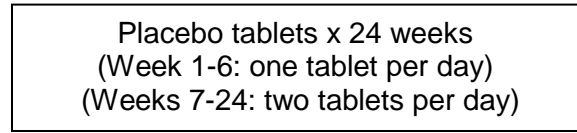
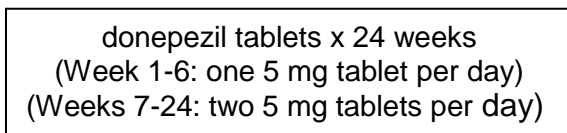
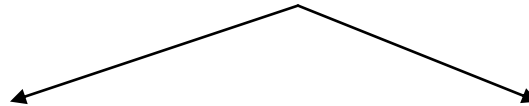
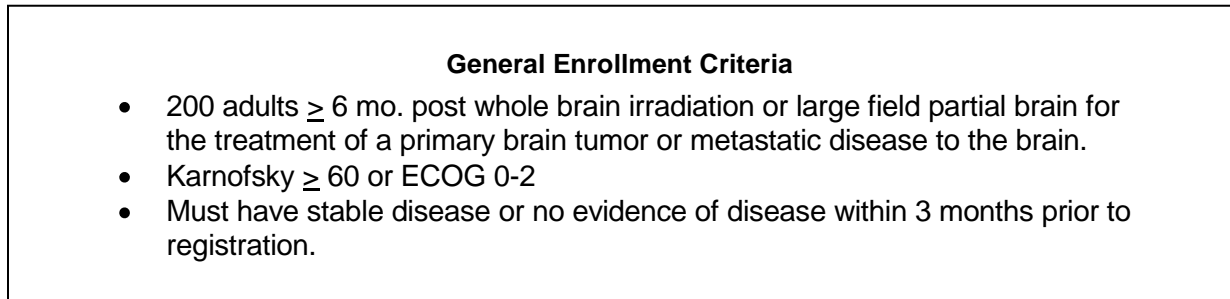


**A Phase III Double Blind, Placebo Controlled Study of Donepezil in
Irradiated Brain Tumor Patients**

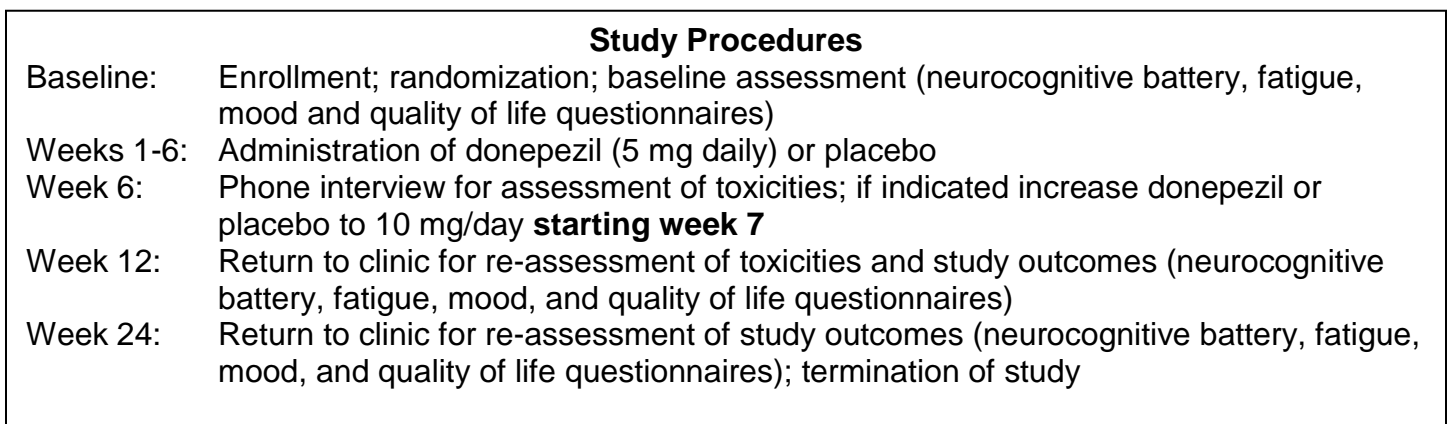
Stephen R. Rapp, Ph.D.

*Accrual Goal: 200 patients

SCHEMA



Stratification will be performed by irradiation type and accrual site.



