documented deficits in learning and memory, verbal fluency, processing speed, executive function and motor speed and dexterity in 62 breast cancer survivors 1-5 years after completing chemotherapy[15] relative to non-cancer norms. Across studies of breast cancer patients receiving chemotherapy, cognitive domains commonly affected are learning and memory, attention and processing speed[5] but other patterns have also been reported[16].

The mechanisms underlying chemotherapy-induced cognitive dysfunction remain unclear[17]. Anticancer agents can affect brain function through direct (neurotoxicity) and indirect pathways (treatment induced metabolic and hormonal abnormalities, inflammatory cytokine activation, medical comorbidities, fatigue and injury to other body organs)[18]. Structural and functional CNS changes occur in as many as 70% of patients[19]. These changes can include periventricular white matter lesions, necrosis, ventriculomegaly and cortical atrophy[20]. Alterations in metabolism and cerebral blood flow have been observed[21] along with atrophy[22].

Damage to the hippocampus may be particularly important in CRCD. The hippocampus, a brain region critical to learning, memory and mood, is rich in cholinergic neurons and highly susceptible to radiotherapy and chemotherapy[23]. Rodents exposed to methotrexate, which crosses the blood brain barrier, exhibit impairment in spatial memory function which is correlated with decreased hippocampal cell proliferation[24]. Smaller gray and white matter volumes in prefrontal, hippocampal and parahippocampal regions in humans have been documented 1 year following chemotherapy and volumes were positively correlated with cognitive performance[22]. Thus, cognitive impairment seen following chemotherapy may be related to neuronal damage in the hippocampus. Cognitive enhancing treatments that operate on hippocampal processes like cholinergic enhancers may offer benefit to patients who have received chemotherapy.

Interventions: A potential role for neurotransmitter modulators
Acetylcholine esterase inhibitors (AChEIs) are the standard of care for individuals with Alzheimer's dementia,[25, 26] and vascular dementia[27] and are frequently used for milder forms of impairment such as Mild Cognitive Impairment syndrome[28]. Furthermore, there is evidence of AChEIs efficacy in treating cognitive impairment associated with Parkinson's disease[29], multiple sclerosis[30], and traumatic brain injury[31, 32]. AChEIs have also improved cognitive functioning in young, healthy adults[33]. In addition to the known direct effects on neuronal function, donepezil, the most commonly prescribed AChEI, also increases cerebral perfusion in critical brain areas related to cognitive processing[34]. Advantages of donepezil are its availability in generic form, its high tolerance profile and a simple dosing regimen.

Preliminary studies

Our research group has tested donepezil in several cancer survivor populations.

Brain tumor patients following brain irradiation. Shaw et al. reported significant improvement in cognitive function, cognitive complaints, mood and quality of life among brain tumor patients treated with 5mg/10mg daily dose of donepezil at least 6 months following completion of brain irradiation therapy[35]. A comprehensive cognitive test battery assessing major domains of cognition (attention, language, episodic memory, working memory, visuomotor speed and dexterity, processing speed, executive function) and standardized questionnaires were used. That uncontrolled phase 2 study was followed by our recently completed phase 3 study (5R01NR009675, Rapp PI) of brain tumor patients who were ≥6 months post partial or whole brain irradiation, in which we found randomization to donepezil did not improve overall cognitive function but cognitive function in individuals with poorer baseline cognitive functioning did improve significantly compared to placebo[36].

Breast cancer patients following chemotherapy. In our recently completed phase 2 feasibility study of 62 breast cancer survivors 1-5 years following chemotherapy who reported moderate to severe cognitive symptoms using the same comprehensive cognitive battery, we found participants randomized to 24 weeks of donepezil (5mg x 6 wk. + 10mg x 18 wk.) had better memory (HVLT-R Total recall, $p = 0.03$; HVLT-R Discrimination, $p = 0.04$) scores after 24 weeks than participants assigned to placebo[15]. Sensitivity analyses revealed that participants with lower baseline memory scores (≤7 on Trial 1 of HVLT-R) who were randomized to donepezil showed greater improvement relative to controls than participants with better memory function assigned to donepezil ($p = 0.002$) and a similar pattern was observed for executive function ($p = .007$). Participant reported treatment compliance was 98%, and toxicities were minimal (mostly Grade 1 and 2; $p>.05$). Accrual was robust (62 participants from 16 sites in 6 months or 10 participants per month), and 24-week retention was very good (76%). There were no significant group differences in subjective cognitive functioning or quality of life. There was a suggestion that those participants on anti-estrogen hormonal therapy (HT) did somewhat worse than participants who were not receiving HT (e.g., composite LS mean .2 vs -.05 at 24 weeks, $p = .14$). However, there was very little evidence that the treatment effect differed for those who were and were not receiving HT (interaction p-values ranged from .36 to .97 for the memory tests and composite). Finally, member sites of the WF NCORP Research Base were surveyed before the phase 2 feasibility study and indicated a keen interest in it and in a larger phase 3 trial.

Thus, studies conducted by our research group demonstrate that donepezil can improve cognitive function, particularly memory and executive function, among brain and breast cancer survivors following both brain irradiation and chemotherapy.

Correlative science: Finding markers of susceptibility

There is wide variability in the severity of CRCD among breast cancer survivors treated with chemotherapy. Scores on standardized cognitive tests often range from severely impaired to normal levels. To better understand and treat CRCD, it will be important to identify markers of susceptibility. Factors studied in relation to other diseases associated with cognitive impairment may offer insights into CRCD[6]. For example, **Apolipoprotein E (APOE) genotype**, **older age**, and lower **'cognitive reserve'** are all associated with a greater risk of developing Alzheimer's dementia (AD) and of transition from mild cognitive impairment to AD and thus may also identify breast cancer survivors who are at greater risk of developing CRCD.

APOE genotype is a multifunctional lipoprotein synthesized by many body organs and is thought to have a role in neuronal repair after injury. The APOE polymorphism is a risk factor for both Alzheimer's dementia and vascular dementia with carriers of the ε4 allele at higher risk than non-carriers[37, 38]. Ahles et al. reported an increased susceptibility to the adverse cognitive effects of chemotherapy among breast cancer survivors an average of 8 years post-treatment among carriers of the APOE ε4 alleles compared to non-carriers[39]. Ahles et al. also recently reported poorer cognitive functioning among breast cancer survivors who were ε4 carriers and who received either chemotherapy with or without anti-estrogen hormonal therapies[40]. In an exploratory analysis, we propose to examine whether APOE genotype is associated with greater cognitive impairment following chemotherapy.

'Cognitive reserve' (CR) refers to acquired compensatory strategies that enhance a person's cognitive and behavioral capacities[41, 42]. Individuals with higher CR should have less cognitive impairment because of their greater adaptive capacity. Common proxies for CR are literacy and educational and occupational attainment. Higher levels of CR have been associated with lower incident rates for age-associated cognitive impairment and longer delayed onset of dementia. CR will be examined as a susceptibility factor for CRCD (low CR individuals will have greater cognitive impairment at baseline than high CR individuals).

There are other potential markers of susceptibility and treatment modifiers including telomere length and other genotypes (e.g., catechol-O-methyltransferase). We propose to collect and store blood for analyses of genetic and non-genetic factors of interest in the future pending outcome of this study.

In summary, CRCD is a common problem following chemotherapy. It can affect various cognitive functions (especially memory, executive function and processing speed) and can last for or develop years following treatment. Little is known about the underlying biological mechanisms, but it appears that chemotherapeutic agents adversely impact the hippocampus, a part of the brain that is heavily involved in learning and memory as well as mood. Treatments that enhance hippocampal-dependent functions, therefore, may have particular benefit for patients who receive chemotherapy. At the WF NCORP Research Base we have completed two phase 2 and one phase 3 studies examining whether donepezil, an acetylcholine esterase inhibitor that affects hippocampal function, reduces CRCD in diverse cancer populations. Encouraging treatment effects and our demonstrated ability to conduct these studies strongly support this larger phase 3 RCT.

3. SUMMARY OF STUDY PLAN

3.1 Study Design

Randomized, double-blind, placebo-controlled study with 24 weeks of exposure to drug or placebo followed by a 12 week wash-out period. A total of 276 patients will be enrolled (138 per arm). We expect

an accrual rate of 7-10 participants per month based on our prior feasibility study. We expect the study to be complete within 40 months.

Study population. Participants will be women ≥18 years old with history of invasive breast cancer treated with ≥4 cycles of cytotoxic adjuvant/neo-adjuvant chemotherapy between 1 and 5 years prior to enrollment; who have no clinical evidence of recurrent disease; who have a complaint of memory/cognitive problems since chemotherapy started; and who have a demonstrated memory deficit on a standardized memory test (score ≤7 on single learning trial of Hopkins Verbal Learning Test-Revised Form 3)

3.2 Intervention Plan

Participants will be asked to take one 5mg tablet of donepezil or one tablet of matching placebo orally once a day for 6 weeks followed by two 5mg tablets (10mg total) of donepezil or two placebo tablets orally once a day for 18 weeks. After 24 weeks, participants will begin a 12 week wash-out period.

Time points for performing study assessments. Participants will be administered the cognitive battery of tests and questionnaires at baseline, week 12, week 24 and week 36. In addition, a single vial of blood will be drawn at baseline for APOE genotyping and subsequent bioassays (pending supplemental funding). Additional monitoring visits are described in Section 7.

3.3 Measurements taken to meet study objectives.

Neurocognitive Performance - Tests have been selected to represent a range of functions reported to be affected by cancer and chemotherapy including attention, memory, working memory, executive function and verbal fluency. All cognitive testing will be performed by a trained and certified research assistant blinded to treatment assignment. Proposed neurocognitive measures are: Hopkins Verbal Learning Test-Revised (HVLT; 10 min)[43, 44](Aim 1); Digit Span-Backwards (DST-B; 2 min) and Digit Symbol Coding (DSC; 3 min) subtests from the Wechsler Adult Intelligence Scale-Revised[45]; Trail Making Test A & B (TMT; 8 min max)[46]; and the Controlled Oral Word Association test (3 letters; 4 min)[47] that has been used with cancer patients[49] and has non-cancer norms[50] (Aim 2). Each cognitive measure proposed has adequate psychometric properties and has been used in cancer research including large national and international clinical trials [51-53]. An alternate version of the HVLT-R word list will be used for screening to reduce practice effects.

