Title: Low Dose RT to Reduce Cerebral Amyloidosis in Early Alzheimer's

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CLINICAL STUDY PROTOCOL

TITLE:	**Phase IIa Trial of Low Dose Radiation Therapy to Reduce Cerebral Amyloidosis in Early Alzheimer's Dementia**
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Study Design

Schema

For Patients with Early Alzheimer's Dementia based on NINCDS-ADRDA Criteria		
Prior to treatment	**Treatment: Radiation therapy**	**Follow-up**
• Signed Consent • History and Physical • Neurocognitive Function Assessments • Psychological Function Assessments • Quality of Life Assessments • FDG- PET Scan • Amyvid PET Scan • Baseline Toxicity scores • Ocular Exam (pts with at least 1 natural lens only)	Whole brain radiation therapy • Cohort 1: Subjects # 1 – 15 10 Gy in 5 daily fractions • Cohort 2: Subjects # 16 – 30 20 Gy in 10 daily fractions	• **6wks, 3mo, 9mo, 12 mo**: Neurocognitive function Assessments Psychological Function Assessments Quality of Life Assessments Physical Exam and Toxicity Assessments • **6mo:** FDG-PET scan Amyvid PET Scan • **9mo:** Ocular exam (pts w/ at least 1 natural lens only)

Subject Population: See Section 5 for Subject Eligibility

Protocol Synopsis

Protocol Number	HM20004955
Protocol Short Title	Low Dose RT to Reduce Cerebral Amyloidosis in early Alzheimer's
Protocol Title	Phase IIa Trial of Low Dose Radiation Therapy (RT) to Reduce Cerebral Amyloidosis in Early Alzheimer's Dementia (AD)
Device	Commercially and widely available linear accelerator
Standard-of-Care Treatment	At the present time there is no "active" treatment for AD. The standard options available are solely for symptomatic relief. This study is designed to directly treat the cerebral amyloid deposits believed to be "triggering" event leading to neurofibrillary tangles and neurocognitive decline with AD
Type of Protocol	Phase IIa
Protocol Design	Single arm, non-randomized trial, employing 2 sequential dose schedules
Study Objective	To assess outcomes following low dose whole brain RT in subjects diagnosed with AD on the basis of clinical and imaging findings. Study outcomes will include cerebral amyloid accumulation, neurocognitive function, safety, and adverse events with each of the 2 sequential RT dosing schedules.
Primary Endpoint	Evaluate safety and toxicity/adverse events associated with delivery of low dose whole brain irradiation in subjects with Alzheimer's dementia. Adverse events and reportable serious adverse event as defined by NCI Common Toxicity Criteria for Adverse Events (CTCAEv.4.0)
Secondary Endpoints	To determine whether low dose whole brain RT stabilizes or decreases cerebral amyloid deposits. To determine if neurocognitive function (NCF), psychological function (PF) ,and quality of life (QOL), assessed by accepted testing methods, is stabilized or improved by low dose whole brain RT. To determine whether there are correlations between NCF, PF, and/or QOL test results and PET imaging with respect to amyloid accumulations, including number, size and location.
Trial Population	Individuals greater than 55 years of age, with probable diagnosis of AD based on NINCDS-ADRDA criteria.
Number of Subjects	30 (15 in each RT dose schedule cohort)
Randomization	N/A
Number of Institutions	1

Eligibility Criteria	Subjects must meet all eligibility criteria: 1. Must be male or female, 55 years of age or older 2. Must be a native English speaker and have the legally authorized representative available for consenting if one has been designated. 3. Must be able to complete neurocognitive function assessments, psychological function assessments, and QOL assessments administered at screening visit 4. Rosen Modified Hachinski Ischemic Score≤ 4 5. Estimated survival of greater than 12 months 6. Meet the clinical definition of AD diagnosis based on NINCDS-ADRDA criteria, with confirmatory PET findings 7. If on any of the following medications for AD treatment must be a stable dose for 60 days or greater: Rivastigmine, Donepezil, Memantine, Glantamine, Tacrine 8. No current or past history of any oncologic disease mitigating low dose whole brain RT 9. No evidence of substance abuse (alcohol/or other drugs or dependence during previous 12 months (DSM-V criteria) 10. No clinically or radiographically significant evidence of stroke 11. No evidence of subdural hygroma or subdural hematoma 12. No active or recent (defined as within 3 months of screening) cerebral infection or hemorrhage 13. No current conditions that may lead to the subject being in an immuno-compromised state 14. No previous history of cranial radiation. 15. No history of seizure activity 16. No history of hydrocephalus 17. No Evidence of active dermatological skin disease of the scalp (except actinic keratosis) 18. No evidence of clinically significant major depressive disorder identified in a psychological diagnostic interview according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, FifthEdition (DSM-V) 19. No evidence of psychotic disorder or psychotic episode or bipolar affective disorder identified in a psychological diagnostic interview according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V) 20. No evidence of active suicidal or homicidal ideation according to psychological diagnostic interview 21. Not currently receiving other experimental treatments 22. Not currently requiring full time institutional care. 23. Not a pregnant, nursing or incarcerated individual.
Screening Testing	The following test / evaluation will be completed prior to initiation of treatment 1. History and Physical 2. Review of any available prior CT, MRI, or PET brain imaging studies 3. Psychological Diagnostic Interview completed by a licensed clinical psychologist 4. Neurocognitive function assessments (WTAR, MMSE, HVLT, BVMT-R, WMS-IV Digit Span and Coding subtests, Trailmaking Tests, California Oral Word Association Test and Semantic Fluency Test, Pegboard Test) 5. Psychological function assessments (PHQ-9, GAD-7) 6. QOL assessments (QOL-AD, QUALID, and ECog)

Baseline Testing	The following test / evaluation will be completed for all participants who met study criteria in the screening visit. The following test / evaluation will be completed prior to initiation of treatment: 1. Neurocognitive function assessments (WTAR, MMSE, HVLT, BVMT-R, WAIS-IV Digit Span and Coding subtests, Trailmaking Tests, Controlled Oral Word Association Test and Semantic Fluency Test, Pegboard Test, BNT, and JLO) 2. Psychological function assessments (PHQ-9, GAD-7) 3. QOL assessments (QOL-AD, QUALID, ECog) 4. Amyvid and FDG PET/ CT Scans 5. Toxicity Evaluation using CTCAE version 4.0for following sites Skin, Eye, Ear and CNS 6. Blood Draw for Neuronal Specific Exosome Analysis
Other Variables	Ocular exams will be performed for each subject who has at least one natural lens and are intended to determine if any subject has a supranuclear cataract
Imaging Requirements	FDG-PET and Amyvid PET scans will be required prior to treatment and at 6 months following completion of therapy. These scans will be read by board certified diagnostic radiologist / nuclear medicine specialist who has been certified to interpret these scans
Treatment Procedure	Subjects will receive whole brain RT using commonly employed and standard external beam techniques. The initial 15 subjects will be in Cohort 1 and receive the lower dose regimen (5 x 200 cGy). If after the last subject in Cohort 1has been followed for 9 months, and there have been no events that cause stoppage of the trial, Cohort 2 will be enrolled using a higher dose regimen of 10 x 200 cGy. Subjects in both Cohorts will be followed for a total of 12 months. All subjects will receive 1 treatment per day and will receive treatments on consecutive week days (Monday through Friday).
Trial Visits and Follow-Up	All subjects will be followed as per study calendar. Scheduled post treatment visits are at 6 weeks, 3, 6, 9 and 12 months
Stopping Rules	This Study will be stopped for any of the following reasons: 1. Any subject's death attributed to the radiation, or any irreversible adverse effects caused by the treatment in either group (excluding alopecia) 2. More than 3 of first 10 subjects develop a Grade 3 adverse event as per CTCAE v.4.0 in either Cohort 3. 50% or more of the subjects in either cohort have increase in amyloid based on FDG and/or Amyvid PET Scan 4. 50% or more of the subjects show greater than a 4-point decrease in MMSE 5. If any subject selects a response 1-3 on item 1.i. of the PHQ-9 at any time during the study, the Suicide Behaviors Questionnaire-Revised (SBQ-R) will be administered and if the score on this scale is ≥7, the study will be stopped and the subject will be referred for appropriate clinical care. 6. Any subject develops a Grade IV adverse event in either Cohort

