Amyloid Plaque Deposition in Chemotherapy-Induced Cognitive Impairment (CICI)

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Imaging Agents to be used:

[^{18}F]Flutemetamol: IND# - 109,760 (FDA approved as Vizamyl 10/25/13)[1]

[^{18}F]fluoro-2-deoxy-D-glucose (FDG): IND# - 113,858

University of Utah IRB # 00069515

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STUDY SUMMARY

Title	Amyloid Deposition in Chemotherapy-Induced Cognitive Impairment
IRB Protocol Number	69515
IND	[^{18}F]Flutemetamol IND# 109,760 (Yap) [^{18}F]fluoro-2-deoxy-D-glucose: FDG IND# 113,858 (Yap)
Phase	Phase II
Design	Three imaging sessions will be required: 1) [^{18}F]Flutemetamol-PET/CT, 2) FDG-PET/CT, and 3) MRI.
Study Duration	36 Months
Study Center(s)	Huntsman Cancer Institute, University of Utah
Objectives	The exploratory objective of this study is to determine the association of amyloid plaque burden determined with [^{18}F]Flutemetamol-PET imaging, brain metabolism determined with FDG, and the anatomical information obtained with MRI and correlate these variables in breast cancer patients experiencing chemotherapy induced cognitive impairment (CICI).
Number of Subjects	15
Diagnosis and Main Eligibility Criteria	Female adults (18 years or older) with a histologically proven Stage I through IIIC Breast Cancer, who are reporting cognitive impairment as a result of undergoing adjuvant chemotherapy.
Study Product, Dose, Route, Regimen	[^{18}F]Flutemetamol is an FDA approved radiopharmaceutical (Vizamyl) that is produced in the cyclotron facility at the Huntsman Cancer Institute for research purposes under IND #109,760. FDG is an FDA approved radiopharmaceutical that is produced in the cyclotron facility at the Huntsman Cancer Institute for research purposes under IND # 113,858.

1. OBJECTIVES

1.1 Purpose of Study

This exploratory study uses [^{18}F]Flutemetamol and [^{18}F]fluoro-2-deoxy-D-glucose (FDG) investigational positron emission tomography (PET) imaging agents, anatomic magnetic resonance imaging (MRI), and functional magnetic resonance imaging (fMRI) in breast cancer patients experiencing Chemotherapy-Induced Cognitive Impairment (CICI) to examine possible brain related changes. It is anticipated that we will enroll up to 15 women who have been diagnosed with breast cancer, completed chemotherapy, and are experiencing CICI, commonly referred to as "chemobrain." The goal is to complete the study in approximately 36 months.

1.2 Primary Objective of Study - Synopsis

The exploratory objective of this study is to determine the association of amyloid plaque burden determined with [^{18}F]Flutemetamol PET imaging, brain metabolism determined with FDG, and the anatomical and functional information obtained with fMRI and correlate these variables in 12 breast cancer patients experiencing CICI. We expect that up to 15 participants may be enrolled in this study. This will assure 12 evaluable patients (patients who have complete imaging results and blood data available for data analysis). In certain patients the blood data is not acceptable for final analysis because of difficulty in drawing it rapidly enough due to the vein collapsing during the rapid sampling required.

1.3 Hypotheses to be Tested - Synopsis

It is our hypothesis that individuals who are experiencing CICI may have a greater than expected prevalence of amyloid plaque burden when compared to individuals who are not experiencing cognitive complaints. The chemotherapy may accelerate the process of amyloid plaque burden deposition and subsequent possible neuronal injury and loss in individuals who have undergone chemotherapy.

The initial goal of our interdisciplinary group of imagers, oncologists, neurologists, neuro-psychologists, and biostatisticians is to obtain "proof of concept" pilot data for eventual submission of a National Cancer Institute Quick-Trial for Imaging and Image-Guided Interventions: Exploratory Grant (R10) depending on the results of this pilot study.

The overall objective is to use [^{18}F]Flutemetamol, FDG-PET, and fMRI to better understand CICI, which effects up to 16 -50% of individuals receiving long-term adjuvant chemotherapy.[2,3] To date there have been few studies examining this problem using multi-modality imaging techniques to better understand this complex and significant problem.

FDG-PET and fMRI are routinely used in clinical practice for the evaluation of cognitive dysfunction in older populations complaining of memory dysfunction. It is well recognized that

FDG-PET can assist with the differentiation and characterization of various cognitive disorders due to unique patterns of cerebral metabolism caused by various cognitive and dementia-causing disorders.[4-6] FDG-PET has been studied extensively in dementia research and has a high reliability in detecting Alzheimer's disease (AD) many years before it can be diagnosed reliably using clinical criteria.[4]

To our knowledge, there has been only a single small study using FDG-PET and bolus water activation paradigms in cancer patients complaining of memory problems.[7] To date, there have been no studies using [^{18}F]Flutemetamol as a PET imaging agent to assess the possibility of increased amyloid plaque burden as a potential contributing factor to the cognitive deficits and complaints seen in patients experiencing CICI. The novel feature of this project is in the combined use of [^{18}F]Flutemetamol-PET, FDG-PET, and fMRI to study a poorly understood but common problem: cognitive impairment in breast cancer patients treated with chemotherapy.

If [^{18}F]Flutemetamol, FDG-PET, and fMRI can provide information on the pathophysiology of this disorder, it will be an important step in better understanding the etiology of this phenomenon and possibly other conditions resulting in cognitive dysfunction. These imaging assessments will make it possible to explore any altered changes in cerebral structure, metabolism, and amyloid deposition that may be responsible for CICI. This may help to predict which individuals may be affected by this problem and provide information for eventual therapeutic strategies to treat this common cancer-associated disorder.

This study will use [^{18}F]Flutemetamol and FDG-PET imaging to assess and quantify the amyloid plaque burden and cerebral glucose metabolism, respectively, in breast cancer patients suffering from CICI and correlate those findings with structural changes on MRI. The [^{18}F]Flutemetamol and FDG-PET scans of these study patients will then be compared to two GE software databases (CortexID-FDG and CortexID-Flutemetamol) which contain scan data from healthy control individuals to evaluate for abnormalities in cerebral glucose metabolism and amyloid plaque burden differing from the values expected for individuals in their age range.

2. BACKGROUND

Currently, a woman living in the US has a 12.2%, or a 1 in 8, lifetime risk of being diagnosed with breast cancer and approximately 232,340 new cases of invasive breast cancer will be diagnosed among women in the United States this year.[8] Presently, the overall 5-year relative survival rate for female breast cancer patients has improved from 63% in the early 1960s to 90% today, an increase due largely to improvements in treatment.[9]

One such treatment is chemotherapy, a treatment that consists of drugs that are toxic to tumor cells or inhibit their growth through various pathways.[10] The majority of women with breast cancer will receive adjuvant therapy including chemotherapy, hormone therapy, or both, which has shown to improve disease-free and overall survival.[11]

Although treatments such as chemotherapy have increased the overall survival rates of women with breast cancer, it is well known that chemotherapy treatment has numerous side effects, to include: nausea, diarrhea, fatigue, anemia, and other systemic side effects.[12,13] These side effects compound the neuropsychological and quality of life effects of having a cancer diagnosis, a diagnosis that often affects individuals overall psychological wellbeing. Many people who undergo chemotherapy, particularly adjuvant chemotherapy, also complain of cognitive dysfunction.[14,15]

This cognitive decline affects 16-50% of individuals receiving long-term adjuvant chemotherapy.[2,3] Some reports suggest this figure may be even higher; Jenkins et al. reported that up to 83% of breast cancer survivors report some form of subjective cognitive dysfunction.[16]

Most research claiming evidence for the existence of CICI has specifically investigated outcomes for women with breast cancer.[17] These women often complain of inability to concentrate, memory dysfunction, word-finding difficulties, slowed processing abilities, and inability to multitask.[17-28] Similar to patients with CICI, individuals with Mild Cognitive Impairment (MCI) typically have cognitive deficits beyond expectations for normal aging, but do not yet demonstrate the severe functional impairments seen in AD.[3,29]

Research suggests that one marker that might indicate the early development of AD is MCI, where MCI is a transitional phase between normal aging and dementia.[29,30] MCI is most widely defined as having: (1) memory complaint; (2) impairment on a memory test after correction for age and education; (3) preserved general cognitive functioning; (4) intact activities of daily living; and (5) absence of dementia.[31] Individuals with MCI progress to AD at much higher rates than their cognitively healthy peers (e.g., 10 – 15% vs. 1 – 2 % per year).[29]

AD is the most common cause of progressive cognitive decline in the United States. Clinically, it is characterized by severe impairments in learning and memory and other cognitive abilities, which significantly interfere with daily functioning. The neuropathologic hallmarks of AD consist of neuritic plaques, neurofibrillary tangles, and selective neuronal cell loss.[32] Neuritic plaques contain Amyloid-beta protein (Abeta) that forms amyloid deposits. Thus, Abeta is believed to play an integral role in the development of AD.[33] Elevated levels of Abeta in the brain are correlated with cognitive decline,[34] and removal of plaques in animal models of AD results in behavioral improvements.[35] AD develops insidiously making it difficult to identify early; yet, treatment will be most effective when begun before neuronal loss is too extensive. Therefore, the search for markers of early AD, such as MCI, have received considerable interest.

The current project will examine biomarkers that are consistent with MCI such as increased amyloid plaque burden and decreased cerebral glucose metabolism. For example, the first amyloid binding radioligand was ^{11}C-PIB (Pittsburgh compound B) and initial studies found that amyloid burden assessed with ^{11}C-PIB was high in patients with AD.[36] Other work using ^{11}C-PIB in patients with MCI has had mixed results, with some studies showing high amyloid burden,[37-39] while others have found low amyloid burden.[40-42] However, the short half-life of ^{11}C-PIB makes it

challenging to work with in large clinical trials, so additional amyloid binding radio ligands have been developed.[43] A longer half-life amyloid binding agent, [^{18}F]Flutemetamol, shows promise in early AD and MCI.