Patient Reported Outcomes - Patient-reported outcomes will complement the neurocognitive battery. We will assess *cognitive symptoms* (Functional Assessment of Cancer Therapy-Cognition (Version 3; FACT-Cog; 5 min)(Aim 3) [54, 55]; *fatigue* (PROMIS 7-item scale; 1 min), *sleep disturbance* (PROMIS 8-item sleep scale; 1 min); and depression (Patient Health Questionnaire-9; 2 min) [56, 57]. This entire battery of neurocognitive tests and questionnaires will take approximately 40 minutes to complete. We have used a similar battery successfully in two phase 2 studies and one phase 3 study involving breast and brain tumor cancer survivors. Data completeness in those studies was over 95%.

Other variables to be measured - Additional variables to be assessed only at baseline include age, education, occupation, race/ethnicity, marital status, menopausal status, cancer treatment received (chemotherapeutic agent, anti-estrogen hormonal agent), and time since end of chemotherapy. Comorbid medical conditions, anti-estrogen status, use of psychotropic medications will be assessed at each assessment point. *Cognitive reserve* will be measured with the Shipley Institute of Living-Version 2 Vocabulary test with educational (years in school) and occupational attainment (standardized 8-level classification) used as additional proxies for CR.

Biomarker - APOE genotype will be derived from whole blood samples taken at baseline at each NCORP site of study enrollment. Prepared shipping kits will be sent to participating NCORP sites from the Wake Forest Biotech Laboratory following procedures used previously in Research Base studies. The lab will provide sample handling, storage, tracking, and logistics. DNA will be isolated from whole blood, collected in yellow-top Vacutainer tubes (with citrate as the preservative). Blood samples will be brought to the Wake Forest Center for Genomics and Personalized Medicine Research laboratories, where they will be entered into a database and the DNA isolated. DNA from whole blood will be isolated using the AutoPure LS instrument (Qiagen, Inc.). SNP genotyping of the APOE haplotype will be performed in the Center for Genomics and Personalized Medicine Research at Wake Forest using the iPlex SNP genotyping system (Sequenom, Inc.), which has been successfully tested and fully integrated into our laboratory. The APOE haplotype will be determined by genotyping the two individual SNPs that make up the haplotype, rs429358 and rs7412, in each individual. Genotypes will be scored using the SpectroTyper software (Sequenom, Inc.), and quality control parameters (e.g., CEPH DNA samples, negative controls) will be determined. Problem samples or SNPs will be reviewed and repeated if necessary.

3.4 Procedures to Monitor Effects of Study Agent

Procedures to monitor effects of study agent on human safety and to minimize risks are described in Section 5.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Women ≥18 years old with history of invasive breast cancer

4.1.2 Must have completed at least 4 cycles of adjuvant/neo-adjuvant cytotoxic chemotherapy between 1 and 5 years prior to enrollment **(**Ongoing herceptin or other chronic HER 2 directed therapies are allowed).

4.1.3 Patients receiving ongoing hormonal therapy for breast cancer must be on the same hormonal agent for at least 3 months prior to study enrollment and plan to continue for the duration of the study (9 months).

4.1.4 Use of psychotropic medications (anti-depressants, anxiolytics, sleeping aids, narcotics) is permitted if the patient whose eligibility is being assessed has been on the medication for at least 12 weeks. The dose of this medication must be stable for at least 4 weeks prior to enrollment.

4.1.4.1 Patients who were previously on one of these psychotropic medications and have subsequently discontinued the drug must have been off the medication for at least 4 weeks prior to enrollment.

4.1.4.2 Patients who have been on a psychotropic medication for at least 12 weeks but have recently switched to a medicine in the same class (for example, switching from one SSRI antidepressant to a different SSRI antidepressant) need to be on a stable dose of the new medication for at least 4 weeks prior to enrollment to be eligible.

4.1.5 Self-reported cognitive problem plus a measured memory deficit (score ≤ 7 on single trial of Eligibility Pre-screen HVLT-R Form 3).

4.1.6 ECOG performance status 0-2

4.1.7 Able to understand and willing to sign a written informed consent document.

4.1.8 Must be able to speak English.

4.1.9 Patients currently taking a moderate risk QTc prolongation medication (see Appendix A) are allowed if one of the following criteria are met:

4.1.9.1 The moderate risk QTc prolongation medication is stopped. The patient should be off the moderate risk QTc prolongation medication for at least 5 half-lives before starting study drug.

4.1.9.2 Patients that continue using a moderate risk QTc prolongation medication must have a normal QTc interval (≤ 460 milliseconds) on a screening ECG following informed consent and prior to study enrollment. These patients will also be monitored at designated study follow-up visits per Section 7.5 (monitored 3-7 days after initiating study drug, at week 3, and 3-7 days after the study drug dose increase with ECG's to assess the QTc interval; the QTc level must be ≤ 500 milliseconds at these time points in order to continue on the study drug).

4.1.9.3 Moderate risk QTc prolongation medications that are only taken occasionally may be stopped at the discretion of the treating site physician. Patients must be off medication for at least 5 half-lives prior to starting study drug to be eligible.

4.1.10 Patients currently taking a moderate risk bradycardia-causing agent (see Appendix B) are allowed if one of the following criteria are met:

4.1.10.1 The moderate risk bradycardia-causing agent is stopped. The patient should be off the moderate risk bradycardia-causing agent for at least 5 half-lives before starting study drug.

4.1.10.2 Patients that continue using a moderate risk bradycardia-causing agent must have a resting heart rate ≥ 55 beats per minute at screening following informed consent. These patients' resting heart rate will be monitored 3-7 days after initiating study drug, at week 3, and 3-7 days after the study drug dose increase per Section 7.5.

4.1.10.3 Moderate risk bradycardia-causing agents that are only taken occasionally may be stopped at the discretion of the treating site physician. Patients must be off medication for at least 5 half-lives prior to starting study drug to be eligible.

4.2 Exclusion Criteria

4.2.1 Evidence of or suspected recurrent or metastatic disease.

4.2.2 Prior brain irradiation.

4.2.3 Planned therapy (surgery, radiation, chemotherapy, or immunotherapy) while on the study for brain and/or extracranial primary/metastatic disease.

4.2.4 Hypersensitivity to donepezil or piperidine derivatives

4.2.5 Current use of ceritinib

4.2.6 Current use of Succinylcholine/Acetylcholinesterase Inhibitors as listed in Appendix C. For patients who have used these medications, they must not have used them within 4 weeks prior to enrollment.

4.2.7 Current use of high-risk QTc prolonging medication(s). See Appendix D.

4.2.8 Current use of quinidine or systemic ketoconazole (topical ketoconazole is acceptable to use while on study).

4.2.9 History of dementia, Alzheimer's disease, multi-infarct dementia or clinically significant Cerebrovascular Accident (history of transient ischemic attack (TIA) is allowed).

4.2.10 Current use of donepezil, galantamine, rivastigmine, tacrine, memantine, methylphenidate, dextroamphetamine, or any other specific cognition enhancing drug(s). For patients who have used these medications, they must not have used them within 4 weeks prior to pre-screening. Patients who plan to start taking a cognition enhancing drug while on this study are also excluded.

4.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to donepezil. Hypersensitivity to donepezil.

4.2.12 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, recent myocardial infarction, or cardiac arrhythmia.

4.2.13 Major medical conditions that affect cognition, traumatic brain injury, multiple sclerosis, acute severe fatigue, chronic fatigue syndrome or fibromyalgia.

4.2.14 Psychiatric illness/social situations that would limit compliance with study requirements including but not limited to a history of schizophrenia, psychosis or substance abuse.

4.2.15 Untreated current severe depression. Currently treated depression is permitted if treatment is stable.

4.2.16 Patients with a resting heart rate less than 55 beats per minute, seizure disorder or peptic ulcer disease (PUD).

4.2.17 Screening QTc of > 460 milliseconds will make the patient ineligible.

4.2.18 History of congenital long QT syndrome or torsades de pointes.

4.2.19 Pregnant women are excluded from this study. Following informed consent, women of child-bearing potential will be screened with a serum or urine pregnancy test within 10 days of enrollment. The effects of donepezil on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because donepezil is known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately.

4.2.20 It is unknown whether donepezil is excreted in breast milk, for this reason women who are currently breast-feeding are not eligible for this study.

4.2.21 On another intervention study involving medication at the time of enrollment or during participation in this study. (Exception: Patients will remain eligible for this study if they are also enrolled on the Alliance for Clinical Trials in Oncology study (NCT02927249): Aspirin in Preventing Recurrence of Cancer in Patients with HER2 Negative Stage II-III Breast Cancer After Chemotherapy, Surgery, and/or Radiation Therapy. Studies that involve only blood draws or questionnaires are also permitted.)

4.2.22 Use of investigational drugs likely to affect cognition within 30 days prior to pre-screening visit.

4.3 Inclusion of Women and Minorities

Women who are members of all races and ethnic groups are eligible for this trial.

	Race/Ethnicity					
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male						
Female	226	41	6	3	0	276
Total	226	41	6	3	0	276

4.4 Recruitment and Retention Plan

We will recruit patients from all participating sites within the WF NCORP Research Base network. Sites will be required to have a centrally trained and certified examiner. We recently completed a phase II, placebo-controlled, double-blind feasibility study comparing the proposed treatment regimen (donepezil 5mg for 6 weeks followed by 10mg daily for 18 weeks versus placebo) in breast cancer survivors who had completed adjuvant chemotherapy 1-5 years prior to enrollment and who reported cognitive dysfunction (WF NCORP Research Base study #97211). The study was open at 16 sites within the WF NCORP Research Base. We enrolled 62 women between 7/24/11 and 1/24/12 for an excellent accrual rate of 10.2 patients per month. Of the women who completed study (76% of those enrolled), self-reported adherence to study drug was 98% and completion of all assessments was 98%. Thus, we have demonstrated that a Phase III clinical trial testing the efficacy of donepezil in comparison to placebo is feasible and that we are well positioned to conduct such a trial. There are no other WF NCORP Research Base studies currently open or planned that will compete with this study.