Data Safety Monitoring Board (DSMB)	This trial will utilize a DSMB consisting of two physicians who have expertise in radiation and an arbitrator who has expertise in Alzheimer's management. They will meet bi-annually to review all new data that has been collected on any subject under treatment or in follow up.
Treatment Cohorts	There will be two dose levels: 1. 5 x 200 cGy 2. 10 x 200 cGy
Trial Duration	12 months follow up after completion of radiation therapy for each subject. It is thought overall time will be 48 months.

Eligibility Criteria Worksheet

Subject #: _____ Subject Initials: _____

Yes	No	Criteria for Eligibility (All responses must be YES)
		1. Male or female and is at least 55 years old.
		2. Must be a native English speaker and have the LAR available for consenting if one has been designated.
		3. Able to complete neurocognitive function assessments, psychological function assessments, and QOL assessments administered at screening visit.
		4. Rosen Modified Hachinski Ischemic Score $\leq$ 4
		5. Estimated Survival of greater than 12 months.
		6. Meets the clinical definition of AD based on NINCDS-ADRDA criteria, with 7. confirmatory FDG-PET and/or Amyvid-PET scan findings
		8. If on any of the following medications, must be on a stable dose for 60 days or 9. greater: Rivastigmine, Donepezil, Memantine, Glantamine, Tacrine.

Yes	No	Criteria for Exclusion (All responses must be NO)
		1. Current or past history of any oncologic disease mitigating low dose whole brain RT
		2. Evidence of substance abuse: alcohol/or other drugs or dependence during previous 12 months (DSM-V criteria)
		3. Clinically or radiographically significant evidence of stroke
		4. Evidence of subdural hygromas or subdural hematomas
		5. Active or recent (defined as within 3 months of screening) cerebral infection or hemorrhage
		6. Any current conditions that may lead to the subject being in an immuno-compromised state
		7. Any previous history of cranial radiation.
		8. History of seizure activity
		9. History of Hydrocephalus
		10. Evidence of active dermatological skin disease of the scalp (except Actinic Keratosis)
		11. Evidence of clinically significant major depressive disorder identified in a psychological diagnostic interview according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V)
		12. Evidence of psychotic disorder or psychotic episode or bipolar affective disorder 13. identified in a psychological diagnostic interview according to the criteria of the 14. Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V)
		15. Evidence of active suicidal or homicidal ideation according to psychological diagnostic interview
		16. Currently receiving other experimental treatments
		17. Currently requiring full-time institutional care
		18. A pregnant, nursing or incarcerated individual.

1 Introduction

Alzheimer's disease (AD) is currently the 7th leading cause of death in the United States with approximately 5.9 million Americans living with the progressive and debilitating condition (1). AD predominantly affects older individuals as 86% of AD cases are in individuals 65 years of age and older (2). Further, approximately $172 billion of health care spending annually can be attributed to costs associated with AD care (3) on top of the 11 million caregivers that provide care in unpaid capacities, such as family members, friends, etc.

In 1975, a cohort of nearly 2,800 people who were 65 years of age and free of dementia provided a basis for an incident study of dementia, as well as for Alzheimer's disease. This cohort was followed for almost 29 years and its sentinel findings included a significantly higher lifetime risk for both Alzheimer's and dementia in women compared to men (4). The estimated lifetime risk was nearly one in five for women compared to one in ten for men (5). In addition to the higher lifetime risk in women, longer life expectancies and the aging of the "baby boomers" combined with improved healthcare is expected to increase the number of Americans who will reach 85 years of age or more (6).It is very clear that as the age increases, so does the incidence of Alzheimer's and other forms of dementia.

Between 2010 and 2050, it is expected that there will be a 30% increase in the number of individuals greater than 85 years of age. Although the absolute number may not appear to be significant, this increase of approximately 17 million people will challenge the healthcare system because of the cost associated with dealing various acute and chronic medical conditions including AD.

While other major causes of death continue to experience decline, those from AD continues to rise. In 1991, only approximately 14,000 death certificates recorded Alzheimer's disease as an underlying cause. In 2006, it was noted that there was an increase of approximately 46% in which Alzheimer's disease was listed as the direct cause of death. This is significant when compared to the present leading cause of death, heart disease, which decreased by 11% in the same time (7).

From a neurophysiological standpoint, what is known about Alzheimer's disease is that there appears to be a progressive process that is associated with the deposition of β Amyloid (8,9). This appears to have a triggering mechanism, which causes the phosphorylation of a TAU protein, which then leads to development neurofibrillary tangles (NFT), which are believed to be responsible for memory loss, especially short-term and other associated problems with Alzheimer's related dementia (10, 11). It also appears that there may be a selective deposition of the β Amyloid in the hippocampus and the prefrontal regions, which are the major short-term memory regions of the brain (12).

Extensive research has been ongoing to try to find various ways in which the excess deposition of βAmyloid, the removal of excess β Amyloid, the initiation sequence that it is involved in with

phosphorylated TAU and other selective processes can be altered in an effort to mitigate the devastating end term results. To date, there have been several trials, including a vaccine trial performed in Europe and in the United States, which seem to show that clearance of the β Amyloid is possible (13). However, there was not significant improvement in neurocognitive function (NCF), which led to the discontinuation of these trials.

This lack of improvement in NCF was believed to be secondary to the fact that the β Amyloid had already resulted in the phosphorylation of the TAU protein and development of NFT. Thus removal of the initiator was accomplished, but only after the end damage had developed. Then why consider irradiation?

The use of radiation in the treatment of non-oncologic human populations has enjoyed a long history and a more recent renaissance. It is now commonly used to prevent heterotopic bone formation (14-15) and re-development of keloids or heterotrophic scars post-operatively (16-17). It has been shown in a randomized trial to effectively treat planter fasciitis (18) and has been used in post-operative treatment of resected pterygium (19-20). It has been used in the treatment of Hidradenitis suppurativa, Duputryen's disease and Ledderhose's disease. (21-22). These sites routinely are treated with low dose fractionated external beam irradiation, commonly in doses that ranging from 7to 24 Gy.

The use of external irradiation has also been reported in the treatment of symptomatic systemic amyloidosis. In published peer reviewed articles treatment sites have include trachea-pulmonary (23-24) ocular (25-26), laryngeal (27) and for use as a conditioning agent for autologous Bone Marrow Transplant in patients with systemic amyloidosis (28).These reports used external beam irradiation that ranged from 5.5 – 45Gy and detail durable local control with these doses.

Because of this effect, a series of basic science experiments were initiated with genetically altered mice: the B6; Cg – Tg (Appswe, PSEN1dE9) 85 Dbo/J (005864)over express amyloid and the B6; 129-Psen1tm1MpmTg (APPswe tauP301L) over express both amyloid and TAU, making them prone to early Alzheimer's disease development.