OBJECTIVES

Primary Protocol Objectives

To determine whether administration of donepezil for 24 weeks to ≥ 6 month survivors of partial or whole brain irradiation will improve the neurocognitive symptom cluster (objective cognitive performance deficits + subjective cognitive functional impairments) as compared to placebo. The specific hypothesis to be tested is:

Objective 1A. Overall cognitive performance will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Objective 1B. Subjective cognitive complaints/symptoms will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Objective 1C. Fatigue will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Secondary Protocol Objectives

To determine whether administration of donepezil for 24 weeks to ≥ 6 month survivors of partial or whole brain irradiation will improve mood and QOL as compared to placebo. The specific hypothesis to be tested is:

Objective 2A. Cancer-related quality of life will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Objective 2B. Overall mood will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Eligibility Criteria

- Adults >18 years old.
- Life expectancy of at least > 30 weeks.
- Must have received a prior course of at least 30 Gy fractionated whole or partial brain irradiation for treatment of a primary brain tumor or metastatic disease to the brain.
- Must have completed radiation > 6 months prior to enrollment and have no radiographic evidence of brain disease, or stable brain disease defined as no evidence of tumor progression in the 3 months prior to enrollment.
- Patients who have undergone one or more treatments with single fraction stereotactic radiosurgery (SRS) in addition to whole or partial brain irradiation are eligible.
- Radiation treatment records must be available for all prior radiation treatments (external beam and/or SRS).
- Patients who have received PCI (prophylactic cranial irradiation) are eligible.
- Karnofsky Performance Status must be > 60 or ECOG 0-2.
- Treatment with steroids, anti-cholinergics, anti-epileptics, anti-depressants, and /or sedatives/benzodiazepines is acceptable, but the patient must be on a stable or decreasing dose at the time of study entry.
- Patients using narcotic analgesics on a stable dose and/or prn basis are eligible.
- Patients currently on a stable dose of Methylphenidate or Dexamphetamine are eligible.
- For patients with brain metastases, if extracranial primary or metastatic disease is present, it must have responded to local and/or systemic treatment. Must be stable in the 3 months prior to enrollment.
- Must not be receiving chemotherapy at the time of enrollment.
- Patient must not have any planned therapy, including surgery, brain radiation of any type, chemotherapy, or immunotherapy during the next 30 weeks for brain or extracranial primary metastatic disease.
- Hormonal therapy for patients with breast or prostate cancer is acceptable.
- Breast patients receiving therapy with Herceptin are allowed.
- Patients must be able to give informed consent to participate in the study, including signing the consent form.
- Patients must have a telephone.

Exclusion Criteria

- Patients cannot be currently taking dementia drugs, cognitive enhancers, neuroleptics, and/or anti-parkinsonian agents. For patients who have used these drugs in the past, they must not have used them in the 2 weeks prior to enrolling on the study.
- Hypersensitivity to donepezil.
- Patients may not currently be taking Ketoconazole or Quinidine
- Arrhythmias including bradycardia or heart block
- Patients who have received, GliSite or other type of brain brachytherapy, (Gliadel Wafers permitted) convection enhanced delivery of immunotoxins, and/or any other investigational modalities for treatment of their brain tumor.
- The effects of donepezil on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men 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 treating physician immediately.
- 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.

Treatment Schedule

For the first 6 weeks of the study patients will take a single 5 mg Donepezil or placebo oral dose in tablet form. Following a positive toxicity review in Week 7, patients will take two 5 mg Donepezil tablets daily (10 mg total) or placebo through Week 24 at study termination. **It will be recommended those patients take tablets (donepezil and placebo) in the evening with or without food.**

Neurocognitive Battery

The neurocognitive battery will consist of 3 test booklets: Baseline Booklet, 12 Week Booklet and 24 Week Booklet. Each booklet will be completed by the patient at the appropriate visit.

You must use the forms indicated for Baseline, 12 week, and 24 weeks assessments.

Certification Procedures

Certification for the administration of the neurocognitive battery and questionnaires will include didactic presentations, role-played administrations with Q&A and feedback. All training will be supervised by experienced test administrators (Dr. Rapp at WFUSM, June Fletcher-Steede, Site Coordinator) who will be responsible for certifying test administrators. They will also be responsible for helping staff maintain certification by having regular meetings to discuss the procedures and providing supplemental training as needed. See Appendix 11 for certification requirements.

Pegboards will be provided on loan by the WFU Research Base. A pegboard will be shipped to the site when the study is opened. Pegboards must be returned to WFU Research Base at completion of the study.

Agent Ordering and Distribution

Donepezil (Aricept) is manufactured and marketed by Eisai Inc., Teaneck NJ and distributed by Roerig Division of Pfizer Inc, New York, NY. Pfizer, Inc. will provide donepezil and placebo at no cost for patients participating in this study.

At randomization, Biologics, Inc will automatically receive notification the patient has been enrolled. Biologics will call the site to obtain further information. Stratification will be performed by irradiation type and accrual site.