Other neuroimaging biomarkers of AD include FDG-PET and hippocampal volume on MRI. FDG-PET measures metabolism of glucose in the brain. Patients with AD show a characteristic pattern of hypometabolism of bilateral temporal and parietal lobes on FDG-PET, which differentiates this condition from other causes of dementia.[36] Hippocampal atrophy, as assessed by reduced volumes of these bilateral structures in the medial temporal lobes, has been shown in multiple studies to be an indicator of the development of AD.[44] Limited work has been done using neuroimaging in CICI and MCI. This study will make an important contribution to the understanding of the earliest changes of cognition and the appropriate role of amyloid, FDG-PET, and MR imaging in breast cancer patients experiencing CICI.

2.1 Review of Previous Research

Current research suggests that the etiology of CICI is multi-factorial with many factors combing to predispose certain individuals to develop CICI[45] A number of theories as to why chemobrain may occur have been proposed, including: neurotoxicity, oxidative stress, decreases in white and gray matter volume, and genetics; these have each been suggested to play a role in the development of chemobrain.[19,46-49]

For many older women, the impact of chemotherapy may be compounded by the natural aging process, which, in and of itself, can be related to the development of cognitive problems.[50,51] For younger women, the cognitive side effects related to chemotherapy may be compounded by the fact that chemotherapy can accelerate the onset of menopause.[52] This is particularly important as menopause itself causes hormonal changes that can affect cognitive functioning.[53] Other cancer treatments, including hormone therapy, immunotherapy, and radiation therapy have also been implicated as causing complaints of cognitive dysfunction.[54] Findings indicated that CICI is a relatively common event that in most of the cases remains under diagnosed, thereby adversely affecting the quality of life of patients with cancer.[55]

The following is a summary table (**Table 1**) of several published studies and the broad types of cognitive deficits that have been described.

Table 1. Types of Cognitive Deficits That Have Been Associated with Chemotherapy						
STUDY		ATTENTION/ CONCENTRATION	VERBAL MEMORY	VISUAL MEMORY	VISUAL/ SPATIAL	SPEED OF INFORMATION PROCESSING
Hodgson (2013)[56]					++	
Kesler (2013)[57]			++			
Bruno (2012)[24]			++			
Nokia (2012)[22]			++			
Meyers (2012)[26]		++	++			
Hedayati (2012)[58]		++	++			++
Jim (2012)[59]			++	++		
Briones (2011)[60]			++			
Deprez (2012)[61]		++				++
Von (2009)[28]			++			
Castellon (2004)[62]				++	++	
Ahles (2002)[63]			++			++
Brezden (2000)[64]			++	++		
Schagen (1999)[65]		++	++	++		++
van Dam (1998)[66]		++		++		++
Wieneke and Dienst (1995)[67]		++	++	++	++	++
NOTE. ++ indicates deficits noted in a particular study.						

One of the largest obstacles in studying the impact of chemotherapy on cognitive is the difficulty in sorting out which problems are due to chemotherapy and which are due to having a serious illness like cancer.[68]

There are multiple life stressors in this population that can result in physical debilitation, depression, sleep disruption, hormone shifts, and fatigue, all of which can affect cognitive functioning. Furthermore, a complex interplay may exist among cognitive function, psychological wellbeing, and quality of life. For example, a decrease in psychological wellbeing in the face of a poor health-related quality of life may have implications for cognitive function. Cognitive impairment that interferes with an individual's daily routine may decrease that person's psychological wellbeing. A number of studies investigating the effects of chemotherapy on health-related quality of life and cognition have been published.[69,70]

The Netherlands Cancer Institute group has published findings from a longitudinal study investigating the long-term effects of chemotherapy on cognition. The initial findings suggested a dose-response effect of chemotherapy on cognition, with cognitive impairment most pronounced in the high-dose group (32%) and least evident (9%) in the group receiving local treatment for breast cancer.[66] Cognitive impairment in attention, mental flexibility, speed of information processing, visual memory, and motor function was observed in 28% of individuals 2 years after cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy treatment.[65] Self-reports of cognitive function were not related to cognitive function as measured by the neuropsychological tests, but instead were related to reports of anxiety and depression. In a two-year follow-up (4 years post-treatment) the individuals who had received CMF showed improved cognitive performance and no longer scored significantly different than the controls.[71] Although this group was the first to attempt a longitudinal study of chemotherapy and cognition, the study lacks a baseline measurement.

This same group completed a prospective study that did include baseline measurements of cognitive function, and reported that a subset of patients receiving high dose cyclophosphamide, thiotepa, and carboplatin chemotherapy experienced a decline in objective cognitive performance and in particular in measurements of executive function.[72] Such an effect was not observed in the standard-dose chemotherapy group, and it is not well understood whether these results generalize to other common high-dose chemotherapy regimens, such as dose dense doxorubicin (Adriamycin) and cyclophosphamide (cytoxan).

Researchers from the M.D. Anderson Cancer Center were among the first to prospectively study cognitive function in relation to chemotherapy. Cognitive impairment was reported in 35% of patients[73] and 33% of patients[74] prior to the beginning of chemotherapy. Sixty-one percent of patients receiving a chemotherapy regimen of 5-fluorouracil, doxorubicin, and cyclophosphamide exhibited cognitive decline following chemotherapy treatment, primarily in areas of attention, learning, and processing speed.[74] In the long-term follow-up, 50% of individuals who had shown a decline in cognitive function did not show improvement in the long-term. Although this study was

limited by a small sample size (n=18), it suggests that cognitive dysfunction occurs in a significant portion of individuals following chemotherapy.

Iconomou and colleagues[75] examined changes of emotional distress, cognitive impairment, and quality of life in a group of Greek cancer patients before treatment and at the end of treatment. Cognitive dysfunction was observed in 15% of the patients at baseline and was unchanged at the end of treatment. The lack of significant differences in this study may be attributable to the heterogeneity of the cancer diagnoses in the participants, as well as the use of the mini mental state exam (MMSE) as the sole objective measure of cognitive performance.

A well designed prospective study by Jenkins[16] using neuropsychological tests and self-reports of cognitive failures and quality of life found that although a decline in cognitive performance was more common in the group receiving chemotherapy compared to local treatment and healthy controls groups, no significant difference was seen immediately after chemotherapy or 18 months after the first assessment. One explanation for this finding may be that the majority of individuals received a relatively low dose of fluorouracil, epirubicin and cyclophosphamide, a treatment that had previously been shown not to increase an individual's risk of cognitive impairment.[66]

In one longitudinal study of cognition and breast cancer,[76] Hermelink reported a decline in cognitive function in 27% of individuals at the end of chemotherapy relative to the beginning of treatment and an improvement in 28% of individuals receiving treatment. It is unlikely that chemotherapy improves cognitive function. This study may have had a flawed baseline measure or may have failed to take into account practice effects from multiple neuropsychological testing periods.

In addition to the numerous studies of cognition in patients with cancer, there have also been several studies that have examined chemotherapy-treated animals. One of these trials showed that rats treated with cyclophosphamide and doxorubicin exhibited disruption of hippocampal neurogenesis.[77] This anatomical change was associated with impaired performance on a novel place recognition task. Another such study using rats also demonstrated learning and memory impairment and decreased hippocampal cell proliferation following the administration of CMF.[60] These studies illustrate that chronic treatment with commonly used chemotherapeutic agents may act to impair cognitive ability through perturbation of neurogenesis in the hippocampus.

There are a number of theories proposing different mechanisms to explain the development of CICI. One hypothesis is that some chemotherapy agents may cross the blood-brain barrier, directly causing neurotoxicity. However, others insist that most cytotoxic drugs are unable to cross the blood-brain barrier, and that the cognitive effects seen in patients with CICI are secondary to systemic inflammation brought on by the chemotherapy.[78] Another theory states that the cognitive problems are due to free radicals produced by the chemotherapeutic agents.[46] Others hypothesize the underlying genetic background makes some patients more susceptible to the effects of

chemotherapy. Finally, there is evidence of long-term injury to both white and gray matter in the brain following high-dose adjuvant chemotherapy.[79]

The true etiology of CICI is most likely multifactorial with a combination of processes that together, predispose certain individuals to develop deficits in cognition. There is still much to be learned about this condition, including why it affects only a subset of patients and why these deficits can persist after completion of chemotherapy. It isn't clear which chemotherapy drugs are more likely to cause cognitive changes or if risk is proportional to dosage. There are currently no medications specifically approved to treat CICI, however, agents used to treat disorders such as depression, attention-deficit hyperactivity disorder and dementia have been investigated.[80-87] Cognitive-behavioral therapy has so far proved to be the most effective treatment to improve cognitive deficits and quality of life. [57,88-90]

Chemotherapy isn't the only cancer treatment that may cause cognitive disturbance and memory complaints. Other cancer treatments that have been implicated as causing complaints of cognitive dysfunction include hormone therapy, immunotherapy, and radiation therapy. Hormone therapy is common in woman being treated with conventional chemotherapy. It is not entirely clear if women undergoing hormone therapy, which alters the amount of systemic estrogen, experience memory problems.[91] Some studies link memory to the amount of estrogen in the brain.[92] Immunotherapy is typically an experimental therapy, which stimulates the immune system to fight cancer. Treatment with cytokines, a type of protein causes inflammation, which in turn may cause problems with memory, multitasking and difficulty with processing information.[93] Radiation to the brain has been associated with cognitive, memory and motor function impairment. As with chemotherapy and immunotherapy, radiation therapy has also been associated with complaints of inability to learn and to multitask.[94] Older adults and individuals receiving higher doses of radiation are at a greater risk of memory problems. It has been noted that individuals who receive both chemotherapy and radiation therapy to the brain have an increased risk for cognitive impairment.[95]

2.2 NEUROPSYCH ASSESSMENTS FOR CICI

Existing literature suggests that chemotherapy has adverse effects on memory, processing speed, and executive functioning.[96] As such, we will focus our neuropsychological assessments on these three cognitive domains. To assess memory, we will utilize the Hopkins Verbal Learning Test – Revised (HVLT-R)[97] and the Brief Visuospatial Memory Test – Revised (BVMT-R).[98] Processing speed will be tapped with Trail Making Test Part A (TMT-A)[99] and the Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale – IV.[100] Executive functioning will be measured with Trail Making Test Part B (TMT-B),[99] Controlled Oral Word Association Test (COWAT),[101] and Stroop Color Word Test (SCWT).[102] Additionally, the Wide Range Achievement Test (WRAT4) will be used to assess premorbid intellect in all participants. Lastly, the Beck Depression Inventory – II (BDI-II)[103] will be used to evaluate depressive symptoms, the Cognitive Failures Questionnaire (CFQ)[104] will be used to determine subjective complaints of memory

difficulties, and the Frontal Systems Behavioral Scale will be used to determine subjective complaints of executive dysfunction.