Both single and fractionated Central Nervous System (CNS) irradiation in a genetically altered mouse model were tested, and have shown similar results with reduction in amyloid plaque number, size and volume. Moreover, the fractionated studies we have demonstrated statistically significant improvement in the treated mice using the Morris Water Maze Test when compared to control non-treated animals, an effect which held up whether the animals were adolescent, mature or aged (up to 18 months old).

The exact mechanism by which radiation therapy confers benefit in the Alzheimer's disease mouse model will be difficult to elucidate as the exact pathobiology of Alzheimer's disease is not known.

Possible mechanisms include the following: reduction of β amyloid by reducing production or increasing clearance; reduction in Tau; induction of beneficial inflammatory mechanisms; induction or inhibition of heat shock proteins; altering cerebral microvasculature; and/or reversal of maladaptive neuroplasticity in the hippocampus. Investigations of these possible mechanisms are currently underway.

One of the complications related to studying Alzheimer's disease is the actual diagnosis. Unlike malignancies where a biopsy can be obtained, Alzheimer's disease is a diagnosis of exclusion or made at autopsy. While the Europeans have recently identified and agreed on cerebral spinal fluid (CSF)biomarkers for diagnosis of Alzheimer's disease, we have not accepted that premise in the United States. At the present time, PET imaging which utilizes various compounds has been utilized to identify depositions of amyloid in the CNS. More recently, there is some suggestive evidence that a specific type of cataract may be seen in a high percentage of patients with Alzheimer's disease related to possible β Amyloid deposition in the lens region (29-30). Many rely on the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA)criteria for clinical diagnosis of Alzheimer's disease.

While it is a diagnosis of exclusion, there are well-accepted neurocognitive tests (NCT) used to monitor Alzheimer's disease progression. The Mini Mental State Exam (MMSE) is one of the general NCT used to help establish the diagnosis of Alzheimer's dementia. There are other more sensitive neurocognitive tests available to track progression of Alzheimer's dementia, which we will use in this study. Table 1 lists the cognitive domains and NCT that will be used to comprehensively evaluate individuals' neurocognitive function (NCF) in this study. Note estimation of premorbid IQ is only completed at the screening appointment and administration of the JLO and BNT only occur at the baseline pre-treatment visit and the 12-months post-treatment follow up visit to minimize participant fatigue and familiarity with the test materials. Administration of the NCT at the screening visit will serve two purposes. Data obtained from the screening visit will ensure that subjects who are enrolled in the trial meet criteria for early AD based on the more comprehensive battery of tests, as diagnosis of dementia is improved with use of quantitative measurement of multiple domains (31). The NCT at this screening visit will also expose participants to the NCT and since practice effects are greatest between the first and second exposure to NCT (32), practice effects will be minimized using this exposure and repeated measures ANOVAs (analysis of variance).

Table 1. Neurocognitive Functioning Assessment Battery

Neurocognitive Domain	Neurocognitive Test
Estimated Premorbid Intelligence Quotient	Wechsler Test of Adult Reading (33)
Dementia Screener	MMSE-2 (33)
Processing Speed	Grooved Pegboard Test (33), Trailmaking Part A and B (34), Wechsler Adult Intelligence Scale-IV (WAIS-IV) Coding subtest (35)
Attention	WAIS-IV Digit Span subtest (35)
Visuospatial Skills	BVMT-R Copy subtest (36), Judgment of Line Orientation Test (JLO)*(33)
Language Skills	Boston Naming Test (BNT)* (33)
Learning and Memory	Hopkins Verbal Learning Test-R (HVLT-R) (37) and Brief Visual Memory Test-R (BVMT-R) (36)
Executive Functions	Controlled Oral Word Association Test (COWAT)and Semantic Fluency (38), Trailmaking Part B (34)

*The BNT and JLO tests will only be administered at baseline and 12 month follow up.

Psychological functioning and quality of life (QOL) will also be evaluated to monitor participants' emotional status throughout the trial. The Patient Health Questionnaire-9 (39) and the Generalized Anxiety Disorder-7 (40) questionnaires will be used to assess depression and anxiety, respectively. If any participant endorses suicidal ideation on the PHQ-9, the Suicide Behaviors Questionnaire-Revised (SBQ-R) (41) will be administered to fully evaluate the participant's suicidal ideation and study stopping rules will be implemented as needed to ensure the individual's safety. QOL will be evaluated by the Quality of Life in Alzheimer's disease (QOL-AD)(42) and Quality of Life in Late-stage Dementia (QUALID)(43) and Everyday Cognition (ECog) questionnaires (patient and caregiver forms) (44).

Concern may be raised regarding the use of whole brain irradiation and its potential deleterious effect on neurocognitive testing. There have been reports on post-radiation neurocognitive testing in the setting of prophylactic cranial irradiation (PCI), which is whole brain fractionated RT commonly employed for patients with pulmonary small cell carcinoma(45-47). The standard whole brain PCI dose is 2.5 Gy x 10, considerably higher than the 2.0 Gy x 5 or 2.0 Gy x 10 schemes planned in the present study. Furthermore, patients in the PCI studies also received chemotherapy in addition to whole brain irradiation, and chemotherapy itself effects long-term NCF (48). In these PCI reports (45-48), if any neurocognitive decline was identified, it was modest, occurred within a short interval, e.g. 6-9months, and improved. We are thus proposing a 9-month follow up period for the 1stsubject cohort (2.0 Gy x 5) before proceeding with the 2nd cohort (2.0 Gy x 10), although both cohorts will undergo NCF and QOL testing through 12 months.

Grosshans and colleagues from M. D. Anderson found that PCI is “unlikely to significantly affect NCF.” They evaluated cognitive function in small cell lung cancer patients who received PCI (mean 2.5 Gy x 10). After chemotherapy, but before PCI, 47% already had evidence of impaired cognitive function. On multivariate analysis, there were no significant further declines after PCI. On univariate analysis, there were unsustained, early decreases in executive and language function, which did not persist with follow-up (45). A Japanese group applied the Hopkins Verbal Learning Test (revised Japanese version, HVLT-R) in 40 whole brain RT patients, at baseline, 4 months, and 8 months. Whole brain fractionation was either 2.5 Gy x 4, 3.0 Gy x 10, or 2.5 Gy x 10. The respective probabilities of decline in HVLT-R total recall at 4 months were, respectively, 40%, 7%, and 0%, and at 8 months 13%, 14% and 0% (48).

Also applicable is a recent report of whole brain (and whole spine) radiation therapy (RT) for medulloblastoma in children, a population believed more vulnerable to cognitive decline from RT. They did not receive chemotherapy, rather RT alone, 36 Gy in 36 fractions (1.0 Gy BID) to the entire brain and spine, followed by a boost to 68 Gy in 68 fractions to the tumor bed, typically posterior fossa. Using the Wechsler Intelligence Scale for Children to give verbal quotient, performance quotient, and full-scale intelligence quotient, cognitive function was preserved for all test domains throughout the study at 3 months, 1 year, and 2 years, with no decline over time (49).