Storage & Stability

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

STUDY PARAMETERS

	Baseline	Wk 6	Wk 12	Wk 24
Informed consent	X			
Demographics	X			
Performance status	X		X	X
Brain MRI (B)	X			
Serum pregnancy test (A)	X			
Flow Sheet/Toxicity Assessment	X	X	X	X
Telephone Contact Form(C)		X		
Patient Survey Form	X			
Current Medication Form	X	X	X	X
Baseline Booklet	X			
12 Week Booklet			X	
24 Week Booklet				X
Pill Count (monthly & each visit)		X	X	X

A– Serum negative pregnancy test is required in women of child-bearing potential within 10 days of registration.

B – Brain MRI Report and CD – Required within histology parameters (Appendix 16) prior to registration. MRI must be obtained with and without contrast. Submit invoice for MRI CD to Attn. Gina Enevold, MSN, 2000 West First Street, Suite 401, Winston Salem, NC 27104.

C-- Phone interview for toxicity assessment.if indicated, increase donepezil/placebo to 10mg/day starting week 7.

HISTOLOGY Parameters for Brain MRI

1. MRI for brain mets & PCI are required within 3 months of registration.

2. MRI requirements are based on histology below:

Who Grade 3 or 4 (3 months prior to registration)

Glioblastoma
Anaplastic Astrocytoma
Anaplastic Oligodendroglioma
Oligoastrocytoma
Anaplastic ependymoma
Anaplastic or malignant meningioma

Who Grade 2 (6 months prior to registration)

Astrocytoma
Oligodendroglioma
Oligoastrocytoma
Ependymoma

Who Grade 1 (1 year prior to registration)

Meningioma
Pilocystic Astrocytoma

Baseline:

- * Initial Labs: None
- * MRI required within histology parameters prior to registration.
- * Study medication will be provided free of charge.

Patients will receive (2) \$20.00 gift after the baseline visit to cover travel expenses. (Maximum total amount per patient not to exceed \$60.00)

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base Protocol # 91105

BRAIN MRI CD SUBMISSION FORM

Patient Name/Initial _____ PID# _____

Date MRI performed ____/____/____ Site submitting _____

Site Contact person _____ Phone # ____/____/____

Label MRI CD with patient's initials and PID#. Place CD in hard plastic cover and protect with bubble wrap. Mail CD and invoice with this form in a protective envelope to address below:

**Attn: Gina Enevold, MSN
2000 West First Street
Suite 401
Winston Salem, NC 27104**

***** Sites will be reimbursed \$25 for providing The MRI CD. *****

Please submit invoice for the MRI CD and provide the following reimbursement information:

Name of person to whom reimbursement is to be sent:

Mailing Address: _____

Phone # ____/____/____

Patient Health Questionnaire (PHQ)

Assessing Participant Emotional Distress

Included in the test booklet is the Patient Health Questionnaire (PHQ), the last questionnaire in each booklet). The PHQ assesses depressive symptom severity which can co-occur with serious medical conditions like brain tumors. The value of the PHQ is to ascertain who among study participants is experiencing moderate to severe distress so s/he can be encouraged to seek treatment. The study drug is not known to cause or increase depression.

The PHQ is scored by first assigning a numeric value to each of the 9 items ('Not at all'=0; 'Several days'=1; 'More than half the days'=2; 'Nearly every day'=3) and then totaling item scores. The minimum score is 0 and the maximum score is 27; a score ≥ 19 indicates moderate to severe depressive symptom severity.

At the end of each assessment period, add up the total score of the PHQ. If it is ≥ 19 or if item '9' is scored 1,2, or 3, then take a few minutes to discuss the participant's distress and what s/he is doing to manage it.

You should mention:

- Distress is common among persons with serious medical conditions
- Treatments are available that might reduce the distress
- Discussing your distress with your doctor, family, friends, pastor or specialist (counselor, therapist) can be helpful
- Offer assistance making a referral to a mental health specialist if the person is interested.
- Inform the participant that you will notify the physician overseeing this study at the site as well as the study PI (Drs. Rapp and Shaw at Wake Forest University School of Medicine)
- Specifically ask:
 - In the past week, have you thought you would be better off dead or wished you were dead?
 - In the past week, have you wanted to harm yourself?
 - In the past week, have you thought about suicide?
 - In the past week, have you developed a suicidal plan?
 - In the past week, have you tried to kill or hurt yourself?
 - Do you think you might commit suicide

If participant indicates s/he is **currently actively suicidal (i.e., has a plan and intent), ask him/her to remain with you while you contact the site physician. If that is not possible, ask for permission to contact a family member.**

- Inform the site physician or family member and seek their guidance on how to get immediate help for the individual.
- If no one is available, you can call 911 or accompany the individual to the nearest Emergency Department. This is exceedingly rare in studies such as this.

If participant is **not actively suicidal, encourage him/her to speak with his/her doctor, family, friends, pastor or mental health professional about getting additional help.**

Note occurrence on PHQ Summary Sheet.