2.3 MRI IMAGING IN PATIENTS WITH CICI

Brain volumetric imaging allows determination of cortical and subcortical atrophy associated with effects of chemotherapy, and should be targeted to identify both brain volume and cortical thickness. Brain volumetric imaging is an important covariate because it is one of the few noninvasive imaging metrics that is associated with dementia.[44] We propose an MRI examination using high quality MPRAGE images to allow comparison with large multisite control populations such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) database.[105]

2.4 [^{18}F]FLUTEMETAMOL as an IMAGING AGENT

Biomarkers of AD recently have become extremely important to improve diagnosis, measure severity of disease, evaluate progression of disease, assess the effects of novel disease-modifying drugs, and to speed development of these novel experimental drugs by reducing the time needed to follow patients, the number of patients to be followed per study, and the cost of research.[106,107]

AD neuropathology consists of neuritic plaques, neurofibrillary tangles, and neuronal cell loss.[32] Amyloid plaques are believed to play an integral role in the development of AD.[33] Plaques are neurotoxic,[108] and elevated levels of Abeta in the brain are correlated with cognitive decline.[34] Removal of plaques in animal models of AD has shown behavioral improvements.[35] Several compounds with affinity for binding amyloid *in vivo* are under investigation. These mainly fall into 3 families: a) naphthyls (e.g. [^{18}F]FDDNP) which bind to plaques and tangles,[109] thioflavins (e.g. PIB) which are selective for amyloid plaques,[110] and c) stilbenes (e.g. ^{11}C-SB13) which are similar to PIB, but have more background uptake variability.[111]

"Pittsburgh Compound B" (^{11}C-PIB), a radioactive carbon-11 labeled benzothiazole analog with the right kinetic affinities to image amyloid beta (Abeta) deposited in neuritic plaques.[112,113] ^{11}C-PIB has statistically significant increased retention in AD cortical areas, relative to controls ($P<0.05$),[112] and lesser amounts in frontotemporal dementia.[114] Recently ^{18}F-39-F-6-OH-BTA1 (^{18}FGE067), a structural thioflavin analog of ^{11}C-PIB has been tested in early phase trials. The market name for ^{18}F-GE067 is Vizamyl ([^{18}F]Flutemetamol). Preliminarily, this agent appears to behave very similar to ^{11}C-PIB but has the advantage of the 120 minute half-life of ^{18}F compared to 20 minutes for ^{11}C, making the agent much more practical for research and clinical use.

Nevertheless, much more research is needed to better understand the diagnostic capabilities of amyloid imaging agents. For example, there are no uniformly accepted standards for distinguishing levels of [^{11}C]PIB or [^{18}F]Flutemetamol binding that should be considered normal. Individual laboratories are reporting widely varying prevalence of [^{11}C]PIB binding in cognitively

normal elderly individuals. This could be accounted for on the basis of scanner characteristics, reconstruction algorithms, subject selection, or modeling. PET studies with FDG and [^{11}C]PIB provide different and complementary information.

Although some investigators report close agreement between FDG and amyloid imaging, this is not at all uniformly true.[114,115] In addition, there is not always a sufficient correlation between amyloid imaging and clinical diagnosis or between FDG-PET and clinical diagnosis. It is likely that discrepancies between FDG-PET and amyloid imaging and clinical diagnosis is due to diagnostic errors, but follow-up studies incorporating autopsies are needed. [114]

2.5 [^{18}F]-FDG as an IMAGING AGENT

FDG is a well-validated and important radiopharmaceutical for measuring glucose metabolism in the assessment, diagnosis, and staging of patients with cancer.[116,117] Investigators at UCLA published the first preliminary study using FDG-PET imaging in chemobrain.[7] The study included resting FDG-PET brain imaging as well as a blood flow study using [^{15}O]H_2O-PET. The study assessed regional brain metabolism and blood flow in 16 women who had adjuvant chemotherapy, 8 women who had breast cancer but did not undergo chemotherapy, and 10 healthy women with no history of breast cancer or chemotherapy. Both groups of cancer survivors underwent resting FDG-PET scans to assess brain metabolism and [^{15}O] H_2O-PET activation scans to assess cerebral blood flow during memory-related tasks.

Women in the chemotherapy group had decreased glucose metabolism in the superior frontal gyrus and in Broca's area in the dominant hemisphere and in its contralateral counterpart, compared with the control group. Poor performance on measures of short-term recall correlated well with decreased metabolism in Broca's area in the chemotherapy group. In addition, women who had undergone chemotherapy had increases in blood flow that were strongest in the inferior frontal gyrus region (Broca's area), compared with women who did not undergo chemotherapy. The researchers also looked at differences in chemotherapy regimens. Women who received chemotherapy and tamoxifen had decreased resting metabolism in the lentiform nucleus. Activation patterns during a short-term recall task were abnormal in the same areas in these women.

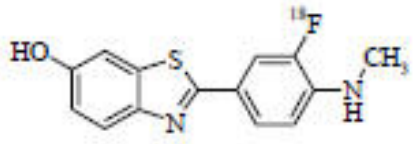
The UCLA study was not a quantitative study as is proposed here. This is important as there may be alterations in the transport of glucose and hexokinase activity secondary to chemotherapy and that can be assessed using dynamic and quantitative FDG-PET as we propose. Altered glucose transport has been seen in other dementing diseases.[118] A complete search of the literature has shown there to be no other PET imaging studies assessing CICI in patients with solid organ cancers. However, two studies have been recently published showing alteration of cerebral glucose metabolism in Hodgkin's[119] and non-Hodgkin's lymphoma.[120]

3. PHARMACOLOGY, METABOLISM, AND BIODISTRIBUTION OF [18F]FLUTEMETAMOL (as described in the [18F]Flutemetamol Investigator's Brochure and Vizamyl Package Insert)[1]

3.1 Pharmacology of [18F]Flutemetamol

[18F]Flutemetamol Injection is a fluorine-18 labeled PET diagnostic agent supplied as a ready to inject solution. Vials for multi-dose use contain up to 10 ml of [18F]Flutemetamol.

The drug substance is [18F]Flutemetamol; its structural representation is shown below. It is derived from the basic structure of the dye thioflavin-T.



The formulation of [18F]Flutemetamol for injection (drug product) contains 7% ethanol (v/v), 0.9% sodium chloride (w/v) and 0.5% polysorbate 80 (w/v) in phosphate buffer (0.014 M). The pH of the drug product is 6.0-8.5. The radiochemical purity (RCP) is greater than 90% throughout shelf life.

18F-Flutemetamol is manufactured by automated radiosynthesis followed by purification, formulation with buffer and aseptic dispensing.

Physical properties of fluorine-18:
Fluorine-18 decays by positron emission (+ decay, 96.7%) and orbital electron capture (3.3%) with a half-life of approximately 110 minutes. The positron undergoes annihilation with an electron to produce two gamma photons each of energy 511 keV (193.4% emission).

3.2 Dosage form

[18F]Flutemetamol for injection is a sterile, aqueous solution of [18F]Flutemetamol and excipients for intravenous administration. The product is supplied with a radioactive content of 150 MBq/ml (4.05 mCi/ml) at the reference date and time as specified on the label in a glass vial sealed with a synthetic rubber closure and aluminum overseal or a unit dose syringe. The patient dose will normally be transported from the manufacturing site in syringes or vial. However, the patient dose may be transported in its original container and withdrawn into syringes at the clinical site. Each vial or syringe is transported in lead or tungsten shielding. Each patient dose will contain up to 185 MBq (5 mCi) ±10% at the time of administration and not more than 6.0 μg/ml [18F]Flutemetamol (non-radioactive analogue of the drug substance). The radioactive dose will be measured in a dose

calibrator before administration. The maximum administered dose volume is approximately 10 ml. The product must not be diluted.
Equipment typically used to administer the drug product should be one or more items from the following list.

- Needle
- Syringe
- Catheter
- Stopcock
- Infusion line

Quality control of the drug product:
The quality control (QC) analysis of a sample of the drug product may be performed in parallel with transportation of the drug product to the imaging suite. The investigator (or nominated deputy) will receive release/reject information for the drug product. Only product for which confirmation of release has been received shall be used.

Storage and handling:
The in-use shelf life of [^{18}F]Flutemetamol for injection is up to 10 hours from the end of production and the product must not be used beyond this limit. The shelf life may be extended as additional stability results become available. [^{18}F]Flutemetamol should be stored at 2-30°C (36-86°F) in a shielded container. However, temperature excursions up to 50°C (122°F) during transport are acceptable. Waste must be disposed of according to national regulations for radioactive material.

Precautions for the safe handling of radioactive materials should be observed.