Low dose whole brain RT has demonstrated safety in many studies, and we will be using even lower doses. These lower radiation therapy doses have a history of excellent success for patients with non-cerebral amyloidosis, and have had durable response combined with the necropsy / neurocognitive testing in genetically altered Alzheimer’s disease mouse model, we decided to proceed with a human trial, using fractionated whole brain radiation doses of 2.0 Gy x 5, then 2.0 Gy x 10.Subjects will be followed with neurocognitive testing at 6 weeks, 3, 9,and 12 months post RT. Additionally, given that the development of supranuclear cataract has been reported in a high percent of AD patients, we will recommend ocular testing at baseline and at 1 year to assess a potential abscopal effect, collateral benefit to the non-targeted lenses from treatment of the primary disease in the brain (29-30).

With respect to the development of cataracts in association with AD, early and accurate diagnosis of Alzheimer’s disease (AD) is still a challenge and the confirmatory diagnosis is made by presence of features including beta-amyloid plaques postmortem. In 2014, Tian et al suggested that AD may have a common pathophysiology with supranuclear deposits of beta-amyloid in the human lens (29). The brain and the lens tissue both arise from the ectoderm tissue (neuroectoderm and surface ectoderm respectively). Their conclusions were based on a meta-analysis of studies, which provided mixed data regarding the correlation of beta-amyloid in the lens samples of patients with AD, Down syndrome and controls. Given the chronicity of the terminally differentiated cell types in the lens that may be affected by Alzheimer disease’s pathology, they concluded that there is a possibility than an ocular biomarker for early AD may exist in the lens. This would suggest that an early ophthalmic examination may provide a

window of hope into early diagnosis of AD. It may also provide an opportunity for early treatment and perhaps monitoring of improvement in supranuclear cataracts with systemic therapy.

A precedent for this is already found in Wilson's disease. Kayser-Fleischer (K-F) ring seen in Wilson's disease (WD) is due to copper deposition in the Descemet's membrane in the sclero-corneal junction in the eye. Although believed to be pathognomic of WD, it may be seen in many other hepatic conditions and intraocular copper-containing foreign bodies. The K-F ring detected in pre-symptomatic cases of WD may lead to speedy diagnosis and early management. Co-relation of K-F ring in WD to the disease severity, disappearance with successful treatment, reappearance with non-compliant treatment aids in management of WD. K-F ring detection in first-degree relatives of the index case is also important.

With the proposed ocular exams at baseline and at 9-months post treatment, we hope to detect any cataracts in the subjects and effects of the proposed radiation treatments. The questions we will have are how often we encounter cataracts in early Alzheimer's and whether they improve (an abscopal effect) after radiation therapy, even though the lenses will be excluded from the RT treatment fields. Exams will only be done for subjects who have at least one natural lens still present. Subjects with previous bilateral cataract corrections will not have ocular exams performed.

2 Study Purpose

The purpose of the study is to evaluate safety and toxicity/adverse events associated with delivery of low dose whole brain irradiation in subjects with early Alzheimer's dementia according to NINCDS-ADRDA Criteria.

As a secondary goal it will establish whether or not the intervention with low dose whole brain irradiation stabilizes or decreases cerebral amyloid deposits and whether these correlate with the recognized progression of Alzheimer's dementia. We will also collect information from the FDG and Amyvid PET Scans to determine if there is any correlation between neurocognitive/quality of life scores and changes in amyloid plaque size, number and location.

3 Study Design and Duration

An initial 15 subjects will be enrolled in the first treatment cohort (2 Gy x 5 fractions) and will be followed at 9 months after completion of treatment to assess safety and any toxicity/adverse events associated with treatment. The second treatment cohort will not be used until the last subject in the first dose cohort has completed 9 months of follow up. At that point, subjects #16-30 will be enrolled in the second dose cohort (10 daily fractions of 2 Gy). A total of 30subjects will be enrolled and each will be followed for a total of 12months to assess safety and toxicity/adverse events.

In Cohort 1 the 15 study participants will be enrolled in total at Virginia Commonwealth University Hospital. Once a total combined 15 subjects are entered, this cohort will be closed. In Cohort 2, the 15 study participants will also be enrolled in total at Virginia Commonwealth University. Once a total combined 15 subjects are entered (30 subjects total), this cohort will be closed, at which point the entire study will be close to accrual.

4 Study Objectives

4.1 Primary Aim

To evaluate the safety and toxicity/adverse events associated with delivery of low dose fractionated whole brain irradiation in subjects with early Alzheimer's dementia (AD).CTCAE Version 4.0will be utilized for toxicity evaluation.

4.2 Secondary Aims

4.2.1 To determine whether low dose whole brain RT stabilizes or decreases cerebral amyloid deposits

4.2.2 To determine by use of established neurocognitive function testing (NCT) whether low dose fractionated whole brain RT, utilizing the doses described, impact the disease progression of subjects with AD

4.2.3 To determine if psychological function (PF) and quality of life (QOL), using the established testing methods, is adversely affected by use of low dose whole brain irradiation.

4.2.4 To determine if there are correlations between NCF/PF/QOL test results and any changes identified by PET scan imaging based on amyloid number, size, and location.

5 Subject Selection: Inclusion and Exclusion Criteria

5.1 Inclusion Criteria

- Male or female subjects at least 55 years old.
- Must be a native English speaker and have the legally authorized representative available for consenting if one has been designated.
- Able to complete neurocognitive function assessments, psychological function assessments, and QOL assessments administered at screening visit.
- Has a Rosen Modified Hachinski Ischemic Score $\leq$4.
- Has estimated survival of greater than 12 months.
- Meets the clinical definition of Alzheimer's Disease based on NINCDS – ADRDA criteria and has confirmatory FDG-PET and/or Amyvid-PET scan findings.
- If on any of the following medications, must be on a stable dose for 60 days or greater: Rivastigmine, Donepezil, Memantine, Galantamine, Tacrine.

5.2 Exclusion Criteria

- Current or past history of any oncologic disease, which may mitigate the ability to receive low dose whole brain irradiation.
- Evidence of substance abuse: alcohol/or other drugs or dependence during previous 12 months (DSM-V criteria)
- Clinically or radiographically significant evidence of stroke
- Evidence of subdural hygromas or subdural hematomas
- Active or recent (defined as within 3 months of screening) cerebral infection or hemorrhage
- Any current conditions that may lead to the subject being in an immuno-compromised state
- Any previous history of cranial radiation.
- History of seizure activity
- History of hydrocephalus
- Evidence of active dermatological skin disease of the scalp (except Actinic Keratosis)
- Evidence of clinically significant major depressive disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V)
- Evidence of psychotic disorder or psychotic episode or bipolar affective disorder according to the criteria of the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-V)
- Evidence of active suicidal or homicidal ideation according to psychological diagnostic interview
- Currently receiving other experimental treatments
- Currently requiring full-time institutional care
- Is pregnant, nursing, or incarcerated

6 Low Dose Fractionated Whole Brain Radiation Therapy Guidelines

6.1 Definitions and Schedule

6.1.1 Equipment

Modality: X-ray beams with a nominal energy between 4 and 6 MV.

6.1.2 Target Volume

The target volume consists of the entire brain and meninges, including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve, superior to the vertex and posterior to the occiput. The caudal border shall be below the skull base at the top of the C2 vertebral level.

6.1.3 Localization

The planning target volume shall be defined by means of a simulator.

6.2 Target Dose

6.2.1 Prescription Point

The prescription point in the cranial volume is at or near the center. NOTE: regardless of the location of the central axis, the dose should be prescribed at the center on the cranial volume (midway between the maximum separations).

6.2.2 Dose Definition

The absorbed dose is specified below in Gy to muscle.

6.2.3 Tissue Heterogeneity

No corrections for bone attenuation shall be made.