Females with a history of breast cancer and who have received prior chemotherapy will be identified by their physicians, resident, research nurse or study staff at each participating Research Base NCORP site. They may review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified will be asked about their interest in participating in a study of the cognitive effects of chemotherapy in clinic or by a letter from their physician informing them about the study, and indicating that a research nurse/study staff will be calling to tell them more about the study. Pre-

screening and screening activities will proceed as described in protocol section 7. Each patient will be followed for 36 weeks. After the 36 week study visit, the patient is no longer followed and data is no longer collected from the patient. Accrual is expected to be 7-10 patients per month. A maximum of 276 patients will be enrolled on this trial. A total N of 276 (138 in each arm) is likely to be enrolled after approximately 40 months.

To ensure adequate minority participation, we will identify Minority Base NCORP sites for recruitment, and provide recruitment information to minority community leaders.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6.2.

5.1 Dose Regimen and Dose Groups

- Donepezil or placebo will be taken once daily by mouth.
- Weeks 1- 6 titration from one 5mg tablet of donepezil or one matching placebo tablet orally once a day to two 5mg tablets of donepezil (10mg total) or 2 tablets of matching placebo orally once a day x 7-24.weeks.

5.2 Study Agent Administration

- Drug will be self-administered orally on an outpatient basis.
- It will be recommended that patients take tablets (donepezil or placebo) at the same time every day. This may be in the morning or evening; with or without food.
- Donepezil is provided as a non-dispersible tablet, therefore the study medication (donepezil and placebo tablets) are over encapsulated and should be swallowed whole.
- Patients may be asked to return completed medication diaries via mail or in-person study visits.
- For the first 6 weeks of the study patients will be instructed to take one 5mg tablet of donepezil or one matching placebo tablet orally once per day.
- At the 6 week study time point, the patient will be contacted and assessed for toxicities. At this time the dose may be modified per Section 5.6.

5.3 Wash Out Procedure

There will be a 12-week wash-out period between end of treatment (24 weeks) and the end of follow-up (36 weeks). The patient will be evaluated for toxicities and will complete study assessments at Week 24 and Week 36 study time points per Sections 7.4 and 7.5, respectively. The wash-out period will help us to determine if there is a worsening of cognitive symptoms and test performance following withdrawal of treatment.

5.4 Contraindications

- Hypersensitivity to donepezil or piperidine derivatives.
- Due to possible metabolism changes when used concomitantly with donepezil, systemic Ketoconazole and quinidine are prohibited.
- Patient must not have any planned therapy (surgery, radiation, chemotherapy, or immunotherapy) while on study for brain and/or extracranial primary/metastatic disease.

5.5 Concomitant Medications

All prescription medications and over the counter medications taken by the patient will be documented on the Concomitant Medication form (brand or generic name) at study time points designated in Section 7.1.

Refer to Section 7.5 for study visits and study medication criteria specific to patients taking a moderate risk QTc prolongation medication that met inclusion criteria 4.1.9 and/or patients taking a moderate risk bradycardia causing agent that met inclusion criteria 4.1.10.

Some medications are known to have neurocognitive effects. Women currently taking donepezil, galantamine, rivastigmine, tacrine, memantine, methylphenidate, dextroamphetamine or any other specific cognition enhancing drugs will be excluded from participation in the study. If cognition enhancing drugs have been used in the past, they must not have been used in the 4 weeks prior to pre-screening.

Use of stable doses of psychotropic medications (anti-depressants, anxiolytics, sleeping aids, narcotics) are allowed if the patient whose eligibility is being assessed has been on the medication for at least 12 weeks. The dose of this medication must be stable for at least 4 weeks prior to enrollment (per section 4.1.4).

Patients should not begin taking a cognition enhancing and/or psychotropic medication while on study. However, patients who do begin taking a cognition enhancing and/or psychotropic medication while on study must immediately stop taking the study agent and should continue study follow-up. The Patient Status Form should be completed.

5.6 Dose Modification

Study patients will take a single oral 5mg tablet of donepezil or one oral tablet of placebo once per day for 6 weeks. At the 6 Week study time point, the patient will be contacted by research personnel to assess toxicities and any changes in medications. Patients will be evaluated using an AE Report Form. If the patient is tolerating donepezil/placebo and does not present with any unacceptable toxicities (grade 3 or greater related to study medication), the donepezil/placebo dose will be increased to two tablets of donepezil (10mg total) or two tablets of placebo orally once per day starting on Week 7 and continuing through Week 24. Patients taking a moderate risk QTc prolongation medication and/or moderate risk bradycardia causing medication will have a study visit 3-7 days after increasing dose. Refer to Section 7.5 for follow-up assessment instructions. Patients will have in-person study visits that will include toxicity assessments at weeks 12, 24 and 36.

Patients that do not tolerate one oral tablet (5mg of donepezil or placebo) will discontinue study drug, but will continue to be followed on study. The Patient Status Form should be completed if the patient discontinues study drug.
If donepezil two tablets (10 mg total) or placebo 2 tablets is not tolerated after escalation, the treating physician should decrease dose to donepezil one 5 mg tablet or one placebo tablet orally once a day for the remaining study period. Any unacceptable drug-related (Grade 3 or greater) toxicities while patient is taking one 5 mg tablet or one placebo tablet per day will require patient to have donepezil/placebo discontinued.

5.7 Adherence/Compliance

5.7.1 To be considered compliant with study medication a patient must take at least 75% of scheduled doses.

5.7.2 Compliance is monitored by daily diaries completed by the patient which are systematically collected at weeks 6, 12 and 24. In addition, compliance is monitored when appointments are made and when medication tolerance is assessed by the research nurse/study staff over the phone at week 3 and again at week 6 when dose escalation occurs. During the week 6 phone contact, patients are requested to return study diaries via mail to the research staff. These data are entered into the study data base for analyses by our biostatistician every 6 months when the study is reviewed by our DSMB.

6. PHARMACEUTICAL INFORMATION

6.1 Study Agent

Donepezil hydrochloride is a reversible inhibitor of the enzyme acetylcholinesterase available only by prescription. It is currently FDA approved for use in the treatment of mild to moderate dementia of the Alzheimer's type. Donepezil hydrochloride is available for oral administration in 5 or 10mg film-coated tablets. It is to be stored at room temperature (15°C to 30°C). Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. The concentration of acetylcholine is increased by reversible inhibition of its hydrolysis by acetylcholinesterase. Donepezil has a relative oral bioavailability of 100%. It reaches peak plasma concentrations in 3 to 4 hours. The elimination half-life is about 70 hours and steady state is reached within 15 days. Donepezil is metabolized by CYP 450 isozymes 2D6and 3A4 and undergoes glucuronidation. In a small study of patients with cirrhosis, the clearance of donepezil was decreased by 20% compared to healthy controls. In a few patients with severe renal impairment, the clearance was unchanged compared to healthy controls. There have been no interactions of donepezil with furosemide, digoxin, warfarin, theophylline, or cimetidine. Inducers of CYP 2D6 and CYP 3A4 could increase the rate of elimination of donepezil but this has not been demonstrated clinically. These drugs include phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital. Ketoconazole and quinidine inhibit donepezil metabolism in vitro but it is not known whether there is a clinical effect.

6.2 Reported Adverse Events and Potential Risks

The most frequent adverse clinical events are due to donepezil's cholinomimetic effect. These include anorexia, nausea, vomiting, diarrhea, fatigue, insomnia, and muscle cramps. These are often mild and transient, resolving with continuation of the drug. There are a few more side effects noted when the drug is titrated from 5mg to 10mg in one week vs. six weeks.

Common, Some May Be Serious (≥20% Chance)

- Diarrhea 5-15 % dose related
- Loss of Appetite 2-8 % dose related
- Muscle Cramps 3-8 %
- Nausea 3-19 % dose related
- Trouble in sleeping 2-14%
- Unusual tiredness or weakness 1-8 %
- Vomiting 3-9 % dose related

Occasional, Some May Be Serious (<20% Chance)

- Headache 3-10 %
- Dizziness 2-8 %
- Weight loss 3-5 % dose related

Rare, Some May Be Serious

- High blood pressure 3%
- Risk of seizures < 1 %
- Slow heart beat ≥ 1 %
- Neuroleptic malignant syndrome (NMS) (fever, severe muscle cramps, confusion, unusual heartbeat) < 1 %
- Irregular heartbeat or palpitations (due to torsades de pointes)

6.3 Availability

Donepezil (Aricept®) was initially manufactured and marketed by Eisai Inc., Teaneck NJ and distributed by Roerig Division of Pfizer Inc, New York, NY. For this study generic donepezil will be purchased from Vensun Pharmaceuticals. Drug and matching placebo will be purchased in bulk in packages containing tablets and provided at no cost for patients participating in this study.

6.4 Agent Ordering and Distribution

Donepezil /placebo will be distributed by RxCrossroads by McKesson, Inc. Irving, Texas (1-800-693-4906; fax: 1-919-256-0794). RxCrossroads by McKesson, Inc. will distribute study drug/placebo directly to participating sites following randomization of study patients. The study medication (donepezil/placebo) will be provided to patients at no cost.

6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, will maintain a careful record of the inventory and disposition of all agents received using the NCI Drug Accountability Record Form (DARF). The Investigator will maintain adequate records of receipt, dispensing and final disposition of study agent. On dispensing record, note quantities and dates study agent was dispensed to and returned by each patient.

Institutions should document drug accountability using the NCI DARF.

6.6 Packaging and Labels

When a patient is enrolled and randomized to the study, WF NCORP Research Base sends RxCrossroads by McKesson, Inc. notification via email.

Upon receipt of an email, RxCrossroads by McKesson will place a call to the study site confirming the order was received, gather patient specific data and arrange day and time of arrival for the study drug. They will require the following information from the site:

- Patient Full Name or Initials
- Site Shipping Address and phone number
- Doctor's name

RxCrossroads by McKesson will pull a total of 294 tablets of the study drug for the patient to complete the entire 24 week treatment. Drug will be packaged in 2 bottles and mailed in one shipment to the site:

- 'Bottle A, Weeks 1-6' containing 42 tablets of study drug to complete weeks 1-6 at a dose of 'one tablet by mouth daily'.

- 'Bottle B, Weeks 7-24' containing 252 tablets of study drug to complete weeks 7-24 at a dose of 'two tablets by mouth daily'.

Study drug is patient specific and each patient specific label will include at least the following information:

- Study Number
- Patient Name
- Patient Study ID Number
- Drug identification
- Lot number and expiration
- Storage conditions
- Dosing instructions (Take as Directed per Protocol)
- Date dispensed
- The number of capsules
- IND caution statement and/or local regulatory statements
- Emergency contact instructions

For all drug shipments from RxCrossroads by McKesson, Inc. a packing slip will be enclosed that includes the date and quantity of drug provided patient name/initials, study ID number, drug identification including lot number and expiration date.