3.3 *In vitro* Metabolism and Plasma Protein Binding of [^{18}F]Flutemetamol

Studies were performed to investigate the *in vitro* metabolism of [^{18}F]Flutemetamol by incubation with hepatic S9 fraction obtained from man, dog, mouse and rat (where the rats had either been not treated or pre-treated with Aroclor 1254, a potent inducer of liver metabolizing enzymes).
The major metabolite in these studies, irrespective of the origin of the hepatic S9, was the N-demethylation product of [^{18}F]Flutemetamol. This is a preliminary indication that metabolism in the human primate is similar to that of the rat and dog, and gives support for these two species being appropriate for non-clinical studies. No metabolism or degradation was observed following incubation of [^{14}C]Flutemetamol with citrated rat, dog or human plasma for up to 3 hours. Low levels of 2 metabolites were seen in citrated human whole blood at 3 hours. The binding of [^{3}H]Flutemetamol to human, dog and rat plasma proteins was shown to be greater than 95% by equilibrium dialysis. Despite this high protein binding, [^{18}F]Flutemetamol is rapidly eliminated from blood after intravenous administration of [^{18}F]Flutemetamol to male and female Wistar rats.

3.4 *In vivo* Metabolism of [^{18}F]Flutemetamol

Data indicate that [^{18}F]Flutemetamol is rapidly metabolized in rat, baboon and humans resulting in at least 2 radioactive hydrophilic metabolites. HPLC profiles of ^{11}C labeled products present in rat and baboon plasma after intravenous administration of [^{11}C]Flutemetamol were studied. In both rat and baboon, [^{11}C]Flutemetamol was rapidly metabolized and at least 2 hydrophilic products were observed and the retention times of these hydrophilic products were comparable in both rat and baboon plasma. After injection of [^{18}F]Flutemetamol in the Phase I study human plasma samples from the subjects were analyzed by HPLC. These samples were primarily taken to assist with brain kinetic modeling but they also showed that metabolism of the injected [^{18}F]Flutemetamol occurred rapidly (only 25% of the parent compound detected in the circulation 20 minutes post injection and approximately 10% detected in the circulation at 180 minutes post injection) and at least 2 hydrophilic metabolites were detected.

Solubility and Stability:

The maximum concentrations of [^{18}F]Flutemetamol achievable in dosing solutions for the *in vitro* and *in vivo* studies were limited by the solubility of [^{18}F]Flutemetamol in the appropriate vehicle for each test (e.g. phosphate buffered saline containing 7% (v/v) ethanol, and dimethylformamide (DMF)). Although polysorbate 80 (0.5% w/v) is now included in the clinical preparation, at the time the toxicology studies were carried out, it was not expected to be part of the clinical formulation and was not included in the preclinical Test Item. Subsequently, the risk of including polysorbate 80 (0.5% w/v) in the clinical formulation and administering it to humans has been assessed and is considered extremely low since it is a component of many approved intravenous preparations.

4. TOXICITY and SAFETY OF FLUTEMETAMOL (as described in the [^{18}F]Flutemetamol Investigator's Brochure and Vizamyl Package Insert)[1]

4.1 Flutemetamol Toxicology

A complete toxicology package is part of the GE Healthcare IND # 101,866 which we have been allowed to cross reference. In brief, Single dose; 7-day and 14-day repeated intravenous dose GLP (Good Laboratory Practice) compliant toxicology studies have been conducted using Flutemetamol Solution for Injection in 2 mammalian species (rat and dog). For genetic toxicology assessment, 2 *in vitro* cell assays; a bacterial reverse mutation test (Ames test) and a mouse lymphoma assay (MLA test), and 2 *in vivo* mammalian tests, a rat bone marrow micronucleus assay (MN), and rat liver unscheduled DNA synthesis (UDS) have also been conducted. Having obtained data in the *in vitro* systems that suggested potential mutagenicity, an additional bone marrow MN assay was carried out as part of a subsequent 14 day repeat dose study in rat. Local tolerance and irritation studies were performed to investigate whether Flutemetamol solution for injection induced signs of intolerance by dermal, ocular (conjunctival sac), intra-arterial, intramuscular, perivenous or intravenous route in rabbits. A further study to assess potential hemolytic effects of the vehicle on red blood cells was also carried out since the vehicle is known to have low osmolarity.

The complete pharm/tox package includes the following studies:

- Expanded Acute Dose Toxicity Study in Rats
- 7-Day Dose Range Finding Study in Rats
- Combined Single Dose and 7-day Dose Range Finding Study in Dogs
- 14-Day Repeated Dose Toxicity Study in Rats
- 14-Day Repeated Dose Toxicity Study in Dogs
- Microbial Mutagenesis Test (Ames) study
- Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells using the Microtitre Fluctuation Technique (MLA)
- Acute Rat Bone Marrow Micronucleus Assay (MN)
- 14-Day Repeat Dose Rat Micronucleus Assay
- Measurement of Unscheduled DNA Synthesis (UDS) in Rat Liver using an *in vivo/in vitro* Procedure
- Genotoxicity study, Reproductive Toxicity analysis, Local Tolerance in Albino Rabbits
- Primary Skin Irritation Study in Rabbits (4-Hour Semi-Occlusive Application)
- Acute Eye Irritation/Corrosion in Albino Rabbits,
- Osmolality and the Lack of Potential to Induce Haemolysis, B067061.

4.2 Previous Human Studies with [^{18}F]Flutemetamol

The below table (**Table 2**) lists the recently published studies using [^{18}F]Flutemetamol.

Table 2. Current Published Studies Using Flutemetamol	
Koole (2009)[121]	Koole M, Lewis DM, Buckley et al. Whole-Body Biodistribution and Radiation Dosimetry of ^{18}F-GE067: A Radioligand for In Vivo Brain Amyloid Imaging. J Nucl Med 2009; 50:818–822.
Nelissen (2009)[122]	Nelissen N, Van Laere K, Thurfjell L et al. Phase 1 study of the Pittsburgh compound B derivative ^{18}F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. J Nucl Med. 2009;50(8):1251-9.
Vandenberghe (2010)[123]	Vandenberghe, R, Van Laere, K, Ivanoiu, A et al. ^{18}F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: A phase 2 trial. Annals of Neurology. 2010; 68(3):319-329.
Wolk (2011)[124]	Wolk DA, Grachev ID, Buckley C, et al. Association between in vivo fluorine 18-labeled flutemetamol amyloid positron emission tomography imaging and in vivo cerebral cortical histopathology. Archives of neurology. Nov 2011;68(11):1398-1403.
Rinne (2012)[125]	Rinne JO, Wong DF, Wolk DA, et al. [(18)F]Flutemetamol PET imaging and cortical biopsy histopathology for fibrillar amyloid beta detection in living subjects with normal pressure hydrocephalus: pooled analysis of four studies. Acta neuropathologica. Dec 2012;124(6):833-845.

Thurfjell (2012)[126]	Thurfjell L, Lotjonen J, Lundqvist R, et al. Combination of biomarkers: PET [^{18}F]flutemetamol imaging and structural MRI in dementia and mild cognitive impairment. Neuro-degenerative diseases. 2012;10(1-4):246-249.
Adamczuk (2013)[127]	Adamczuk K, De Weer AS, Nelissen N, et al. Polymorphism of brain derived neurotrophic factor influences beta amyloid load in cognitively intact apolipoprotein E epsilon4 carriers. NeuroImage. Clinical. 2013;2:512-520.
Duara (2013)[128]	Duara R, Loewenstein DA, Shen Q, et al. Amyloid positron emission tomography with (18)F-flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association. May 2013;9(3):295-301.
Duff (2013)[129]	Duff K, Foster NL, Dennett K, et al. Amyloid deposition and cognition in older adults: the effects of premorbid intellect. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists. Nov 2013;28(7):665-671.
Leinonen (2013)[130]	Leinonen V, Rinne JO, Virtanen KA, et al. Positron emission tomography with [18F]flutemetamol and [^{11}C]PiB for in vivo detection of cerebral cortical amyloid in normal pressure hydrocephalus patients. European journal of neurology : the official journal of the European Federation of Neurological Societies. Jul 2013;20(7):1043-1052.
Rinne (2013)[131]	Rinne JO, Frantzen J, Leinonen V, et al. Prospective Flutemetamol Positron Emission Tomography and Histopathology in Normal Pressure Hydrocephalus. Neuro-degenerative diseases. Nov 27 2013.
Wong (2013)[132]	Wong DF, Moghekar AR, Rigamonti D, et al. An in vivo evaluation of cerebral cortical amyloid with [^{18}F]flutemetamol using positron emission tomography compared with parietal biopsy samples in living normal pressure hydrocephalus patients. Molecular imaging and biology : MIB : the official publication of the Academy of Molecular Imaging. Apr 2013;15(2):230-237.
Hatashita (2014)[133]	Hatashita S, Yamasaki H, Suzuki Y, Tanaka K, Wakebe D, Hayakawa H. [(18)F]Flutemetamol amyloid-beta PET imaging compared with [(11)C]PIB across the spectrum of Alzheimer's disease. European journal of nuclear medicine and molecular imaging. Feb 2014;41(2):290-300.
Thurfjell (2014)[134]	Thurfjell L, Lilja J, Lundqvist R, et. al. Automated quantification of 18F-flutemetamol PET activity for categorizing scans as negative or positive for brain amyloid: concordance with visual image reads. J Nucl Med. 2014;55(10):1623-1628

In addition, the GE Healthcare Investigator's Drug Brochure which is part of GE Healthcare IND # 101,866 and subsequent amendments which we are allowed to cross reference (see cross reference letter) contains additional previous human experience which is summarized below.