6.2.4 Prescribed Dose and Fractionation

The total dose to the prescription point will be 10 Gy for the initial 15 subjects, then 20 Gy for subjects 16-30. This dose will be delivered in 5 fractions or 10 fractions of 2Gy. All radiation fields shall be treated once each day. The treatment shall be given 5 days a week.

6.2.5 Dose Uniformity

The dose variations in the target volume shall be within +7% (- 5% of the prescription-point dose).

6.2.6 Treatment Interruptions

No corrections shall be made for treatment interruptions less than seven days. For interruptions greater than seven days, please contact [redacted]

6.3 Treatment Technique

6.3.1 Subject Position

It is recommended that the subject be treatment supine. Use of Aquaplast immobilization mask is encouraged but not mandatory.

6.3.2 Beam Configuration

The cranial volume is treated with two lateral, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp. “Compensating beams” that block hot spots (these hot spots are typically present along the midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity.

6.3.3 Field Shaping

Shall be done with blocks that are at least 5 half-value layers (HVL) thick. Multi-leaf collimation is allowed.

7 Amyvid (Florbetapir) Neuritic Plaque Guidelines

7.1 Indication and Usage

Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations.

7.2 Limitations of Use

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.
- Safety and effectiveness of Amyvid have not been established for:
- Predicting development of dementia or other neurologic condition;
- Monitoring responses to therapies.

7.3 Dosage and Administration

The recommended dose for Amyvid is 370 MBq (10 mCi), maximum 50 µg mass dose, administered as a single intravenous bolus in a total volume of 10 mL or less. Follow the injection with an intravenous flush of 0.9% sterile sodium chloride.

7.4 Image Acquisition Guidelines

A 10-minute PET image should be acquired starting 30 to 50 minutes after Amyvid intravenous injection. The patient should be supine and the head positioned to center the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Image reconstruction should include attenuation correction with resulting transaxial pixel sizes between2 and 3 mm.

7.5 Image Display and Interpretation

Amyvid images should be interpreted only by readers who successfully complete a special training program. Training is provided by the manufacturer using either an in-person tutorial or an electronic process. The objective of Amyvid image interpretation is to provide an estimate of the brain β-amyloid neuritic plaque density, not to make a clinical diagnosis. Image interpretation is performed independently of a patient's clinical features and relies upon the recognition of unique image features.

7.6 Radiation Dosimetry

The estimated radiation absorbed doses for adults from intravenous injection of Amyvid are shown in Table 2.

Table 2: Estimated Radiation Absorbed Dose, Amyvid (Florbetapir F18 injection)

Organ/Tissue	Mean Absorbed Dose Per Unit Administered Activity (uGy/MBq)
Adrenal	14
Bone- Osteogenic Cells	28
Bone –Red Marrow	14
Brain	10
Breasts	6
Gall Bladder Wall	143
GI[a] - Lower Large Intestine Wall	28
GI – Small Intestine	66
GI – Stomach Wall	12
GI – Upper Large Intestine Wall	74
Heart Wall	13
Kidneys	14
Liver	64
Lungs	9
Muscle	9
Ovaries	18
Pancreas	14
Skin	6
Spleen	9
Testes	7
Thymus	7
Thyroid	7
Urinary Bladder Wall	27
Uterus	16
Total Body	12
Effective Dose (uSv/MBq)[b]	19

[a] Gastrointestinal

[b] Assumed radiation weighting factor, w_r, (formerly defined as quality factor, Q) of 1 for conversion of absorbed dose (Gray or rads) to dose equivalent (Sieverts or rem) for F 18. To obtain radiation absorbed dose in rad/mCi from above table, multiply the dose in µGy/MBq by 0.0037, (e.g., 14 µGy/MBq x 0.0037 =0.0518 rad/mCi)

The effective dose resulting from a 370 MBq (10 mCi) dose of Amyvid is 7.0 mSv in an adult, (19 x 370 = 7030 µSv = 7.030 mSv). The use of a CT scan to calculate attenuation correction for reconstruction of Amyvid images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). The actual radiation dose is operator and scanner dependent. The total radiation exposure from Amyvid administration and subsequent scan on a PET/CT scanner is estimated to be 9 mSv.

8 FDG (18F-fluorodeoxyglucose) PET-CT Metabolic Imaging Guidelines

8.1 FDG PET-CT Subject Prep and Dosing Guidelines

FDG PET/CT scans will be obtained on a GE Discovery 690 (General Electric Company, Fairfield, CT, USA) after routine subject preparation (NPO for at least 4 hours, no nicotine or caffeine for 12 hours, no intravenous glucose for 4 hours). Subjects will receive an intravenous (IV) infusion of 18F-fluorodeoxyglucose (FDG) after resting in a dimly lit, quiet room for at least 15 minutes. FDG dose will be determined as follows: 12-18 mCi (444 MBq-666MBq) <220 lbs. 16-24 mCi (592 MBq-888MBq) >220 lbs. Imaging will be conducted 45-60 minutes after IV FDG infusion.

8.2 FDG PET-CT Scam Acquisition Parameters

Helical computed tomography (CT) scans will be obtained at 120 kVp with auto mA (150 max, 10 min). FDG PET scans will be then obtained in 3D mode, with 10 minute emission acquisitions. Standard filtered back projection CT and iterative PET reconstructions will be obtained with CT matrix size 512, 4.25 mm interval.

8.3 FDG PET-CT Interpretation

All FDG PET Scans will be read by a board certified radiologist that has been credentialed in reading / interpreting these scans.

9 Isolation of Neuronal Specific Exosomes

Analysis of plasma exosomal protein and miRNA may provide clues to the underlying mechanisms of how RT improves cognitive function in AD patients.

This approach is based on recent studies demonstrating that small membrane vesicles between 40 and 100 nm in diameter, derived from the endosomal system, are secreted by most cell types. They are isolated not only from the tissues from which they are derived but also in biological fluids such as blood, urine, CSF, milk, and saliva. They contain a number of interesting proteins and miRNA. One proposed role for these exosomes is intercellular communication since they can fuse with the plasma membrane transferring their contents from one cell to another. Neural-specific exosomes isolated from the plasma of patients with AD contain not only elevated levels of Aβ peptides and P-S396-tau, P-T181-tau also the α- and β-secretases involved in cleavage of the amyloid precursor protein and the generation of Aβ (Seminars Cell and Developmental Biol 40:89, 2015; Alzheimers and Dementia 11:600, 2015). In contrast plasma neural derived exosomes contained lower levels of survival proteins including LRP6, a mediator of Wnt signaling and its downstream target REST, both of which are critical for diverse neurodevelopmental processes (Ann.Clin. Transl.Neurol 2:769, 2015). A 16-miRNA signature derived from exosomes from patients with AD was prognostic for the diseases as assessed by psychological and neuroimaging assessment (Molecular Psychiatry, 2014 page 1). Many of these miRNA have been implicated in AD pathogenesis using mouse and cell models. For example, hsa-miR-101 targets the 3' untranslated region of APP to significantly reduce APP levels and the accumulation of Aβ. The miR-15 family regulates Tau

phosphorylation through ERK1 leading to neuronal death in Neuro2a cells and primary cortical neurones. miR-424- 5p shares the same seed sequence as miR-15, thus belonging to the same miR-15 family. Hsa-miR-1306 is predicted to target the 3' untranslated region of α-secretase responsible for the generation of secreted APP.