RxCrossroads by McKesson, Inc. will process and ship "same day" of patient randomization if received before 2:00 p.m. E.T Monday through Friday. Orders received after 2:00 pm E.T. Monday through Friday will be processed and shipped the next business morning.

All drug orders are shipped via *FedEx for Priority Overnight* delivery. Study Drug is shipped in a RxCrossroads by McKesson, Inc. branded box designed to maintain temperature stability.

Once study drug is received at the clinical trial site, the designated site coordinator validates contents of package matches information provided on packing slip with study medication received. The inventory and disposition of donepezil or placebo pills must be recorded using the NCI Drug Accountability Record Form (DARF). See section 6.5 Agent Accountability.

6.7 Storage

Study medication should be stored at room temperature. (15°C to 30°C /59°F to 86°F)

6.8 Emergency Unblinding Methods

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 (active study drug(s) or placebo), the following procedure should be followed:

- Step 1: During regular business hours (8:00am – 5:00pm EST), the site should contact the WF NCORP Research Base Site Coordinator at (336) 713-6519 or (336) 713-6907. If after hours or on the weekend, the patient's physician or a designated health care professional should call the Wake Forest University Baptist Medical Center Physician Access Line (336-716-7654) and ask that Dr. Glenn Lesser, Principal Investigator of the WF NCORP Research Base, be contacted immediately. In the event Dr. Lesser cannot be reached, the PAL operator

should contact Kate Weaver, PhD. Site staff may also try contacting Dr. Lesser, glesser@wakehealth.edu, or Dr. Weaver, keweaver@wakehealth.edu, by email if the PAL line is unsuccessful in reaching them.

- 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 @ RxCrossroads by McKesson, Inc.(phone: 1-800-850-4306). There is an "on-call" service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The RxCrossroads by McKesson 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 RxCrossroads by McKesson, 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 severe adverse events (if applicable), should be followed for each protocol for all Phase II and Phase III Clinical Trials. The event will be reviewed by the WF NCORP Clinical Research Oversight Committee and reviewed by the NCORP Research Base Data Safety and Monitoring Board.

6.9 Unblinding Study Patients at Study Completion

Study patients may be unblinded 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 NCORP Research Base Administrator or Site Coordinator with a list of PID #s. After confirming with the DMC that patient specific data for the patient at the requesting site have been received, completed and entered into the RB database, RxCrossroads by McKesson Inc will be notified. An email from RxCrossroads by McKesson containing the unblinding information will be sent directly to the requesting site.

6.10 Agent Destruction/Disposal

Unused drug should be destroyed on site following site institutional policies and procedures.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events

Pre-screening and screening are to be conducted within 30 days prior to enrollment/randomization. Baseline procedures may be obtained within 7 days post enrollment/randomization.

Protocol therapy must begin within 7 days post baseline evaluation.

Assessment	Pre-Screen	Screen	Enrollment	Baseline	Baseline + 3-7 Days[A]	3 Week	6 Week[F]	6 Week + 3-7 Days[K]	12 Week	24 Week	36 Week
Memory Question	X										
HVLT-R Form 3 Trial 1	X										
Informed Consent		X[B,L]									
Serum or Urine Pregnancy Test		X[C]									
Height				X							
Weight				X							
Heart Rate		X			X[D]	X[D]		X[D]			
ECG		X			X[E]	X[E]		X[E]			
Randomization			X								
ECOG Performance Status		X							X	X	X
APOE Genotyping				X							
Flow Sheet		X		X	X	X	X		X	X	X
Adverse Event Report Form					X	X	X		X	X	X
Concomitant Medication Form				X			X		X	X	X
Donepezil Medication Diary (Pill Count)							X		X	X	
Telephone Contact Form						X[F]	X[F]				
Baseline Assessment Booklet				X[H]							
12 Week Assessment Booklet									X[H]		
24 Week Assessment Booklet										X[H]	
36 Week Assessment Booklet											X[H]
Patient Status Form			X[J]								

A Post study agent initiation.
B Consent must be obtained prior to screening activities.
C Negative serum or urine pregnancy test is required within 10 days prior to enrollment for women of child-bearing potential.
D For patients on moderate risk bradycardia-causing agents (Appendix B) only, resting heart rate will be obtained by a trained individual. See Section 7.5.
E For patients on moderate QTc prolonging agents (Appendix A) only. See Section 7.5.
F Refer to Section 5 for dose modification information.
G Pre-screen consists of 2 parts and will be completed on the Pre-Screen form. 1) Memory question – must answer "mildly worse", "moderately worse" or "much worse" to proceed. 2) HVLT-R Form 3 single trial score must be ≤ 7 to meet eligibility requirements.
H Booklet instruments are provided in Section 7.8.
I Request completed medication diaries be returned at 6, 12 and 24 week assessment, may be collected via mail.
J Complete the Patient Status Form if the patient stops taking study medication for any reason, withdraws from the study, or completes study intervention and study follow-up.
K Post study agent dose increase.
L Reconsent all patients, as of amendment 3. See Appendix E.

7.2 Pre-study Evaluation and Consent

All pre-screening and screening evaluations must be done in person. The Decline Form is to be completed by all potential participants if they decline to participate. Submit all Decline Forms at the end of each month per section 11.1.

7.2.1 Pre-Screening

Prospective participants will be identified by research personnel, a review of cancer registry, medical chart information or by patient's response to advertisements or flyers posted in the clinics. All potential participants will first be verbally consented by asking "May we ask you a few questions to determine if your activities meet the requirements to take part in the study?" The verbal consent process will be documented by study staff administering the verbal consent. If a "no" response is given the prospective participant will be thanked for her time and no longer be considered possibly eligible. If a "yes" response is given, the potential participant will be asked the self-reported cognitive problem question "*How would you rate the change in your ability to think including remembering, organizing your thoughts and speaking since you were first diagnosed with cancer?*" Response choices will be 'No change or better', 'mildly worse', 'moderately worse', 'much worse'. Only if a potential participant responds with "*mildly worse*", "*moderately worse*" or "*much worse*" will she proceed to the HVLT-R Form 3 Trial 1. Study staff will administer and score the HVLT- R Form 3 Trial 1. An entry level score of ≤ 7 words recalled is required. Potential participants who score > 7 are not eligible to participate. All pre-screening data collected on ineligible and eligible patients who choose to not participate will be submitted to the WF NCORP Research Base per Section 11.1. Use the site CTEP ID and patients' initials on pre-screening forms.

Pre-screened patients who meet study criteria after completing the Memory Question and HVLT-R Form 3 Trial 1 will be provided additional study information and offered participation in the study. If the patient agrees to participate a protocol specific consent form will be signed with a copy provided to the patient.

7.2.2 Screening

Screening activities will occur after eligible patients have completed pre-screening and signed consent. Screened patients will be identified using the site CTEP ID and patients' initials on completed forms.

Patients will have a screening ECG performed to measure their QTc. Patients with a screening QTc interval > 460 milliseconds will no longer be eligible and will be excluded from study participation. The screening ECG QTc interval should be recorded on the Cardiac Monitoring Form.

Patients who are on Bradycardia-causing agents will have their resting heart rate taken by trained individuals at screening. Patients who present with a pulse less than 55 beats per minute will no longer be eligible and will be excluded from study participation. The resting heart rate taken at screening should be recorded on the Cardiac Monitoring Form.

Patients who are of child-bearing potential and have not had a negative serum or urine pregnancy test clinically performed within 10 days of enrollment will be screened with a serum or urine pregnancy test. Patients who test positive for pregnancy will no longer be eligible and will be

excluded from study participation. Record date performed and results of the serum or urine pregnancy test on the Flow Sheet.

Patients who meet pre-screening eligibility criteria, sign informed consent, and meet screening eligibility criteria will be enrolled to the study as described in Section 7.3.

Patients who screen fail will no longer be eligible, will not be enrolled, and will be excluded from further study participation. The Pre-Screen form, Eligibility Checklist and Flow Sheet must be submitted to the WF NCORP DMC on all patients who screen fail.

7.3 Patient Enrollment and Randomization

Electronic enrollment must be completed after eligibility has been determined, consent has been signed, and no later than 30 days after pre-screening began. Refer to Section 7.1 and 7.2 for pre-screening and screening study assessments to be completed prior to enrollment. At the time of electronic enrollment, patients will be electronically randomized and study drug (donepezil or placebo) will be provided to the enrolling site per Section 6.6.

NCORP site staff will electronically enroll their study patients in the Wake Forest NCORP Research Base website, CCRBIS, at https://ccrbis.phs.wakehealth.edu.

- Log in to the database website using your CCRBIS username and password.
- In the drop-down menu next to Enroll Patient/Patient Info select 97116, then click Enroll Patient/Patient Info.
- Click on Enroll New Patient.
- Complete the Eligibility Checklist/Enrollment Form then click submit.
- Following successful submission, a confirmation page will appear with the assigned PID, print this page for your records.

If you have questions related to the patient enrollment process or require assistance with enrollment, please contact the Wake Forest NCORP Research Base between 8:00am and 5:00pm EST, Monday through Friday at (336) 716-0891 or by email at NCORP@wakehealth.edu.

7.4 Baseline Evaluations

Baseline evaluations should be obtained within 7 days post enrollment and before the patient takes the first dose of donepezil/placebo. Baseline evaluations will include: study assessment including pt. and family history, concomitant medications, Baseline Assessment Booklet and toxicity assessment.

APOE Genotyping - A blood sample of approximately 8ml will be taken from a vein in the arm/central line for lab analysis. Blood samples will be stored with a unique identifier and will not include any information protected by HIPAA regulations. Blood samples will be stored at Wake Forest. Refer to Section 9.0 for specimen management.

7.5 Evaluations During Study Intervention

Patients taking a moderate risk QTc prolonging medication who met eligibility criteria 4.1.9 will have a study visit 3-7 days after initiation of the study agent. An ECG will be performed and results will be recorded on the Cardiac Monitoring Form and toxicities will be assessed. If the patient's QTc interval is

> 500ms they should stop taking the study agent and continue study follow-up visits. If the participant stops taking the study agent, complete a Patient Status Form.