Three clinical trials have been conducted to assess the effects in humans. In the first 2 clinical trials [^{11}C]Flutemetamol ([^{11}C]AH110690) was used. These are summarized in the GE Healthcare IND 101,866 as clinical trials ALZ101 and ALZ102. In the last clinical trial [^{18}F] Flutemetamol ([^{18}F]AH110691) was used. This is known as trial ALZ103 with results being published in 2009.[122]

4.2.1 ALZ101 Study

A Phase 1, Proof of Concept Study to Evaluate the Uptake of [^{11}C]AH110690 and [^{18}F]AH110691 in the Brain of Healthy Volunteers and Subjects with Probable Alzheimer's Disease

The study was conducted at 1 center in Turku, Finland, in the period September 2004 to February 2005. The primary objective of the study was to establish proof of concept and select the preferred candidate for entry into early development by comparing brain uptake of 2 agents, [^{11}C]Flutemetamol and [^{18}F]AH110691. Each of the agents were given as a single intravenous dose containing approximately 5 µg of drug substance and a radioactivity dose of maximum550 MBq or maximum 382 MBq, respectively, by rapid bolus intravenous injection (less than 40 seconds). In addition to the drug substance, the [^{11}C]Flutemetamol injection contained 12% propylene glycol, 7% ethanol and phosphate buffer.

In this study [^{11}C]Flutemetamol was administered to 3 young healthy volunteers (HV; 30 years and younger), 10 older HV (from 50 to 85 years of age) and 10 probable AD cases (based on established criteria). Seventeen of these 23 subjects (3 young HV, 6 subjects with probable AD and 8 older HV) received [^{18}F]AH110691.

Visual assessment of the positron emission tomography (PET) images was performed and uptake ratios (URs; both standard uptake values [SUV] and distribution volume ratios [DVR]) were calculated from pre-specified regions of the brain in all subjects. These URs were compared between subjects with probable AD and young HV and between subjects with probable AD and older HV.

Efficacy Results of the ALZ101 Study

[^{11}C]Flutemetamol was able to differentiate between subjects with probable AD and HV on the basis of differences in regional and specific brain amyloid binding patterns. These differences were detectable visually and when using URs derived both from SUVs and DVRs relative to the cerebellum (i.e., the reference region).

Evaluation of [^{11}C]Flutemetamol scans using SUVs: In the frontal cortex, parietal cortex, occipital cortex, striatum, anterior cingular cortex and posterior cingular cortex, there was a tendency for higher URs with [^{11}C]Flutemetamol in the subjects with probable AD than in the older HV. Brain areas with the most significant difference in [^{11}C]Flutemetamol uptake between subjects with probable AD and HV were the frontal, parietal, anterior and posterior cingular cortices.

Evaluation of [^{11}C]Flutemetamol scans using DVRs: In all examined areas of the brain except the medial temporal cortex, subcortical white matter and pons, there was a tendency for higher DVRs with [^{11}C]Flutemetamol in the subjects with probable AD than in the older HV. Brain areas with the most significant difference in [^{11}C]Flutemetamol uptake between subjects with probable AD and HV were the frontal, parietal, anterior and posterior cingular cortices. The higher URs and DVRs noted with [^{11}C]Flutemetamol in these areas in subjects with probable AD suggested that [^{11}C]Flutemetamol could be used to differentiate between healthy subjects and subjects with probable AD.

When comparing [^{11}C]Flutemetamol URs or DVRs in subjects with probable AD and older HV, significant test results were obtained in the frontal cortex (left and right), parietal cortex (left), anterior cingular cortex (left and right) and posterior cingular cortex (left and right [DVR only]). The higher URs and DVRs noted with [^{11}C]Flutemetamol in these brain areas in subjects with probable AD suggested that [^{11}C]Flutemetamol could have potential utility in diagnosing AD.

The SUV and DVR analyses yielded comparable results suggesting that either or both methods can be used for future studies. In all examined areas of the brain, the URs with [^{18}F]AH110691 were similar in the subjects with probable AD, young HV and older HV. Therefore, [^{18}F]AH110691 was not able to differentiate between subjects with probable AD and HV using URs or DVRs.

Safety Results of the ALZ101 Study
Three subjects (13%) experienced a total of 4 adverse events (AEs). Two of 10 subjects with probable AD (20%) experienced 3 AEs and 1 older HV (10%) experienced 1 AE. The 3 young HV did not experience any AEs. Three AEs were of mild intensity and 1 AE was of moderate intensity. All AEs resolved during the study. None of the AEs were considered related to the investigational medicinal products (IMP). No SAEs or deaths were reported and no subjects were withdrawn due to AEs.

Of the 23 subjects who received [^{11}C]Flutemetamol or [^{11}C]Flutemetamol and [^{18}F]AH110691, 2 subjects (9%) experienced AEs within the MedDRA body system of ‘nervous system disorders’. No other body system was evidenced in more than 1 subject. The most frequent AE was ‘headache’ (2 subjects). The remaining 2 AEs, which occurred in 1 subject each, were ‘injection site extravasation’ and ‘vomiting’. The ‘injection site extravasation’ AE was actually a procedural complication with the arterial line used to take arterial blood samples and is not related to the drug product.

Two AEs required action to be taken. One subject had the arterial line removed due to injection site extravasation’ and 1 subject was given medication for a headache. Examination of the occurrence of AEs, their intensities, and relationship to [^{11}C-] Flutemetamol and/or [^{18}F]AH110691 across the subject groups revealed no safety signal.

Based on the number and nature of the AEs and the fact that no SAEs occurred, the results of The ALZ101study indicate [^{11}C]Flutemetamol to be safe and well tolerated. There was no specific profile for occurring AEs. The few AEs reported were primarily mild in intensity, resolved during the study, were deemed to be unrelated to [^{11}C]Flutemetamol and did not result in withdrawals. Assessment of laboratory parameters for hematology, serum biochemistry and urinalyses, as well as vital signs and ECGs revealed no trends or other signals that were indicative of a safety concern.

4.2.2 ALZ102 Study

A Phase 1, 1-Year Follow-Up Study to Evaluate the Uptake of [^{11}C]AH110690 in the Brain of Healthy Volunteers and Subjects with Probable Alzheimer's Disease who Participated in Study ALZ101

This study was conducted at 1 clinical site in Turku, Finland, in the period November 2005 to March 2006.

ALZ102 was a clinical and PET imaging follow-up study to the ALZ101 study designed to further demonstrate the utility of the PET tracer [^{11}C]Flutemetamol for imaging the amyloid burden and its changes over time in the brain of subjects with probable AD and HV. The areas of the brain where uptake was quantified comprised the frontal, medial temporal (hippocampus and amygdala), parietal, and occipital cortices, striatum, anterior and posterior cingular cortex, cerebellum, and white matter (subcortical and pons).

In this study [^{11}C]Flutemetamol was administered to 10 HV and 9 subjects with probable AD. The subjects were at least 50 years old and had already participated in study ALZ101. Nineteen subjects were dosed and evaluable for the safety analysis, and 18 subjects were evaluable for the efficacy analysis. One HV was excluded from the statistical analysis as he had developed an abnormal cognitive profile (mini-mental state examination [MMSE <27]) since Study ALX101. PET scanning commenced shortly before [^{11}C]Flutemetamol injection and continued for 90 minutes. Each subject received a single intravenous dose of [^{11}C]Flutemetamol (approximately 5 µg and less than 10 µg) by rapid bolus intravenous injection (less than 40 seconds). The activity of [^{11}C]Flutemetamol did not exceed 550 MBq as already established in study ALZ101. The formulation of the IMP was the same as in ALZ101.

Efficacy Results of the ALZ102 Study

In this study, [^{11}C]Flutemetamol imaging of the brain showed the potential to differentiate between subjects with probable AD and HV, both visually and using URs (derived from SUVs) and DVRs. In frontal, left parietal and the anterior and posterior cingular cortices there was a significantly higher UR in subjects with probable AD than HV. In the same areas of the brain, plus the left occipital cortex, there was a significantly higher DVR in subjects with probable AD than HV.

In the frontal, anterior and posterior cortices, 5 out of 9 subjects with a clinical diagnosis of AD had elevated DVRs, whereas 4 of the AD subjects had similar DVRs to those seen in HV. This pattern was consistent with that described in post-mortem studies of amyloid deposition in AD brain showing, from early stages of the disease process, amyloid plaque deposition distributed fairly evenly across neocortical association cortices whereas medial temporal lobe areas show relatively low amyloid burden. In terms of uptake distribution, ALZ102 results are in keeping with previous [^{11}C]PIB studies[135] and with the ALZ101 study results previously reported with [^{11}C]Flutemetamol.

Quantitatively, the ALZ102 study showed a 1.42 fold increase for [^{11}C]Flutemetamol uptake (DVR) in frontal cortex of AD subjects (mean DVR 1.56□0.41) compared to normal subjects (mean DVR 1.10□0.15). Other cortical areas showed a lower DVR increase. In HV, [^{11}C] Flutemetamol retention in the pons and subcortical white matter was greater than in cortical areas and very similar to the uptake values found in the pons and subcortical white matter of AD subjects. In AD subjects, retention in pons and white matter was greater than in association cortical areas. This suggests a higher non-specific retention of [^{11}C]Flutemetamol in white matter than in grey matter areas.

When compared with the ALZ101 study results, no significant changes in [^{11}C]Flutemetamol brain uptake were observed in AD subjects or HV over the 1-year follow-up. In conclusion, this study showed that [^{11}C]Flutemetamol brain retention provided a quantifiable discrimination between AD subjects and HV. Both URs and DVRs showed similar results in this study suggesting both methods of analysis are suitable for future use. The brain regions with the highest potential for the diagnosis of AD using [^{11}C]Flutemetamol were the frontal, parietal, left and right anterior and posterior cingular cortices.