9.1 Sample Processing, Storage, and Analysis

At pretreatment baseline, at 6 weeks, and at 3, 6, 9, and 12 months post-treatment, 10 ml blood samples will be obtained by phlebotomy from each patient. The blood samples will be brought to [redacted] laboratory on the day they are drawn and after centrifugation, the serum plasma is frozen in multiple 0.5 cc aliquots and stored in a liquid nitrogen vapor freezer for future molecular profiling analyses as described below.

Once the blood samples are collected they are labeled with the protocol number, case ID number, collection date and time and they are then brought to [redacted] laboratory for centrifugation and processing into serum samples. These processed samples are stored in a locked liquid nitrogen vapor freezer within [redacted] Lab. This lab in Goodwin Research Laboratories has limited ID access control authorized by Massey cancer Center. Specimen logs are maintained by [redacted] lab. Personnel in [redacted] laboratory including [redacted] do not have access to the patient PHI or identifiers.

Serum samples are used for identification of biomarkers for radiation induced toxicity These serum samples are also used to obtain exosomes which are released from cells and contain specific miRNA that are potential biomarkers for neurodegenerative diseases. The miRNA is isolated from the exosomes and sequenced. The sequence data is provided to [redacted] for further analysis with patient outcomes.

10 Study Procedures

After informed consent has been provided, the subjects in this study will have screening and pre-treatment procedures completed prior to the study treatment. After the study treatment, subject will be scheduled for follow up visits and testing at 6 weeks, 3, 6, 9, and 12 months post treatment.

10.1 Study procedures:

10.1.1 Screening:

- The Psychological Diagnostic Interview, the Neurocognitive function tests (WTAR, MMSE, HVLT, BVMT-R, WMS-IV Digit Span and Coding subtests, Trailmaking Tests, California Verbal Fluency Tests, Pegboard Test, BNT, and JLO), the Psychological Function Assessments (PHQ-9 and GAD-7), and the Quality of Life Assessments (Quality of Life in Alzheimer's disease (QOL-AD), Quality of Life in Late-stage

Dementia (QUALID), and Everyday Cognition (ECog-patient and caregiver questionnaires) will be completed by a neuropsychology specialist.

- The medical history will be reviewed.
- Data obtained from the screening visit will ensure that subjects who are enrolled in the trial meet criteria for early AD based on the more comprehensive battery of tests, as diagnosis of dementia is improved with use of quantitative measurement of multiple domains (31). If the subject does not meet the criteria for early AD, they will be withdrawn from the study prior to undergoing the Pre-Treatment Assessments including the FDG PET scan and AmyVID PET scan.

10.1.2 Pre-Treatment:

- The Neurocognitive function tests (not including JLO and BNT), and the Quality of Life Assessments will be completed by a neuropsychology specialist after at least 30 days have elapsed since the Screening Neurocognitive function testing was completed.
- The Ocular exam will be completed by an Ophthalmologist for subjects who have at least one natural lens.
- A medical history and physical exam will be completed, including baseline CTCAE Toxicity assessment scoring.
- A blood sample will be collected. A 10 ml blood samples will be obtained by phlebotomy from each patient. The blood samples will be brought to [redacted] laboratory on the day they are drawn and processed as described in Section 9.1.
- The FDG-PET scan and Amyvid PET scans will be completed. The Amyvid PET Scan is used to image macroscopic amyloid plaque, giving information on number, size and location.

If the subject does not meet the clinical definition of AD based on NINCDS-ADRDA criteria with confirmatory PET findings, they will be withdrawn from the study prior to receiving the study radiation treatment.

10.1.3 Study Treatment:

- Cranial irradiation will be given over 5 consecutive days (M-F x1) for Cohort 1, and over 10 days (M-F x 2 consecutive weeks) for Cohort 2

10.1.4 Follow-up:

- Follow-up assessments will be completed at 6 weeks, 3 months, 6 months, 9 months and 12 months after the study treatment:
    - **At 6 weeks post-treatment**, the Neurocognitive function tests (not including JLO and BNT), Psychological Function Tests, and Quality of Life Assessments will be completed by the neuropsychology specialist, medical history and

physical exam with concomitant medications review and CTCAE Toxicity assessment will be completed by a study investigator, and a blood sample will be collected and processed as described in Section 9.1.

- **At 3 months post-treatment**, the Neurocognitive function tests (not including JLO and BNT), Psychological Function Tests, and Quality of Life Assessments will be completed by the neuropsychology specialist, medical history and physical exam with concomitant medications review and CTCAE Toxicity assessment will be completed by a study investigator, and a blood sample will be collected and processed as described in Section 9.1.
- **At 6-months post-treatment**, the FDG-PET scan and Amyvid PET scan will be completed, concomitant medications will be reviewed by study staff, and a blood sample will be collected and processed as described in Section 9.1.
- **At 9 months post-treatment**, the Neurocognitive function tests (not including JLO and BNT), Psychological Function Tests, Quality of Life Assessments will be completed by the neuropsychology specialist, medical history and physical exam with concomitant medications review and CTCAE Toxicity assessment will be completed by a study investigator, and a blood sample will be collected and processed as described in Section 9.1. For subjects with at least one natural lens, the Ocular exam will be completed by an Ophthalmologist.
- **At 12 months post-treatment**, the Neurocognitive function tests(including JLO and BNT), Psychological Function Tests, Quality of Life Assessments neuropsychology specialist, medical history and physical exam with concomitant medications review, CTCAE Toxicity assessment will be completed by a study investigator, and a blood sample will be collected and processed as described in Section 9.1

10.2 Toxicity Assessments

Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0) will be used to assess any toxicity associated with this study, not only the effects on the CNS, but any general adverse effects which may or may not be associated with the treatment.
Using the CTCAE Adverse Event Evaluation Form (Appendix 1), each subject will be assigned score at pre-treatment, and at the 6-week, 3-month, 9-month and 12-month follow-up visits in the following categories:

1. **Skin** (CTCAE Sections: Alopecia, Dermitis radiation, Hyperpigmentation, Hypopigmentation)
2. **Eye** (CTCAE Sections: Cataract, Dry Eye Syndrome)
3. **Ear** (CTCAE Sections: Hearing Impaired)
4. **CNS** (CTCAE Sections: Concentration Impairment, Memory Impairment, Neurology - other/specify)
5. **Other** (CTCAE Sections: Fatigue, Nausea, Vomiting)

11 LAR/Caregiver Participation

The Legally Authorized Representative (LAR) or Caregiver will be asked to complete Everyday Cognition (ECog) questionnaires regarding the caregiver's assessment of the subject's current ability to perform everyday tasks in the present time and compare this to the subject's ability to perform these same everyday tasks ten years previously. For this reason, LAR/Caregivers will be asked to sign a separate informed consent for their participation in the study and will have specified inclusion criteria used. These questionnaires will be completed at the same visits (Screening, Pre-treatment, and following treatment at 6 weeks, 3 months, 9 months, and 12 months) that the study subject completes neurocognitive assessments, and will be administered by the study neuropsychologist. The LAR/Caregiver will complete the questionnaires in a different room as the study participant to ensure privacy and confidentiality. The LAR/Caregiver will have the ability to decline or withdraw from participation in their portion of the study. If this occurs, the study subject will continue participation as outlined in the protocol with no questionnaires being completed by the LAR/Caregiver.