Patients taking a moderate risk bradycardia causing agent will have a study visit 3-7 days after initiating the study agent. Resting heart rate will be recorded on the Cardiac Monitoring Form and toxicities will be assessed. If the patient's resting heart rate is < 55 beats per minute, the participant should stop taking the study agent and continue study follow-up visits. If the participant stops taking the study agent, complete a Patient Status Form.

At Week 3 the patient will be evaluated for any toxicities associated with the study agent, this may be done by phone. Patients taking a moderate risk QTc prolonging medication who met eligibility criteria 4.1.9 will have a Week 3 in person study visit and an ECG will be performed in addition to evaluation of any toxicities. If the patient's QTc interval is > 500ms they should stop taking the study agent and continue study follow-up visits. Patients taking a moderate risk bradycardia causing agent will have a Week 3 in person study visit and their resting heart rate will be recorded in addition to evaluation of any toxicities. If the patient's resting heart rate is < 55 beats per minute, the participant should stop taking study agent and continue study follow-up visits.

At week 6 the patient will be evaluated for any toxicities associated with the study agent, this may be done by phone. If patient is tolerating donepezil/placebo without any unacceptable toxicities at week 6, donepezil/placebo dose will be modified per Section 5.6 and continued through Week 24. Patients will be asked to return completed medication diaries via mail.

Patients taking a moderate risk QTc prolonging medication, who had a normal ECG assessment at the 3-7 day and 3 week visits will be permitted to modify the study agent dose per Section 5.6. These patients will have a study visit 3-7 days after the dose increase. An ECG will be performed and recorded on the Cardiac Monitoring Form. If the patient's QTc interval is > 500ms they should reduce study agent dose to 5mg and continue through Week 24.

Patients taking a moderate risk bradycardia causing agent, who had a normal resting heart rate at the 3-7 day and 3 week visits will be permitted to modify the study agent dose per Section 5.6. These patients will have a study visit 3-7 days after the dose increase. The patient's resting heart rate will be recorded on the Cardiac Monitoring Form. If the patient's resting heart rate is <55 beats per minute, the patient should reduce the study agent dose to 5mg and continue through Week 24.

At Week 12 the patient will return to the clinic to complete a study assessment, the 12 Week Assessment Booklet and toxicity assessment. Concomitant medications will be reviewed in addition to the study medication. Medication diaries will be collected to verify compliance of study medication.

The Cardiac Monitoring Form should be used to record heart rate and ECG at all applicable study time points. The Flow Sheet should be used to record ECOG performance status at specified study time points. Toxicities must be reported using the Adverse Event Report Form and per Section 10. The Patient Status Form must be completed if the patient stops taking the study agent and per Section 8.

7.6 Evaluations at Completion of Study Intervention

Study agent will be discontinued at week 24 prior to a 12-week wash-out phase per Section 5.3. The patient will return to the clinic to complete a study assessment, the 24 Week Assessment Booklet and toxicity assessment. Concomitant medications will be reviewed in addition to the study medication. Medication diaries will be collected to verify compliance of study medication. Record ECOG performance status on the Flow Sheet. Toxicities must be reported using the Adverse Event Report Form

and per Section 10. The Patient Status Form must be completed if the patient stops taking the study agent and per Section 8.

7.7 Post-intervention Follow-up Period

The 12-week wash-out phase of the study will begin at Week 24 and continue through Week 36 following which the patient will return to the clinic for a study assessment, 34 Week Assessment Booklet, toxicity assessment and review of concomitant medications.

7.8 Methods for Neurocognitive and Patient Related Outcomes Tests

This entire battery of neurocognitive tests and questionnaires will take approximately 30 - 45 minutes to complete, which is equivalent to the time needed in our WF NCORP Research Base studies of donepezil among brain tumor survivors and breast cancer survivors. Retention in these studies exceeded 90% and data completeness was over 95%.

7.8.1 Specific Training and Certification Procedures

Each participating site will be required to have at least one examiner who is trained and certified in the administration and scoring of the cognitive battery (neurocognitive tests and questionnaires). Training will follow the procedures developed in prior WF NCORP neurocognitive studies such as our recently completed Phase II feasibility study trial of donepezil in breast cancer survivors previously exposed to chemotherapy. We will train using didactic presentations (describing the purpose and instructions for each test and questionnaire), live and video demonstrations of a complete battery administration, live practice sessions supervised by a certified examiner and trainer with specific feedback, and a review by certified trainers of an audio-recorded administration. If needed, remediation will occur with review of subsequent recorded administrations with corrective feedback. Once the examiner has met study criteria s/he will be certified to administer and score the battery at his/her site. Periodic re-certifications will be required. This procedure has been successfully used in our studies of cognitive effects of cancer and its treatments as well as by Dr. Rapp and his team in large scale, multi-site clinical trials and observational studies (e.g., WHIMS, CoSTAR, SPRINT, Look AHEAD, LIFE, MESA).

7.8.2 Neurocognitive Function Assessments

Neurocognitive tests have been selected to represent a range of cognitive abilities which have been reported in the literature to be affected by chemotherapy including attention, verbal memory, working memory, executive function, speed of mental processing, and verbal fluency. All cognitive testing will be performed by a trained and certified research assistant blinded to treatment assignment. The WF NCORP Research Base has conducted training workshops for administering this cognitive test battery for our on-going trials of donepezil among irradiated brain patients, and maintains a stringent certification process. Each cognitive test has adequate psychometric properties and has been used in cancer research including large national and international clinical trials.

Hopkins Verbal Learning Test-Revised (HVLT-R): The HVLT-R measures verbal learning and memory. It consists of a 12-item word list which is read to patients on three successive learning trials. Free recall scores are recorded for each learning trial. After a 20-minute interval during which patients 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 patients are asked to

identify all target words by responding "yes," and to reject 12 non-target words by responding "no". Test-retest reliability of the HVLT-R is quite good. 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-R. There are 6 alternate forms of the HVLT-R. Forms A, B, D, and E will be used for assessments at baseline and weeks 12, 24 and 36. A single trial with Form 3 will be used to screen patients for the study.

Trail Making Test, Parts A & B (TMT-A, TMT-B): Part A of the TMT measures attention and visual motor skills and processing speed and requires patients to connect 25 numbered circles in the proper sequence (1-2-3-…) as quickly as possible. TMT-B is similar except patients 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 function. 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.

Controlled Oral Word Association Test (COWA): The COWA measures speed of mental processing, verbal fluency, and executive function. Patients are asked to name as many words as possible all beginning with a specified letter. A total of three trials are administered, each with a different letter (F-A-S). The score on the COWA is the total number of words named across the three trials minus repetitions.

Digit Span Test-Backwards (DST-B): The DST-B assesses attention and working memory. It requires respondents to repeat back in reverse order spans of numbers. Seven pairs of spans of increasing lengths are presented and repeated. A total score is the number of correctly repeated spans.

Digit Symbol Coding: The DSC test measures processing speed. It requires respondents to transcribe symbols (e.g., >) associated with a number (0-9) into empty boxes beneath a series of randomly ordered numbers. Total score is number of correctly transcribed symbols in 2 minutes. Scores range from 0-133.

7.8.3 Cognitive Reserve

Shipley Institute of Living Scale-Version 2 Vocabulary: This vocabulary test requires respondents to read a target word and select one of four words that most closely means the same thing. Score it total correct of 40 items. This provides an assessment of premorbid intellectual functioning comparable to a verbal IQ and thus is a proxy for *cognitive reserve*. It will be administered only at baseline.

7.8.4 Patient Reported Outcomes (PRO) Assessment

Functional Assessment of Cancer Therapy-Cognition (Version 3): The FACT-Cog is a validated self-report questionnaire that assesses patients' perceptions of their cognitive function and the impact of cognitive problems on overall quality of life over the prior 7 days. The FACT-Cog (Version 3) has 37 items grouped into four subscales—Perceived Cognitive Impairments (PI; 20 items, 18 scored), Comments from Others (CO; 4 items), Perceived Cognitive Abilities (PA; 9 items) and Impact on Quality of Life (IQOL; 4 items). For each subscale items are scored on a Likert scale ranging from 0 (Never) to 4 (Several times a day). Negatively worded items are

reverse coded and summed for each subscale. Higher scores reflect better cognitive functioning and less impairment.

Personal Health Questionnaire-9 Depression scale: The PHQ-9 is a widely used self-report scale for assessing depression severity. It has 9 items assessing cardinal features of major depression which are rated from zero ("Not at all") to 5 ("nearly every day").

PROMIS 7-item Fatigue Scale: This self-report scale assesses fatigue.

PROMIS 8-item Sleep Disturbance Scale: Self-reported sleep disturbance will be measured with the PROMIS Sleep Disturbance scale.

8 Off-Agent/Off-Study

8.1 Off Agent Criteria

Patients may stop taking study agent for one or more of the following reasons: completed the protocol-prescribed intervention, adverse event (AE) or serious adverse event (SAE), inadequate agent supply, refusal to continue with study procedures, the need for contraindicated concomitant medications, medical contraindication, disease progression, death or treating physician decision.

Date and reason off agent should be documented on the Patient Status Form. Reasons that are not specified on the form should be coded as 'Other' and a brief description provided. Patients who go off-agent must be followed for adverse events (AEs) for up to 30 days from their last treatment.

Note that patients who go off-agent should be encouraged to stay in the study and provide data at the regularly scheduled visits.

8.2 Off Study Criteria

Patients may go 'off-study' for one or more of the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, refusal to continue with study procedures, the need for contraindicated concomitant medication, medical contraindication, disease progression, withdraw consent, death, determination of ineligibility (including screen failure), pregnancy, or treating physician decision.

Any patient with a cancer recurrence must be evaluated by the treating physician and followed by a discussion with the Wake Forest NCORP Research Base Study PI or their representative to determine if the patient meets the off-study criteria.

Note that a patient is not automatically taken off-study if they refuse further treatment. In fact, these patients should be encouraged to remain in the study and provide data at their regularly scheduled visits. Date and reason off-study should be documented on the Patient Status Form. Reasons that are not specified on the form should be coded as 'Other' and a brief description provided.

A final evaluation of the patient may be performed if/when they withdraw from the study. If a patient decides to discontinue participation in study (withdraw) at any time prior to study completion, the patient should be asked to complete the entire battery of neurocognitive tests and forms prior to withdrawing from the study. This should be completed using the next

Neurocognitive and PRO tests they would have received as well as all other items in the Schedule of Events (section 7.1) for the visit.