Safety Results of the ALZ102 Study
All 19 subjects (10 HV and 9 subjects with probable AD) receiving [^{11}C]Flutemetamol were evaluable for safety. All subjects' safety was monitored continuously during the course of the study and as part of a 24-hour telephone safety follow-up. ECG was monitored continuously from before injection to 15 minutes after injection (Lead II ECG). Vital signs (including 12-lead ECG) were monitored at 0.5 and 1.5 hours after injection and the injection site was monitored from before injection to 1.5 hours after injection. AEs were monitored continuously following injection.

No AEs were experienced by HV subjects. Of the 9 subjects with probable AD, 2 subjects (22%) experienced 3 AEs (extrasystoles and 2 events of electrocardiogram QT prolongation). All of these events were mild in intensity and were considered not to be related to [^{11}C] Flutemetamol. No AEs required action to be taken and all events resolved. No SAEs or deaths were reported and no subjects were withdrawn due to AEs.

An examination of the occurrence of AEs, their intensities, and relationship to [^{11}C]Flutemetamol across the subject groups revealed no safety signal. There were no individual clinically significant

laboratory abnormalities that were considered related to administration of [^{11}C]Flutemetamol or indicative of a significant trend or safety signal. No laboratory abnormality resulted in a change in subject management or was reported as an AE. Systolic and diastolic blood pressure, heart rate, body temperature, respiratory rate and oxygen saturation measurements for all subjects were generally within the normal ranges and showed overall stability comparing baseline to post-baseline measurements. The number of subjects who experienced changes greater than the specified magnitude for these parameters were attributed to normal variations expected in this population. No significant trends indicative of a safety concern were apparent.

All ECGs from this study were read by an independent cardiologist. The following ECG intervals were measured in ms: PR, QRS, RR, and QTc using Bazett's (QTcB) and Fridericia's (QTcF) correction methods. Each QT value from this study was the maximum QT value among the 12 leads in a given ECG, corrected as indicated for heart rate. QTc interval changes were assessed with reference to the levels suggested by the Committee for Medicinal Products for Human Use (CHMP). The CHMP categories suggest QTc interval prolongations of 30 to 60 ms as of potential clinical concern and prolongations 60 ms as of significant clinical concern. The number of subjects with absolute QTc intervals 440 ms was also assessed.

A further exploratory analysis of QTc interval prolongation using a 20 ms prolongation\ threshold was performed. The maximum mean increase from baseline for QTc was 9 ms in subjects with probable AD and 11 ms in HV using Bazett's correction method (occurring 1.5 hours after injection) and 11 ms in subjects with probable AD and 12 ms in HV using Fridericia's correction method (occurring 30 minutes after injection). The frequency of subjects with QT interval values >440 ms were similar, irrespective of the correction method used; 5 subjects using Bazett's and Fridericia's correction (2 subjects with probable AD and 3 HV) had at least 1 QTc value >440 ms. Three of the 5 subjects who had post-injection QTc >440 ms also had at least 1 pre-injection QTc measurement >440 ms for both the Bazett's and Fridericia's corrections. Therefore, only 2 subjects showed de novo QTc measurements >440 ms post-injection. Only 1 subject demonstrated a 45 ms post-baseline increase (HV, increase in Bazett's QTc of 48 ms at 24 hours post-dose) in QTc interval using either correction method. The number of subjects with QTc interval prolongation 30 ms was low, 4 subjects, using Bazett's correction method and 1 subject using Fridericia's correction method. The frequency of subjects with QTc interval prolongation 30 ms was higher using Bazett's correction (4 subjects) compared to Fridericia's correction (1 subject). A review of changes in QTc interval 20 ms changes across all time points showed no cause for clinical concern when data was examined using both correction methods. There was no evidence for a temporal relationship to IMP.

In total, 7 dosed subjects demonstrated a 20 ms post-baseline increase in QTc interval using Bazett's correction method and 11 subjects using Fridericia's correction method. These changes were attributable to normal daily variability in this study population.

In conclusion, although QTc interval prolongation 30 ms was observed in 4 subjects, extensive review of the data showed no findings of clinical concern. There were no individual clinically significant ECG abnormalities following administration of [^{11}C]Flutemetamol indicative of a significant trend or safety signal. In this study of 19 subjects who were dosed with [^{11}C]Flutemetamol and who had ECG data recorded, no evidence was found that administration of [^{11}C]Flutemetamol led to clinically relevant changes in ECG intervals or waveforms.

4.2.3 ALZ103 Study

A Phase 1, Open-label Study to Assess Safety, Biodistribution, and Radiation Dosimetry and to optimize the Imaging Protocol of [^{18}F]AH110690 Injection in Healthy Volunteers and Subjects with Probable Alzheimer's Disease[121,122]

This study was conducted at 1 center in Leuven, Belgium in the period October 2007 to March 2008. In this study [^{18}F]Flutemetamol was used for the first time. [^{18}F]Flutemetamol is a PIB benzothiazole derivative radiolabelled with ^{18}F with the potential as a diagnostic biomarker for beta amyloid deposition in human. ^{18}F labeling was chosen rather than ^{11}C because of the longer half-life. ^{18}F has a half-life of approximately 109 minutes while ^{11}C half-life is only 20.4 min. This was a phase 1, single center, single dose, open-label, non-randomized study to evaluate the safety, biodistribution, and radiation dosimetry and to optimize the imaging procedure of [^{18}F]Flutemetamol injection in HV and subjects with probable AD. Twenty-two evaluable subjects – 8 subjects with a diagnosis of probable AD and 14 HV – aged 50 years or older were included in the study. The presence of probable AD and/or the lack of dementia (i.e., HV) were verified by comprehensive cognitive/neuropsychological examinations.

The study consisted of a minimum of 2 visits for each subject. Each subject attended a screening visit within 30 days before injection of the IMP, i.e., [^{18}F]Flutemetamol injection. During the screening visit the subjects had to satisfy all entry criteria and undergo safety assessments. On the day of PET imaging, each subject received a single dose of [^{18}F]Flutemetamol by bolus IV injection. A computed tomography (CT) scan (i.e., CT attenuation correction scan) was performed prior to the initial PET scan and then repeated as required prior to any subsequent scan following an out of scanner break and repositioning. All subjects' safety was monitored continuously during the course of the study and as part of a 24-hour telephone safety follow-up. Enrollment into the study proceeded in a 3-step fashion. The structure of the specific visits varied depending upon the step into which the subject was enrolled.

Step 1 consisted of the evaluation of biodistribution, internal radiation dosimetry, ED, interim safety and an analysis of the % content of radioactive parent (active ingredient) and any of its derivative metabolites present in 6 HV. Subjects within this group underwent a whole body PET scan. Time-activity curves were generated and integrated to obtain the cumulated activity in each source organ or region which was then used to determine the internal radiation dosimetry using the Medical Internal Radiation Dosimetry (MIRD) schema.

In order to ensure individual subject safety, the decision to proceed to dosing additional subjects was made after an interim review of safety and internal radiation dosimetry data had been conducted on the first 2 evaluable subjects who received an injected activity of 100 MBq. The dosing of the remaining 4 subjects in Step 1 was then revised to 150 MBq. A 2nd review of safety and internal radiation dosimetry data was conducted once all 6 evaluable subjects had been completed.

No safety concerns were raised after injection of [^{18}F]Flutemetamol in the 6 HV in Step 1, and Step 2 was initiated with the recruitment of 3 subjects with a diagnosis of probable AD and 3 additional HV. Interim efficacy/safety data and kinetic modeling of the brain distribution of [^{18}F]Flutemetamol was performed in this population. Dynamic PET scans with 185 MBq [^{18}F]Flutemetamol were acquired and volume of interest (VOI) analysis carried out for each subject. Time-activity curves of the brain were generated to compare the time-dependent distribution of the IMP in the brain of subjects with probable AD and HV. This comparison was expected to help in defining the best model for representing the kinetics of tracer uptake.

Just prior to IMP administration an arterial line was established and maintained throughout the duration of the scanning period in each subject. Arterial blood samples were taken to derive safety measurements and ^{18}F-activity measurements. Arterial and venous blood samples were taken to perform an analysis of the % content of radioactive parent and any radiolabelled derivative compounds present.

Dynamic imaging coupled with arterial sampling provided additional information on the imaging characteristics of the brain. Data generated during this step of the protocol was used to refine the optimal imaging window used in Step 3. For Step 2 and Step 3, brain magnetic resonance imaging (MRI) scans were performed during the screening period (before PET scanning) with the images used to rule out cerebro-vascular, structural disorders and to assist production of a template for VOI analysis of the PET tracer uptake.

No safety concerns were raised following an analysis of the data from Step 2, and enrolment into Step 3 was initiated. This final step consisted of imaging optimization and additional safety and efficacy assessments. Five additional subjects with a diagnosis of probable AD and 5 additional HV were recruited. A single dynamic PET scan was acquired after injection of 185 MBq [^{18}F]Flutemetamol and VOI analysis carried out for each subject. However, the specific start time point after tracer administration was influenced by the results obtained from Step 2. Time-activity curves of the brain were generated to compare the time-dependent distribution of the IMP in the brain of HV and subjects with probable AD. This comparison was expected to help in defining the optimal time from injection to start of acquisition as well as the minimum injected activity and duration of acquisition.

Efficacy Results of the ALZ103 Study

Efficacy from Step 2 and Step 3: URs were calculated and compared for [^{18}F]Flutemetamol in HV and subjects with probable AD. In all examined areas of the brain except the pons, there was a tendency for higher URs with [^{18}F]Flutemetamol in the subjects with probable AD than in the HV. Statistical analysis (Wilcoxon-Mann-Whitney test) to compare URs in subjects with probable AD and HV showed that significant test results were obtained for all cortical brain areas, except the anterior cingular cortex for the 85-minute scan start time. Therefore, [^{18}F]Flutemetamol was able to differentiate between subjects with probable AD and HV using URs. A visual assessment showed that 2 AD subjects had images similar to the HV images and 1 HV had images similar to the AD images. Calcification of the brain was detected in Step 3 in AD subject 017 and was classified by the Principal Investigator (PI) as an incidental finding with no clinical significance. The PI reassured that this subject fulfilled all entrance and exclusion criteria. The impact of different scanning windows on the discrimination between subjects with probable AD and HV was analyzed using the Wilcoxon statistical test.