LAR/Caregiver Inclusion Criteria

1. Must be the patient's LAR or primary caregiver
2. Must be a fluent English speaker
3. Must be able and willing to provide consent
4. Must be able to complete questionnaires with the neuropsychologist throughout the trial

12 Study Calendar

				Follow-up (Post-Treatment)				
	Screening (up to 120 days before Tx)	**Pre-Treatment** (up to 35 days before Tx)	**Treat-ment**	**6 wks** (± 1 wk) **Post-Tx**	**3 mo** (± 1 wk) **Post-Tx**	**6 mo** (± 1 wk) **Post-Tx**	**9 mo** **(± 1 wk)** **Post-Tx**	**12 mo** (± 1 wk) **Post-Tx**
Psychological Diagnostic Interview	**X**							
Neuro-cognitive function (NCF) Tests (JLO and BNT)	**X**							**X**
Neuro-cognitive function (NCF) Tests (WTAR, MMSE, HVLT, BVMT-R, WMS-IV, Digit span and Coding Subsets, Trailmaking Tests, California Oral Word Association Test, Semantic Fluency Tests, Pegboard Test)	**X**	**X[1]**		**X**	**X**		**X**	**X**
Psychological Function Assessments(PHQ-9, GAD-7, ECog)	**X**	**X[1]**		**X**	**X**		**X**	**X**

				Follow-up (Post-Treatment)				
	Screening (up to 120 days before Tx)	**Pre-Treatment** (up to 35 days before Tx)	**Treat-ment**	**6 wks** (± 1 wk) **Post-Tx**	**3 mo** (± 1 wk) **Post-Tx**	**6 mo** (± 1 wk) **Post-Tx**	**9 mo (± 1 wk) Post-Tx**	**12 mo** (± 1 wk) **Post-Tx**
Quality of Life Assessments (QOL-AD and QUALID)	X	X[1]		X	X		X	X
Medical History	X	X		X	X		X	X
Physical Exam		X		X	X		X	X
Concomitant Medications	X	X		X	X		X	X
Ocular Exam		X[2, 3]					X[3]	
FDG-PET Scan		X				X		
AmyVID PET Scan		X				X		
Study Treatment: Cranial Irradiation			X[4]					
Toxicity Evaluation (CTCAE, Version 4.0)			X	X	X		X	X
Blood Collection		X[5]		X[5]	X[5]	X[5]	X[5]	X[5]
Adverse Event Assessment		X	X	X	X	X	X	X

[1] At least 30 days must elapse between completion of NCF testing, PF questionnaires, and QOL-AD/QUALID at Screening Visit and same testing done at Pre-treatment Visit

[2] Initial Ocular exam can be performed any time after Subject meets eligibility criteria and up to 2 weeks after Study Treatment

[3] Ocular exams will only be done for subjects who have at least one natural lens.

[4] Cranial irradiation will be given over 5 consecutive days (M-F x1) for Cohort 1, and over 10 days (M-F x 2 consecutive weeks) for Cohort 2

[5] Blood draw will be performed to collect 10ml of whole blood and will be used to isolate neuronal specific exosomes for analysis of their protein and miRNA cargo.

13 Adverse Events

13.1 Adverse Event (AE):

For the purpose of this study, an Adverse Event is an untoward medical condition experience by a study participant **during treatment or in follow up** or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, **regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.**

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

13.2 Serious Adverse Event (SAE):

An SAE is defined as any untoward medical occurrence that meets any on of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participant's offspring)
- Requires intervention to prevent any of the above, per the investigator/sponsor

13.3 Acute and Late AE/SAE Assessment

Each subject will be monitored during the study treatment for toxicity and adverse events.

Each subject will be assessed for toxicity and adverse events at the 6-week, 3-month, 9-month and 12-month post-treatment follow-up visits. The CTCAE Adverse Event Evaluation Form (Appendix 1) will be used to assign a score in each of the five categories as listed in section 10.2.

If at any time during the study there is an increase of 2 or more grades in any category section other than Alopecia, an evaluation by the Data Safety Monitoring Board will take place within the week to determine if it is therapy related or due to other non-study related events. Should this happen during the course of the treatment, therapy will be immediately stopped and all medical attempts will be made to correct the cause of the noted increase in CTCAE section score. The records and information related to the event will be reported to the IRB using standard reporting mechanism.

In addition, any general adverse effect will also be scored which may or may not be related to the treatment delivered.

All SAEs are to be followed by investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology, or until subject is lost to follow up.

13.4 Anticipated Treatment Toxicities (Acute and Late)

Risk associated with whole brain irradiation at the dose levels described may include, but are not limited to:

1. Hair loss.
2. Decreased hearing.
3. Nausea.
4. Vomiting.
5. Visual changes.
6. Skin reaction.

The following are the grades, or severity, of Adverse Events that are common with the planned radiation dose for this trial based on the Criteria:

- Skin: Grade 2 (Alopecia)
- Eye: Grade 0
- Ear: Grade 1
- CNS: Grade 1
- Other: Grade 1

14 Study Stopping Rules

This study will be stopped for any of the following reasons:

1. Any subject death attributed to radiation / or any irreversible adverse effects caused by radiation, or thereafter until the follow up period has been completed (excluding alopecia).
2. More than 3 of the first 10 subjects in either of the treatment cohorts develop grade 3 adverse event as per CTCAE v. 4.0.
3. 50 % or more of subjects in either cohort show greater than 4-point decline in MMSE.
4. Development of suicidal ideation ≥7 on the Suicide Behaviors Questionnaire-Revised (SBQ-R)
5. Any subject who develops a grade IV adverse event in either treatment cohort.

These stopping rules are to assess any unexpected serious adverse event and evaluate if the study should continue or not. Any unexpected adverse event will be reviewed by the Data Safety Monitoring Board (DSMB).

15 Data Safety Monitoring Board

The trial will utilize an internal Data Safety Monitoring Board (DSMB). [redacted] The DSMB will have scheduled bi-annual meetings, and will review all new data related to any subjects under treatment or in follow up. This can include but is not limited to physical exam information, initial and updated toxicity scores, NCF, PF, and QOL results. The study coordinator will prepare the information and distribute it three days before each meeting. During each meeting, each study participant will be reviewed and will include review of the quality of data obtained thus far. Telephone participation is allowed.

If at any time a serious adverse event occurs the DSMB will meet within 4 business days either in person and / or by phone to discuss the event to determine if it is therapy related. Both of the DSMB physicians must be in attendance for these special meetings. If it is determined to be therapy related, the trial shall be temporarily closed and a notification-registered letter forwarded to the IRB with explanation. The trial will not be permitted to accrue new subjects until clearance to do so is received from IRB. After every bi-annual DSMB meeting a report will be forwarded by the DSMB to the IRB, use standard

reporting procedures of the IRB, detailing but not limited to data collected, quality of data collected, toxicity scoring, any changes in the physical exam, and imaging information. If there is a disagreement between the two DSMB members, a third arbitrator who has extensive knowledge of Neurology and Alzheimer's Disease, will be used to make the final determination.

We will also monitor MMSE scores periodically during follow up. Based on literature review the following will be noted: it is expected that the MMSE score will drop about four points / year. If any subject exhibits a greater than four-point drop in the MMSE score they will have review of case parameter to determine if this drop should be assigned as treatment related or is a result of other causes. Any score change found to be related to therapy will be reported through the DMSB to IRB for review and comment. No new subjects will be allowed on Clinical Trial until study is re-approved or accrual by IRB.

16 Endpoints

16.1 Primary Endpoint

To evaluate safety and toxicity/adverse event associated with delivery of low dose fractionated whole brain irradiation in subjects with Alzheimer's dementia (AD). CTCAE Version 4.0 will be utilized, for toxicity evaluation while neurocognitive functioning tests in Table 1 will be used to evaluate any neurocognitive changes.