Patients who go off study will not be replaced.

9. SPECIMEN MANAGEMENT

A single blood draw will be made at the baseline visit. Samples will be sent to the Wake Forest School of Medicine Center for Genomics and Personalized Medicine Research Lab for storage and processing. APOE genotype will be derived from the whole blood samples

9.1 Storage of Blood for Future Research Testing (if applicable)

All blood samples will receive a unique identifier and stored at the Wake Forest School of Medicine Center for Genomics and Personalized Medicine Research Lab located in Winston-Salem, NC. Only researchers approved by Dr. Stephen Rapp, the principal investigator at Wake Forest School of Medicine will receive the sample.

9.2 Laboratories

DNA will be isolated from whole blood, collected in one (8 ml max) yellow-top Vacutainer tubes (with citrate as the preservative). Blood samples received from all sites will be brought to the Wake Forest School of Medicine Center for Genomics and Personalized Medicine Research laboratories, where they will be entered into a database and the DNA isolated. DNA from whole blood will be isolated using the AutoPure LS instrument (Qiagen, Inc.).

SNP genotyping of the APOE haplotype will be performed in the Center for Genomics and Personalized Medicine Research at Wake Forest School of Medicine using the iPlex SNP genotyping system (Sequenom, Inc.), which has been successfully tested and fully integrated into our laboratory. The APOE haplotype will be determined by genotyping the two individual SNPs that make up the haplotype, rs429358 and rs7412, in each individual. Genotypes will be scored using the SpectroTyper software (Sequenom, Inc.), and quality control parameters (e.g., CEPH DNA samples, negative controls) will be determined. Problem samples or SNPs will be reviewed and repeated if necessary.

9.3 Collection and Handling Procedures

Prepared shipping kits will be sent to participating NCORP sites from the Wake Forest Biotech Laboratory following procedures used previously in Research Base studies. The lab will provide sample handling, storage, tracking, and logistics.

9.4 Shipping instructions

Sites should request shipping kits at the time of study approval in advance of putting patients on study. The Wake Forest NCORP Research Base will provide shipping kit request forms and shipping instructions to participating sites.

10. REPORTING ADVERSE EVENTS

Adverse event (AE) any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign,

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 patient is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in Section 6.2 Reported Adverse Events and Potential Risks, as well as the package insert.

10.1 Adverse Events

10.1.1 Reportable AEs

All AEs that fit reporting criteria after the informed consent is signed and baseline assessments are completed must be recorded on the AE Report Form whether or not related to study agent as detailed below.

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations.

10.1.2 AE Data Elements:

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

10.1.3 CTCAE term (AE description) and Grade

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Identify the AE using the CTCAE version 5.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0 as stated below.

CTCAE v5.0 general severity guidelines:

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 activities of daily living (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.

ADL

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers 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 AE is related to study agent will be classified as one of the following attribution: Unrelated, unlikely, possible, probable, definite.

Attribution: An assessment of the relationship between the adverse event and study agent/intervention, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to the study agent (or product)/intervention
Unlikely	The AE is doubtfully related to study agent /intervention
Possible	The AE may be related to study agent/intervention
Probable	The AE is likely related to study agent/intervention
Definite	The AE is clearly related to study agent/intervention

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

Serious Adverse Event (SAE): A serious adverse event is defined by regulation 21 CFR §312.32 as any adverse medical event (experience) that results in at least one of the outcomes listed below:

- Death
- A life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital anomaly or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

10.3 Reporting for Adverse Events (AEs)

All adverse events, whether observed by study staff or investigator, elicited from or volunteered by the patient, should be documented. Each adverse event will include the date of onset, date of resolution, severity, and the relationship to the study agent or intervention, and any action taken with respect to the study agent or intervention.

- Donepezil (Aricept®) is a widely used medication taken routinely on an outpatient basis. An identical regimen was used in Wake Forest phase 2 and phase 3 studies. In both studies tolerance of donepezil was quite good. Side effects are well documented, therefore Grade 1 and 2 adverse events (AEs) will not be collected.
- All expected adverse events (AEs) grade 3 and unexpected that are unrelated or unlikely adverse events (AEs) grade 3 will also not be collected.
- All expected adverse events (AEs) grade 4 will also not be collected.
- All other adverse events will be reported to the Wake Forest NCORP Research Base using the AE Report Form. Serious adverse events requiring expedited reporting via CTEP-AERS are described below. Serious adverse events not requiring expedited reporting through CTEP-AERS should be entered into AE Report Form within 10 calendar days of learning of the event and sent to the Wake Forest NCORP Research Base.
- Site staff and/or Principal Investigators will also notify WF NCORP Research Base via AE Report Form and report to CTEP-AERS within 24 hours of discovering the details of all **unexpected severe, life-threatening (grade 4) that are possible, probably or definitely related to the drug and/or all fatal adverse events (grade 5).**
- All recorded adverse events reported to the Wake Forest NCORP Research Base will be reported to the Data Safety Monitoring Committee

Adverse Events								
	Grade 1 & 2		Grade 3		Grade 4		Grade 5	
	Expected	Unexpected	Expected	Unexpected	Expected	Unexpected	Expected	Unexpected
Unrelated						AE Report Form	AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS
Unlikely						AE Report Form	AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS
Possible				AE Report Form		AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS
Probable				AE Report Form		AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS
Definite				AE Report Form		AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS	AE Report Form & CTEP-AERS

The Research Base Grant PI, DSMB 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.

Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All CTEP-AERS reports should be sent to the local IRB in accordance with the local IRB policies.

10.4 Responsibilities for Expedited Reporting (CTEP-AERS)

Wake Forest NCORP affiliates (local sites) are required to notify the WF NCORP Research Base if a patient has an adverse event requiring expedited reporting. All SAEs that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task

IMPORTANT: When reporting in CTEP-AERS please ensure a copy of the report is sent to WF NCORP RB by adding NCORP@wakehealth.edu to the distribution list within the reporting system. Any correspondence between CTEP-AERS and/or the FDA about a reportable SAE should be forwarded to NCORP@wakehealth.edu also.

Commercial reporting requirements are provided in the table below. The commercial agent used in this study is Donepezil (Aricept®).

Expedited reporting requirements for adverse events experienced by patients who are receiving study agent/intervention (including within 30 days of the last administration of commercial study agent/intervention) should be reported as follows:

Attribution	Grade 4		Grade 5	
	Expected	Unexpected	Expected	Unexpected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite		CTEP-AERS	CTEP-AERS	CTEP-AERS

1) This includes all deaths within 30 days of the last dose of study agent with a commercial agent/intervention, regardless of attribution. Any death that occurs more than 30 days after the last dose of study commercial agent/intervention and is attributed (possibly, probably or definitely) to the agent/intervention and is not due to cancer recurrence must be reported according to the instructions above.

2) Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the CTEP-AERS, cIRB or WF NCORP RB in order to complete the evaluation of the event.

For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Contact Information for NCI Safety Reporting:

Website for submitting expedited reports	http://eapps-ctep.nci.nih.gov/ctepaers
AEMD Help Desk (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP Trials	301-230-0159 (Back-up FAX: 301-897-7404)
AEMD Help Email:	aemd@tech-res.com
Technical (E.G., IT or computer issues ONLY) Help Phone *	1-888-283-7457 or 301-840-8202
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov
CTCAE v 4 Help/Questions Email	ncicctcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://eapps-ctep.nci.nih.gov.ctepaers/help/webhelp/CTEP-AERS%20FAQ.htm
CTEP-AERS Computer based training	https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

Office phone and fax are accessible 24 hours per day 7 days a week.The AEMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

11. STUDY MONITORING

11.1 Data Management Schedule

Data forms must be submitted to the Wake Forest NCORP Research Base within 14 days of the study visit and Decline Forms and screening logs must be submitted at the end of each month by email, NCORP@wakehealth.edu, or fax, (336) 713-6476.

11.2 Case Report Forms

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

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 Data Safety Monitoring Board meets every six months to review all phase II and phase III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences, biostatistics and ethics. The DSMB report is generated by the Research Base statistician. Areas of review may include the following: Study Objectives; Patient Accrual; Patient Status and Retention; Study Status; Last Contact Status; Patient Compliance; Number of Biopsies/Labs as needed; Patient Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to Drug, Arm assigned; 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 for 5 years 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.

11.6 CDUS Reporting

The WF NCORP 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

A randomized, placebo controlled, double-blind, parallel group Phase 3 design will be used to assess the effect of 24 weeks of donepezil on cognitive function (memory) in breast cancer survivors who report having cognitive dysfunction and demonstrate memory impairment 1-5 year post chemotherapy. Patients who meet the eligibility criteria will be stratified by age (<50, 50-59, 60-69, ≥70) and randomized to donepezil or placebo with equal probability. The primary objective of this trial is to assess the effect of donepezil on memory as quantified by the HVLT-R Immediate Recall score. Secondary objectives will be to assess the impact of donepezil on i) executive functions: Trail Making Test B/A; working memory: Digit Span Backward; processing speed: Digit Symbol Coding; verbal fluency: COWA); and self-reported cognitive problems (FACT Cog) and iii) toxicities and adverse events. For exploratory aims 5 and 6, we will assess the treatment interaction effects for APOE genotype and cognitive reserve.

The measures used to quantify these outcomes are described above. 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 or not the participants were treated according to protocol.

12.2 Sample Size

For design purposes, we will base our sample size on data collected in our recently completed phase 2 pilot (feasibility) study. Baseline means and adjusted post-randomization standard deviations (obtained from ANCOVA models using the baseline and 24 week data) are shown below in Table 1, along with the estimates of the treatment effects. These are provided for the overall sample and for those participants who had lower memory scores at baseline.