Analysis of the results showed that different scan lengths (5 to 40 minutes) had a negligible effect on discrimination. The same analysis of the effect of different start times post-injection of IMP also showed a very small difference, but with a minor improvement in discrimination for later scan start times. Dosimetry estimates in Step 1 HV determined that the injected activity for subsequent studies using [^{18}F]Flutemetamol could be increased to 185 MBq, corresponding to an effective dose (ED) of 6.2 mSv for the PET scans for each subject. From analysis of Step 2 and Step 3 subjects, the recommended parameters for a Phase 2 study would be: approximately 185 MBq [^{18}F]Flutemetamol, scanning start time approximately 90 minutes post injection, scan duration approximately 30 minutes, and data acquisition in 5 minute bins.

Safety Results for the ALZ103 Study
[^{18}F]Flutemetamol was safe and well tolerated. No deaths, SAEs, or withdrawals due to AEs occurred during the study. There was no specific AE profile. Only 2 AEs (diarrhea and back pain) occurred during the study; both were mild in intensity, resolved during the study, and were deemed unrelated to [^{18}F]Flutemetamol. Assessment of laboratory parameters (hematology, coagulation, serum biochemistry and urinalyses), vital signs and ECGs showed no clinically important trends or safety signals. One post-study SAE was reported after the study finished (a diagnosis of B-cell non-Hodgkin's lymphoma in a HV 17 weeks after study completion). The relationship of [^{18}F]Flutemetamol to this SAE was assessed as 'not reasonable cause'.

The results of ALZ103 have been published in two separate manuscripts. The first was the result of the Phase I study[121] and the second was the radiation dosimetry.[121]

5. TOXICITY and SAFETY OF FDG

5. 1 Safety and Toxicity of FDG in Humans
There are no known toxic effects of FDG.

6. Radiation Dosimetry of [18F]FLUTEMETAMOL and FDG PET/CT STUDIES

6.1 Human Radiation Dosimetry for [^{18}F]Flutemetamol

The amount of injected [^{18}F]Flutemetamol activity used in this protocol will be 185 MBq (5.0 mCi). Higher administered doses have been used without safety or toxicity concerns. Please refer to the GE Healthcare IND # 101,866. The dosimetry for the compound was previously published.[121] However, the dosimetry estimates for [^{18}F]Flutemetamol have been revised in the recent FDA Product label and are used to estimate radiation dose and risks in this protocol. The greatest organ absorbed doses for a 185 MBq (5 mCi) injection of [^{18}F]Flutemetamol are the gallbladder (53.1 mGy) and the bladder (26.83 mGy), while the effective dose is 5.92 mSv (Table 3).

6.2 Human Radiation Dosimetry for [^{18}F]FDG

The amount of injected [^{18}F]FDG activity used in this protocol will be 370 MBq (10.0 mCi). This is the typical activity used for a clinical brain PET study and higher activities up to 740 MBq (20.0 mCi) are used in whole-body oncology PET studies. The radiation dosimetry estimates for [^{18}F]FDG are based on Publication 106 issued by The International Commission on Radiation Protection (ICRP).[136] The greatest organ absorbed doses for a 370 MBq (10 mCi) injection of [^{18}F]FDG are the bladder (48.1 mGy) and the heart (24.79 mGy), while the effective dose is 7.03 mSv (Table 3).

6.3 Human Radiation Dosimetry for CT-based Attenuation Correction for PET Imaging

The study will be performed on the research GE Discovery 710 PET/CT scanner in the Molecular Imaging Suite at HCI. Each PET imaging study will require CT imaging for attenuation correction. Hence, there will be a total of 2 CT exams for each patient, one for the [^{18}F]Flutemetamol-PET/CT study and another for the FDG-PET/CT. After positioning the patient in the gantry of the PET/CT system, a topogram of the head will be obtained to confirm the correct positioning and identify the anatomic range for a single PET bed position covering the entire brain. A helical CT scan is then performed over the same anatomic range corresponding to the PET scan in order to perform for attenuation correction. The PET emission scan will commence immediately after the CT scan. The CT acquisition parameters will be 120 kVp, 0.5s rotation speed, 50 mA tube current, 8 x 1.25 mm collimation, and a pitch of 1.35. This results in a CT Dose Index (CTDIvol) of 3.675 mGy based on a 16 cm phantom. A standard length of 1 PET bed position results in a Dose Length Product (DLP) of 61.92 mGy x cm. The estimated effective dose using the DLP scaling method is 0.13 mSv.[137] In order to estimate the absorbed doses of individual organs and the resulting effective dose, the ImPACT Scan CT Patient Dosimetry Calculator (Version 1.0.4) was used with the specific acquisition parameters used in this protocol and the NRPB monte carlo dose data sets for the GE Lightspeed Ultra CT scanner produced in report SR250 dosimetry tables. Note that the topogram contributes a negligible radiation exposure to the helical CT exam. The greatest organ absorbed doses for a single head CT scan using the

aforementioned acquisition parameters are the eye lenses (3.5 mGy) and the brain (2.89 mGy), while the effective dose is 0.12 mSv (Table 3).

6.4 Cumulative Radiation Dosimetry for [^{18}F]Flutemetamol and [^{18}F]FDG PET/CT Studies

The cumulative radiation dose to a patient participating in this clinical trial has been compiled from the dosimetry estimates for [^{18}F]Flutemetamol (Section 6.1), [^{18}F]FDG (Section 6.2), and the 2 head CT scans that will be performed as part of the PET/CT procedures. The greatest cumulative organ absorbed doses for the study are the bladder (74.9 mGy) and the gallbladder (57.9 mGy), while the effective dose is 13.2 mSv (**Table 3**).

Table 3. Radiation Dosimetry for [18F]Flutemetamol and [18F]FDG PET/CT Studies

	FDG PET/CT Study		Flutametamol PET/CT Study		Cumulative
	FDG dose @ 10 mCi	Low Dose Head CT	Flutametamol dose @ 5 mCi	Low Dose Head CT	Organ Dose
Organ	ICRP 106 (mGy)	IMPACT/NRPB (mGy)	Vizamyl Product Label (mGy)	IMPACT/NRPB (mGy)	(mGy)
Adrenals	4.44	0.00048	2.41	0.00048	6.85
Bladder	48.10	0.00000	26.83	0.00000	74.93
Bone surfaces	4.07	0.87500	N/A	0.87500	5.82
Brain	14.06	2.88750	2.04	2.88750	21.87
Breasts	3.26	0.00175	0.93	0.00175	4.18
Colon	4.81	0.00001	N/A	0.00001	4.81
Eye Lenses	N/A	3.50000	N/A	3.50000	7.00
Gallbladder	4.81	0.00014	53.10	0.00014	57.91
Heart	24.79	0.00123	2.59	0.00123	27.38
Kidneys	6.29	0.00010	5.74	0.00010	12.03
Liver	7.77	0.00033	10.55	0.00033	18.32
Lower large intestine	5.18	N/A	7.77	N/A	12.95
Lungs	7.40	0.00534	2.96	0.00534	10.37
Muscles	3.70	0.06738	1.67	0.06738	5.50
Oesophagus	4.44	0.00306	N/A	0.00306	4.45
Osteogenic cells		N/A	2.04	N/A	2.04
Ovaries	5.18	0.00000	4.63	0.00000	9.81
Pancreas	4.81	0.00021	2.78	0.00021	7.59
Red marrow	4.07	0.18375	2.41	0.18375	6.84
Skin	2.89	0.21875	0.93	0.21875	4.25
Small intestine	4.44	0.00001	18.87	0.00001	23.31
Spleen	4.07	0.00038	2.78	0.00038	6.85
Stomach	4.07	0.00018	2.22	0.00018	6.29
Testes	4.07	0.00000	1.48	0.00000	5.55
Thymus	4.44	0.00306	1.11	0.00306	5.56
Thyroid	3.70	0.10500	1.11	0.10500	5.02
Upper large intestine	4.44	N/A	21.65	N/A	26.09
Uterus	6.66	0.00000	4.63	0.00000	11.29
Remaining organs	4.44	N/A	N/A	N/A	4.44
Effective dose(mSv)	7.03	0.12250	5.92	0.12250	13.20

7. RATIONALE, GOALS, AND HYPOTHESES

7.1 Rationale and Goals of Study

The primary goal of this study is to better understand the effects of chemotherapy on cognitive impairment in patients with breast cancer. Toward this end, we will be administering a variety of questionnaires and neuropsychological tests in addition to using two novel PET imaging agents ([^{18}F]Flutemetamol and FDG) and an anatomical MRI to assess the potential pathophysiology of CICI.

7.2 Significance

The significance of this project is that we will investigate the possibility that amyloid plaque burden may have a major association to the cognitive dysfunction seen in some breast cancer patients with CICI. This study may help identify factors (such as, amyloid plaque burden), which may increase an individual's risk of developing chemobrain.

While one previous study has used FDG-PET and [^{15}O]H_2O-PET Imaging to assess cognitive function,[7] to our knowledge there have been no studies that have used the combination of [^{18}F]Flutemetamol, FDG, and MRI. Furthermore, we aim to investigate those individuals who are most likely to develop chemobrain and whether factors such as depression and anxiety, chemotherapy regimen, and coping mechanisms correlate with the development of CICI.