16.1.1 Treatment Toxicities (Acute and Late)

Risk associated with whole brain irradiation at the dose levels described may include, but are not limited to:

1. Hair loss.
2. Decreased hearing.
3. Nausea.
4. Vomiting.
5. Visual changes.
6. Skin reaction.

The following are the grades, or severity, of Adverse Event that is common with the planned radiation dose for this trial based on the Criteria:

- Skin: Grade 2 (Alopecia)
- Eye: Grade 0
- Ear: Grade 1
- CNS: Grade 1
- Other: Grade 1

16.1.2 To determine, using established neurocognitive testing, if low dose fractionated whole brain irradiation described may impact the neurocognitive progression of subjects with AD.

16.2 Secondary Endpoints

16.2.1 To determine if low dose whole brain radiation therapy (RT) stabilizes or decreases cerebral amyloid.

16.2.2 To determine if neurocognitive function (NCF), psychological function (PF), and quality of life (QOL), as assess by accepted testing methods, is stabilized or improved by low dose whole brain RT.

16.2.3 To determine if there are correlations between neurocognitive test/psychological functioning/quality of life test results and results of FDG and Amyvid PET imaging for amyloid number, size and location.

17 Statistical Plan

Data will be entered on an ongoing basis and managed using REDCap electronic data capture tools hosted at VCU. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. REDCap is provided to the VCU community by Award Number UL1TR000058 from the National Center for Research Resources (50).

For the primary endpoint, the toxicity scores based on CTCAE toxicity grading system will be compared between each radiation dose group using 2-sample inference procedures to see if low dose radiation affects safety and toxicity. For NCT data, the data will consist of descriptive statistics for demographic data and means and standard deviations of outcome measures. To control for baseline neuropsychological status, repeated measures ANOVA will be used to explore within and between group differences on target neuropsychological outcomes. Estimated effect sizes (i.e. Cohen's *d*) calculated from this RCT will be used in later power analyses to determine necessary sample size for an efficacy study of these programs in individuals with AD.

For the secondary endpoints, paired 2-sample tests would be used to determine 1) whether low dose whole brain RT stabilizes or decreases cerebral amyloid deposits between the baseline and the end of the study; 2) whether low dose whole brain RT stabilizes or improves NCF, PF, and QOL.

Pearson's correlation coefficient or Spearman's rank correlation coefficient would be used to assess the relationship about NCF, PF and/or QOL results with PET imaging with respect to amyloid accumulations, including but not limiting to number, size and location.

18 Plan for Loss to Follow-up

In order to prevent biased results of the clinical trial due to subjects who drop out, a plan has been established to reduce or eliminate loss to follow up. The inclusion/exclusion criteria and consent process stresses to the clinical trial participants the importance of follow up to participate in the clinical trial. Study staff is instructed to communicate to study participants' the dates and times of their follow up appointments, make reminder calls within 1 week before scheduled appointment, contact subject by phone and/or letter for missed appointments and obtain secondary phone numbers for emergency contacts to assist with maintaining follow up appointments.

- For each subject that does not complete follow up, the sponsor will investigate/find, record and list the reasons for loss to follow-up (e.g., subject moved out of state, etc.), and also record the time of the missed follow up.
- In case of a subject drop out (e.g., move out-of-state, or subject's death) before the scheduled visit time (e.g., 3 months, 9 months or 12 months), the sponsor may consider a replacement with a new subject.

Appendix 1: CTCAE Adverse Event Evaluation Form

HM20004955: Phase IIa Trial of Low Dose Radiation Therapy to Reduce Cerebral Amyloidosis in Early Alzheimer's Dementia

CTCAE ADVERSE EVENT EVALUATION FORM

SUBJECT ID:_____ ASSESSMENT DATE: _____

ASSESSEMENT INTERVAL: ❑ Baseline ❑ Treatment Day #___ Post-treatment: ❑ 6 wks ❑ 3 mo ❑ 9 mo ❑ 12 mo ❑ Unscheduled Visit

Grade refers to the severity of the AE. The CTCAE displays Grasdes 1 – 5 with unique clinical descriptions of severity for each AE based on this guideline:

- GRADE 0 – None, no symptoms
- GRADE 1 – MILD: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- GRADE 2 – MODERATE: Moderate, minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
- GRADE 3 – SEVERE: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- GRADE 4 – LIFE THREATENING: Life-threatening consequences; urgent intervention indicated.
- GRADE 5 – DEATH: Death related to AE
- A semi-colon indicates 'or' within the description of the Grade. See CTCAE v4.0 Guide for effects not listed below.

ATTRIBUTION CODES:
1=Unrelated
2=Unlikely
3=Possible
4=Probably
5=Definite

Category:	Section:	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	GRADE:	Attribution Code:	Category Score:
SKIN	Alopecia	None	Hair loss up to 50% of normal observed only on close inspection	Hair loss > 50% of normal; readily apparent to others	---	---	Death			
	Dermatitis Radiation	None	Faint erythema or dry desquamation	Mod to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; mod edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death			
	Hyperpigmentation	None	Slight or localized	Marked or generalized	---	---	Death			
	Hypopigmentation	None	Slight or localized	Marked or generalized	---	---	Death			
EYE	Cataract	None	Asymptomatic, detected on exam only	Symptomatic, with mod decrease in visual acuity (20/40 or better); decreased visual function correctable with glasses	Symptomatic with marked decrease in visual acuity (worse than 20/40); operative intervention indicated (e.g., cataract surgery)	---	Death			
	Dry Eye Syndrome	None	Mild, intervention not indicated	Symptomatic, interfering with function but not interfering with ADL; medical intervention	Symptomatic or decrease in visual acuity interfering with ADL; operative intervention indicated	---	Death			

HM20004955: Phase IIa Trial of Low Dose Radiation Therapy to Reduce Cerebral Amyloidosis in Early Alzheimer's Dementia

CTCAE ADVERSE EVENT EVALUATION FORM

SUBJECT ID:_____ **ASSESSMENT DATE:** _____

ASSESSEMENT INTERVAL: ❑ Baseline ❑ Treatment Day #___ **Post-treatment:** ❑ 6 wks ❑ 3 mo ❑ 9 mo ❑ 12 mo ❑ Unscheduled Visit

Category:	Section:	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	GRADE:	Attribution Code:	Category Score:
EAR	Hearing Impaired	None	Adults enrolled on a monitoring program (a1,2,3,4,6, and 8 kHz audiogram): Threshold shift of 15-25 dB averaged at 2 contiguous test frequency in at least one ear or subjective change in the absence of Grade 1 threshold shift	Adults enrolled on a monitoring program (a1,2,3,4,6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequency in at least one ear Not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL	Adults enrolled on a monitoring program (a1,2,3,4,6, and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequency in at least one ear Not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL	Adults profound bilateral hearing loss (>80 dB at 2 kHz and above); non-serviceable hearing	Death			
CNS	Concentration Impairment	None	Mild inattention or decreased level of concentration	Mod impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self-care ADL	---	Death			
	Memory Impairment	None	Not interfering with function	Interfering with function, but not ADL	Interfering with ADL	Amnesia	Death			
	Neurology – other Specify:	None	Mild	Moderate	Severe	Life-threatening	Death			
OTHER	Fatigue	None	Relieved by rest	Not relieved by rest; liming instrumental ADL	Not relieved by rest; limiting self care ADL	Fatigue	Death			
	Nausea	None	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-------	Death			
	Vomiting	None	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death			

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