Table 1. Estimates of the means, adjusted standard deviations, and treatment effects for some of the proposed outcomes – overall and [within the subgroup with poor initial memory scores]*

Outcome	Baseline Mean	Adjusted SD	Raw Treatment Effect (SE)**	Standardized Effect Size***
HVLT_IR	24.2 [21.8]	4.33 [4.26]	2.61 (1.32) [4.88 (1.57)]	0.60 [1.15]
HVLT_DR	8.5 [7.7]	1.81 [1.75]	0.28 (0.55) [0.70 (0.64)]	0.15 [0.40]
HVLT_Recog	11.1 [10.8]	1.02 [1.19]	0.30 (0.32) [0.21 (0.44)]	0.29 [0.18]
HVLT_sav	86.2 [83.5]	16.8 [19.4]	0.25 (5.08) [-2.78 (7.08)]	0.01 [-0.14]
HVLT_discrim	10.5 [10.1]	1.37 [1.48]	1.05 (0.42) [1.23 (0.54)]	0.77 [0.83]
COWA	35.0 [33.8]	7.53 [6.93]	2.41 (2.30) [0.65 (2.62)]	0.32 [0.09]
TMT_A	33.7 [33.8]	8.12 [8.57]	-1.09 (2.46) [1.66 (3.18)]	-0.13 [0.19]
TMT_B	86.7 [90.7]	24.4 [26.9]	6.29 (7.37) [11.1 (9.92)]	0.26 [0.41]
DST_F	10.3 [10.2]	1.40 [1.39]	0.29 (0.43) [0.14 (0.55)]	0.21 [0.10]
DST_B	6.1 [5.6]	1.45 [1.47]	-0.19 (0.44) [-0.41 (0.54)]	-0.13 [-0.28]
DST_T	16.3 [15.8]	2.41 [2.50]	0.11 (0.73) [-0.27 (0.96)]	0.04 [-0.11]

Notes: HVLT-R = Hopkins Verbal Learning Test-Revised; COWA = Controlled Oral Word Association test; TMT = Trail Making Test; DST = Digit Span Test (F = Forward, B = Backward, T = Total).

* Estimates obtained from the pilot study discussed above in Section 2.3.

** Donepezil minus Placebo (positive effects favor donepezil except for TMT)

*** Treatment difference between group means divided by adjusted standard deviation (positive effects favor donepezil except for TMT)

Our primary outcome variable will be a memory score as quantified by the HVLT-R Immediate Recall (total of 3 trials). In our pilot study, the adjusted post-randomization standard deviation was 4.33 (SD of the outcome at 24 weeks, adjusted for its correlation with the baseline level) and the difference (SE) was 2.61 (1.32) (p=.03). In the subgroup of participants with poor initial memory scores, the adjusted post-randomization standard deviation was 4.26 and the difference (SE) was 4.88 (1.57) (p<.01). Assuming that standard deviations will be similar in the proposed study and equal in the two groups, the sample sizes required to detect mean differences between groups of 1 to 3 words with 80% and 90% power are shown in Table 2, assuming a 5% two-sided level of significance. These calculations use data from the subgroup of participants with poor initial memory scores and assume a single stage design will be implemented, an ANCOVA model will be used to compare the treatment arms, and that 73% of the participants will have 24 week data (25% drop-out and 2% missing data, based on our pilot #97211).

Table 2. Total sample size needed to ensure sufficient power for detecting clinically meaningful differences in HVLT-R immediate recall at the 5% two-sided level of significance

Absolute Difference	80% power	90% power
1.0	784	1050
1.5	351	469
2.0	200	266
2.5	129	170
3.0	91	121

We see that 266 participants are required to detect a treatment difference of 2 words with 90% power at the 5% two-sided level of significance. We observed a larger treatment effect in the pilot study so that targeted difference is attainable. Table 3 shows the differences that are detectable in the secondary outcomes with 90% power (using a Bonferroni corrected significance level of .005 for each test). We see that we will have sufficient power for detecting relative differences between groups of less than 20% in all outcomes and relative differences of less than 15% for most outcomes.

Table 3. Differences detectable in secondary outcomes with 90% power*

Outcome	Absolute Difference	Relative Difference (%)**
HVLT_DR	1.04	13.5
HVLT_Recog	0.71	6.5
HVLT_sav	11.5	13.8
HVLT_discrim	0.88	8.7
COWA	4.11	12.2
TMT_A	5.08	15.0
TMT_B	16.0	17.6
DST_F	0.82	8.1
DST_B	0.87	15.6
DST_T	1.48	9.4

* Using a Bonferroni corrected significance level of .005 for each test.
** Assuming post-treatment means remain at baseline levels in the control group.

12.3 Randomization and Stratification

Participants will be stratified by age (<50, 50-59, 60-69, ≥70) and assigned with equal probability to donepezil or placebo using variably sized permuted block randomization. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous assignments. Treatment assignments will be generated using nQuery Advisor 7.0 and incorporated into the randomization table in our enrollment facility which is accessible to the site via the internet 24/7. Participants, investigators, research staff, and statisticians will all be blinded to treatment assignment. Only RxCrossroads by

McKesson, the company that distributes the drugs and placebo, will be unblinded. If requested by the DSMB, RxCrossroads by McKesson can unblind the study statistician.

12.4 Primary Endpoint(s)

The primary outcome, HVLT_IR is a continuous variable that will be measured at baseline, 12, 24 (end of treatment) and 36 weeks. This outcome will be analyzed using a mixed effects repeated measures analysis of covariance (RMANCOVA) model which includes treatment arm, time, the time*treatment interaction, the baseline levels of the outcomes, and the stratification factors as covariates, the latter included to ensure that the analysis matches the design. An unstructured covariance matrix will be used to account for the within participant correlation over time. The major hypothesis will be assessed using a linear contrast to test the significance of the group effect at 24 weeks. Least squares means and 95% confidence intervals will be provided for each outcome, stratified by treatment arm and time, and for the difference between treatment arms at each time.

Subsequent RMANCOVA models that include several additional pre-specified, baseline covariates will be performed as a sensitivity analysis to the primary analysis. These additional covariates have been selected as those that are highly prognostic of cognitive outcomes and include education, race/ethnicity, fatigue, depressive symptom severity, and sleep quality (and APOE genotype and cognitive reserve for exploratory aims).Through inclusion of these additional covariates, we will correct for chance imbalances in pre-specified important prognostic variables and account for that part of the variability in the outcome measure that is due to the covariates, thus improving the precision of the treatment effect. Additionally, to address our tertiary exploratory objectives, we will include covariate by treatment interactions for APOE status and cognitive reserve in these models, thus allowing the determination of whether the effect of donepezil differs based on the level of the covariates. One model will be fit that includes all the covariates and their interactions with treatment. Non-significant interactions will be removed from the model. Regression diagnostics, residual plots, and exploratory analyses will be done to identify appropriate transformations for the variables in these analyses. Order of priority in choosing a transformation will be to satisfy the 1) linearity assumption, 2) homogeneity of variances assumption, and 3) normality assumption. Interim analyses will be undertaken after 1/2 of the participants have been accrued and followed for 24 weeks. Results of the interim analysis will be compared to the stopping rules detailed below and will be presented to the Cancer Center DSMB.

12.5 Secondary Endpoint(s)

The secondary outcomes include additional neurocognitive measures as well as patient reported outcomes such as self-report cognitive function, fatigue, sleep disturbance, and depression (see Section 7.2). These outcomes are primarily continuous variables that will be measured at baseline, 12, 24 (end of treatment) and 36 weeks. They will be analyzed as described in Section 12.4 for the primary outcome.

12.6 Retention and Compliance

Drop-outs are a difficult problem and one that is best handled proactively rather than retrospectively. We will make a concerted effort to minimize the number of drop-outs, beginning with the participants who are accrued. If a participant seems unwilling to participate or indicates that she may not be able to be compliant, we will not press her to participate. In addition, participants who refuse treatment at some point during the course of therapy will be encouraged to stay in the study and provide outcome data. Despite our best efforts, some data will be missing due to missed visits or participants refusing further participation. We propose to analyze the data using SAS Proc Mixed, a program that provides several computational methods for obtaining maximum likelihood estimates for repeated measures problems, allows for unbalanced designs, missing data at some times, structured or unstructured covariance matrices, and growth curve parameterizations of time effects. Additionally, we will employ multiple imputation methods to assess the treatment effect on the outcomes using the SAS multiple imputation procedures. Both the mixed models and imputation analyses assume participants 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 are missing. However, we will use logistic regression to see if we can determine which covariates, if any, are related to missingness, and these covariates will be used to create a propensity-to-be-missing score which will used to generate a stratified analysis as described by Baker et al[58]. Additionally, exploratory analyses using multiple imputations will assess the treatment effect over a range of assumptions regarding the missingness, allowing us to assess the sensitivity of our assumptions.

Compliance is defined as the number of pills consumed over the course of the trial divided by the ideal number that should have been consumed over that period. It will be calculated based on the patient's self-reported pill diaries. The primary analyses estimating treatment efficacy will include all randomized participants, regardless of compliance. Additional exploratory analyses will assess the treatment effect in those patients who were at least 75% compliant.

12.7 Reporting and Exclusions

Descriptive reports will consist of summary statistics (means, standard deviations, proportions, etc.) for participant characteristics and outcome measures by treatment arm, actual versus projected accrual, participation by the various NCORP sites, quality control information (retention, missing data, etc.), and a summary of toxicities and adverse events. Tables, graphs, and charts will be used to illustrate the data when appropriate. These reports will be prepared and presented to the WF DSMB committee every six months. All life threatening or greater toxicities (using CTCAE version 4 criteria) and severe adverse events will also be reported to the IRB and the WF Cancer Center Toxicity Review Committee for further action.

12.8 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of donepezil. Toxicities will be determined using the CTCAE v4.0 for Toxicity and Adverse Event Reporting, and participants will be evaluable for toxicity from the time of their first dose of donepezil or placebo. Fisher exact tests will be used to assess treatment differences in the incidence of individual toxicities, and logistic regression will be used to assess treatment differences in the incidence of any grade 3 or higher toxicity adjusting for baseline participant characteristics.

12.9 Evaluation of Response

Tumor response will not be evaluated in this trial.

12.10 Interim Analysis

For ethical considerations, we will incorporate a single interim analysis into the design that allows stopping for rejection of the null hypothesis. We will not allow early stopping for acceptance of the null hypothesis as the effect of donepezil on the secondary outcomes would still be of interest. The rejection boundaries were determined by the S-Plus software module SeqTrial (using an alternative boundary shape parameter of .75). This two-stage design will require a maximum sample size that is approximately 3.5% greater than the fixed sample design; a maximum of 276 participants will be randomized, approximately 138 to each arm. The interim analysis will occur after 138 participants have been accrued and followed for 24 weeks. If the two-sided p-value of the test statistic comparing the two treatment arms is less than 0.0154 during the interim analysis, the study will be stopped and the null hypothesis rejected. Otherwise the trial will continue until 276 participants have been accrued, at which point the null hypothesis will be

rejected if the two-sided p-value < .0416. Although the two-stage design has a larger maximum sample size (276 vs 266), it does have a smaller expected sample size compared to that of a single stage design under the alternative hypothesis. Under the null hypothesis, the probability of stopping at the first stage is 2%, and the expected sample size is approximately 273. Under the alternative hypothesis, the probability of stopping early is 46%, and the expected sample size is approximately 213.

13. SITE REGISTRATION

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilized five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list

all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Act as the site-protocol Principal Investigator (PI) on the IRB approval

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

Protocol documents are found on the CTSU website, but supplemental documents may be available on the Wake Forest NCORP Research Base website.

Permission to view and download the neurocognitive test packet are restricted and is based on person specific training and is housed on the Wake Forest NCORP Research Base website.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least on participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Included the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements:

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Protocol Specific Requirements for WF-97116 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Neurocognitive training and certification through the Wake Forest NCORP Research Base is required prior to patients being enrolled.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log onto the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' side of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' website using your CTEP-IAM username and password;
- Click on *Regulatory* at the top of your screen;
- Click on the *Site Registration*;
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

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Appendix A – Moderate Risk QTc Prolonging Medications

A
- Albuterol
- Alfuzosin
- Amantadine
- Amisulpride
- Amitriptyline
- Amoxapine
- Apomorphine
- Arformoterol
- ARIPiprazole
- ARIPiprazole Lauroxil
- Atazanavir
- AtoMOXetine

B
- Bortezomib
- Bosutinib
- Buserelin

C
- Capecitabine
- Chloral Hydrate
- ClomiPRAMINE

D
- Dabrafenib
- Dasatinib
- Degarelix
- Desflurane
- Desipramine
- DiphenhydrAMINE (systemic)
- Doxepin (systemic)
- Doxepin (topical)

E
- Ebastine
- Eperisone
- EriBULin
- Ezogabine

F
- Famotidine
- Felbamate
- Fingolimod
- Fluconazole
- Fluroruracil (systemic)
- Formoterol
- Foscarnet
- Fosphenytoin

G
- Gadofosveset
- Galantamine

H
- Halothane
- Histrelin
- HydrOXYzine

I
- Ibandronate
- Imipramine
- Indacaterol
- Indapamide
- Isoflurane
- Isoproterenol
- Isradipine
- Itraconazole
- Ivabradine

L
- Lacidipine
- Lapatinib
- Levalbuterol
- Levosimendan
- Levosulpiride
- Lithium
- Loperamide
- Loperamide Oxide

M
- Maprotiline
- Mefloquine
- Methotrimeprazine
- Metoclopramide
- MetroNIDAZOLE (systemic)
- Mianserin
- Mirabegron
- Mirtazapine
- Moexipril

N
- Nelfinavir
- NIcarDIPINE
- Norfloxacin
- Nortriptyline

O
- Octreotide
- OLANZapine
- Olodaterol
- Oteracil
- Oxaliplatin
- Oxytocin

P
- PARoxetine
- Pasireotide
- Pentamidine (Oral Inhalation)
- Periciazine
- Posaconazole
- Promethazine
- Propofol
- Protriptyline

R
- Ranolazine
- Rilpivirine
- RisperiDONE
- Ritonavir
- RomiDEPsin

S
- Sameterol
- Sertraline
- Sevoflurane
- Solifenacin
- SORAfenib
- Sulfamethoxazole
- SUNItinib

T
- Tacroliumus (Systemic)
- Tamoxifen
- Tegafur
- Terbutaline
- Thiothixene
- TiZANidine
- Tolerodine
- TraZODone
- Treprostinil
- Trifluridine
- Tipiracil
- Trimethoprim
- Trimipramine
- Triptorelin
- Tropisetron

V
- Vardenafil
- Venlafaxine
- Vilanterol
- Vorconazole
- Vorinostat

See up to date link: https://www.uptodate.com/drug-interactions/?search=donepezil&usage_type=default&source=responsive_results&display_rank=3#di-analyze

Appendix B – Moderate Risk Bradycardia-Causing Agents

A
- Acebutolol
- Ajmaline
- Alectinib
- Amiodarone
- Arotinolol
- Atenolol

B
- Beractant
- Betaxolol (Systemic)
- Bisoprolol
- Bovine Lipid Extract Surfactant
- Bovine Lung Extract

C
- Calfactant
- Carteolol (Ophthalmic)
- Carvedilol
- CloNIDine
- Crizotinib

D
- Dexmedetomidine
- Digitoxin
- Digoxin
- DiltiaZEM
- Dronedarone

E
- Esmolol

F
- Fingolimod

G
- Galantamine
- GuanFACINE

I
- Ivabradine

L
- Labetalol
- Lanreotide
- Levobunolol
- Lofexidine
- Lucinactant

M
- Methyldopa
- Metiprandolol
- Metoprolol

N
- Nadolol
- Nebivolol

O
- Octreotide
- Oxprenolol

P
- Pasireotide
- Penbutolol
- Pilsicainide
- Pindolol
- Poractant Alfa
- Propanfenone
- Propranolol

R
- Rivastigmine

S
- Sotalol
- SUFentanil

T
- Timolol (Ophthalmic)
- Timolol (Systemic)
- TiZANidine

V
- Verapamil

See up to date link: https://www.uptodate.com/drug-interactions/?search=donepezil&usage_type=default&source=responsive_results&display_rank=3#di-analyze

Appendix C – Succinylcholine/Acetylcholinesterase Inhibitors

- Distigmine
- Edrophonium
- Neostigmine
- Physostigmine
- Pyridostigmine

See up to date link: https://www.uptodate.com/drug-interactions/?search=donepezil&usage_type=default&source=responsive_results&display_rank=3#di-analyze

Appendix D – High Risk QTc Prolonging Medications

A
- Ajmaline
- Amiodarone
- Anagrelide
- Arsenic Trioxide
- Artemether
- Asenapine
- Astemizole

B
- Bepridil
- Buprenorphine

C
- Cisapride
- Citalopram

D
- Disopyramide
- Dofetilide
- Domperidone
- Dosulepin
- Dronedarone

E
- Eliglustat
- Escitalopram

F
- FLUoxetine
- Flupentixol

H
- Halofantrine

I
- Ibutilide

Iloperidone

L
- Lopinavir
- Lumefantrine

M
- MiFEPRIStone

N
- Nilotinib

P
- Paliperidone
- Pimavansrin
- Pimozide
- Pipamperone [INT]
- Procainamide

Q
- QUEtiapine
- QuiNIDine
- QuiNINE

S
- Sotalol
- Sparfloxacin
- Sulpiride

T
- Terfenadine
- Tetrabenazine
- Thioridazine
- Toremifene

V
- Vandetanib
- Vemurafenib
- Vernakalant

Z
- Ziprasidone
- Zuclopenthixol

See up to date link: https://www.uptodate.com/drug-interactions/?search=donepezil&usage_type=default&source=responsive_results&display_rank=3#di-analyze

Appendix E – Guidelines for Reconsenting Patients
(A Result of Changes per Amendment 3, Released 5/16/2019)

1) All Patients:

    a. All patients currently on study should be reconsented to make them aware of potential interactions of study drug and certain concurrently taken medications

    b. All patients still receiving study drug will require an ECG to rule out unrecognized QTc prolongation or bradycardia

2) Patients currently taking the study drug and a moderate risk QTc prolongation medication (reference Appendix A):

    a. Patients taking the study drug and a moderate risk QTc prolongation medication (reference Appendix A) should be notified of the new amendment requirements and reconsented immediately. These patients will receive an ECG and heart rate assessment at the time of reconsent as per 1b above.

        i. Reconsented patients who have an **acceptable** QTc interval (< 500ms) on their ECG and who are **within the first 6 weeks** of study drug (Baseline – 6 Week) should refer to section 7.5 in the protocol for timing of additional ECG monitoring required in the amended protocol.
        ii. Reconsented patients who have an **acceptable** QTc interval (< 500ms) on their ECG and who are **beyond the study drug dose increase time point** (6 Week) will not require any further cardiac monitoring
        iii. Reconsented patients who have an **unacceptable** QTc interval (≥ 500ms) on their ECG and who **are within the first 6 weeks of study drug** (Baseline – 6 Week) should stop study drug and be followed as per protocol guidelines
        iv. Reconsented patients who have an **unacceptable** QTc interval (≥ 500ms) on their ECG and who are **beyond the study drug dose increase time point** (6 Week) may have the dose of study drug reduced by half (i.e. back to initial dose level of study drug). Such a patient would then require repeat ECG testing in 3-7 days at which time they would be allowed to continue on reduced dose of study drug (if QTc is < 500ms) or be taken off the study drug and followed per protocol guidelines (if QTc ≥ 500ms).

3) Patients currently taking the study drug and a moderate risk bradycardia-causing agent (reference Appendix B):

    a. Patients taking the study drug and a moderate risk bradycardia-causing agent (reference Appendix B) should be notified of the new amendment requirements and reconsented immediately. These patients should receive a heart rate assessment at the time of reconsent (use the ECG required as per 1b above).

        i. Reconsented patients who have an **acceptable** heart rate (≥ 55) and who are **within the first 6 weeks** of study drug (Baseline – 6 Week) should refer to section 7.5 in the protocol for timing of additional heart rate monitoring required in the amended protocol.

ii. Reconsented patients who have an **acceptable** heart rate (≥ 55) and who are **beyond the study drug dose increase time point** (6 Week) will not require any further heart rate monitoring.
iii. Reconsented patients who have an **unacceptable** heart rate (< 55) and who **are within the first 6 weeks of study drug** (Baseline – 6 Week) should stop study drug and be followed as per protocol guidelines.
iv. Reconsented patients who have an **unacceptable** heart rate (< 55) and who are **beyond the study drug dose increase time point** (6 Week) may have the dose of study drug reduced by half (i.e. back to initial dose level of study drug). Such a patient would then require repeat heart rate testing in 3-7 days at which time they would be allowed to continue on reduced dose of study drug (heart rate ≥55) or be taken off the study drug and followed per protocol guidelines (if heart rate < 55).

The results of these ECG and heart rate assessments, along with the date of the assessment, should be recorded on the Cardiac Monitoring Form under Other Assessment and should be submitted to the WF NCORP RB.