7.3 Primary Endpoint

Our primary hypothesis is that individuals with chemotherapy induced cognitive impairment will have a greater than expected amyloid plaque burden when compared to a control group of individuals who are not experiencing cognitive complaints. The chemotherapy may accelerate the process of amyloid plaque burden deposition and subsequent possible neuronal injury and loss in individuals who have undergone CICI. The primary endpoint will be amyloid plaque burden assessed by visual criteria as outlined in the recently approved Vizamyl (flutemetamol F 18 injection) prescribing information.[1] This will be a binary assessment of the images being positive or negative by visual criteria for abnormal [^{18}F]Flutemetamol uptake. A secondary analysis of [^{18}F]Flutemetamol binding will occur using a regional semi-quantitative technique as described by Vanderberghe et al.[123] and Thufjell et al[134].

7.4 Exploratory Endpoints

The following exploratory endpoints will be evaluated:
Objective cognitive impairment correlated with subjective reports of cognitive impairment as measured by administered questionnaires.
Amyloid plaque burden using regional semi-quantitative determinations is associated with greater objective cognitive impairment.
Those individuals with the most profound cognitive impairment may have associated regional FDG metabolic changes consistent with neuronal loss or damage.

8. STUDY DESIGN

8.1 Overview of Study Design

All enrolled subjects will complete three imaging sessions on separate days that consist of: 1) [^{18}F]Flutemetamol-PET/CT, 2) FDG-PET/CT, and 3) MRI. The order of the performance of these studies will be based upon subject and radioisotope availability, but they will all be completed

within 2 months of each other. The total enrollment will be 12 evaluable patients (with all imaging sessions having been completed).

8.2 Participant Eligibility

Study participants: Female Adults (18 to 70 years of age) with previously diagnosed breast cancer Stage I through IIIC who have completed chemotherapy and who now report chemotherapy induced cognitive impairment. We expect that up to 15 total participants may be enrolled in this study. This will assure that 12 evaluable patients (patients who have complete imaging results and blood data available for data analysis.

8.3 Inclusion Criteria

- Female patients must be 18 years or older for inclusion in this research study. There is inadequate experience with the safety of [^{18}F]Flutemetamol in children and therefore this radiopharmaceutical should not be used in patients under the age of 18. Individuals over 70 years age will be excluded as the incidence of amyloid positivity increases significantly even with no cognitive problems and will not allow for testing of our primary hypothesis.
- The patient must have a histologically proven diagnosis of Stage I through IIIC Breast Cancer.
- The patient must have completed adjuvant chemotherapy more than 6 months ago, but no more than 36 months prior to initial study scan.
- The patient must report persistent cognitive problems following the initiation of chemotherapy, defined as being one or more standard deviations above normative data on our two scales of subjective cognitive dysfunction. This is defined as a total score of 45 or higher on the Cognitive Failure Questionnaire, and a T-score of 60 or higher on the Frontal System Behavioral Scale Questionnaire.
- Patients must agree to have clinical and radiographic endpoints and the results of histopathologic tissue analysis and other laboratory information entered into a research database, as evidenced by signing the informed consent form.
- All patients, or their legal guardians, must sign a written informed consent and HIPAA authorization in accordance with institutional guidelines.

8.4 Exclusion Criteria

- Patients with known allergic or hypersensitivity reactions to previously administered radiopharmaceuticals. Patients with significant drug or other allergies or autoimmune diseases may be enrolled at the Investigator's discretion.
- Adult patients who require monitored anesthesia for PET scanning.
- Patients who are too claustrophobic to undergo MRI or PET imaging.

- History of neurological disease known to affect cognition prior to initiating chemotherapy (e.g., stroke, head injury with loss of consciousness of >30 minutes, seizure disorder, demyelinating disorder, mental retardation, primary brain tumor, brain metastases, etc.)
- Current or past major psychiatric illness (e.g., schizophrenia, bipolar affective disorder)
- Evidence of stroke or mass lesion on CT or MRI scan
- History of alcoholism or other substance abuse
- Current use of cholinesterase inhibitors, other cognitive enhancers, antipsychotics, antidepressants, or anticonvulsant medications
- Current use of gabapentin or venlafaxine for hot flashes
- History of radiation therapy to the brain
- Uncontrolled diabetes or blood glucose >175 mg/dl on the day of the FDG-PET scan
- Currently pregnant
- Color blindness (cannot complete D-KEFS Stroop test)
- Moderate or Severe Depression as measured on the Beck Depression Inventory (BDI) – Short Form. The cut-off score for the BDI will be 8/9.

8.5 Participant Registration

Participants must meet all of the eligibility requirements listed above and in Appendix A prior to registration.

Study related screening procedures can only begin once the participant has signed a consent form. Participants must not begin protocol procedures prior to registration.

To register eligible patients on study, a Clinical Trials Office Patient Registration Form will be completed and submitted to: CTORegistrations@hci.utah.edu.

9 STUDY PROCEDURES, SCHEDULE of EVENTS, and TRACER ADMINISTRATION

9.1 Initial Visits Prior to PET Imaging

The patient will be screened using: Beck Depression Inventory Short Form to rule out Moderate to Severe Depression, and two subjective scales of cognitive functioning (Cognitive Failure Questionnaire and Frontal System Behavioral Scale). In addition, a review of the patient medical records will be conducted. The following patient data will be obtained: histological diagnosis (when available following surgery), age at radiological diagnosis, chemotherapy regime and date administered, current age and gender.

9.2 Genetic Analysis

We intend to investigate how genetics mediate measures of health-related quality of life and cognitive impairment in breast cancer patients. These factors are of interest because they may

contribute to chemotherapy-induced cognitive impairment. Prior to completing the first PET imaging scan, one tube of blood (5-7 ml) will be obtained for DNA analysis and APOe4 SNP genotyping. This will be labeled with patient study number.The DNA will be stored in the laboratory, and APOe4 genotyping will be done by ARUP.

Genetic factors are of interest because it may be that chemotherapy merely accelerates age-related cognitive decline. According to this theory, those individuals who have a genetic predisposition toward the development of dementia or Alzheimer's disease would be more likely to develop cognitive impairments associated with chemotherapy. One study has specifically linked the epsilon 4 allele of APOE, a lipoprotein that has been studied for its role in Alzheimer's disease, to significantly lower scores on tests of psychomotor functioning, visual memory and spatial ability in long-term breast cancer and lymphoma survivors.[138] A blood draw for APOE assessment will be obtained prior to completion of the first PET imaging scan. No patient identifiers will be attached with the samples, and these results will not go into patient charts. Results will not be returned to participants.

9.3 Neuropsychological Exams

To assess memory, we will utilize the Hopkins Verbal Learning Test – Revised (HVLT-R) and the Brief Visuospatial Memory Test – Revised (BVMT-R). Processing speed will be tapped with Trail Making Test Part A (TMT-A) and the Coding and Symbol Search subtests of the Wechsler Adult Intelligence Scale – IV. Executive functioning will be measured with Trail Making Test Part B (TMT-B), Controlled Oral Word Association Test (COWAT), and Stroop Color Word Test (SCWT). Additionally, the Wide Range Achievement Test (WRAT4) will be used to assess premorbid intellect in all participants.

9.4 Functional MRI Imaging

Functional Magnetic Resonance Images (fMRI) will be obtained using a Siemens 3.0 Tesla whole-body scanner equipped with a 32-channel multiband sed/receive head coil enabling rapid acquisition echo-planar imaging (EPI). Functional runs will consist of 405 frames per run [repetition time (TR) = 720 ms; echo time (TE) = 33.1 ms; flip angle = 52°, slice thickness = 2 mm; FOV = 208 mm; matrix = 104x90; voxel size = 2.0 mm3] of 72 transverse slices per volume. The first three EPI volumes acquired during each functional run will be excluded from further analysis in order to allow for steady-state transverse relaxation. Coplanar high-resolution anatomical images will be acquired using a isotropic gradient echo (MPRAGE) sequence [TR = 2.4s, TE = 2.14ms, TI = 1s, FA = 8, FOV = 224x224; vox size = 0.7 mm3] as well as an in-plane T2-weighted sequence [TR = 3.2 s; TE = 565 ms; FOV = 224x224 mm; slice thickness = 2 mm; matrix = 192 x 256] to allow precise localization of functional maps on brain anatomy.

Stimuli will be recorded and presented using ePrime running on a laptop personal computer. Functional image volumes will be acquired according to a boxcar-type stimulus paradigm

consisting of alternating (A-B-A-B) stimulus-ON and stimulus-OFF conditions. Each functional run will consist of repeated cycles divided into two alternating stimulus-ON and stimulus-OFF epochs. During stimulus-ON epochs, stimuli will be presented, whereas no stimuli (silence) will be presented during stimulus-OFF epochs. In addition, each functional run will be preceded by a short period of silence during which three pre-experimental baseline EPI volumes will be acquired. While in the MR scanner, subjects will be instructed to attend to the stimulus being presented, and to perform the task according to functional protocols.

Two functional runs will be collected according to the above protocol, using two independent task conditions designed to specifically probe higher cognitive functions implicated in chemobrain, namely working memory and relational processing.

Working memory task:
The category-specific representations are used to probe working memory during this task condition. Participants will be presented with blocks of trials that consist of pictures of places, tools, faces and body parts (non-mutilated parts of bodies with no "nudity"). Within each run, the 4 different stimulus types will be presented in separate blocks. Within each run, 1⁄2 of the blocks use a 2-back working memory task and 1⁄2 use a 0-back working memory task (as a working memory load comparison). A 2.5 second cue indicates the task type (and target for 0-back) at the start of the block. Each of the two runs contains 8 task blocks (10 trials of 2.5 seconds each, for 25 seconds) and 4 fixation blocks (15 seconds). On each trial, the stimulus is presented for 2 seconds, followed by a 500 ms inter-task interval (ITI). Total scan time is 5:01.

Relational Processing task:
This task is adapted from Smith *et al.* 2007. Stimuli are 6 different shapes filled with 1 of 6 different textures. In the relational processing condition, participants are presented with 2 pairs of objects, with one pair at the top of the screen and the other pair at the bottom of the screen. They are told that they should first decide what dimension differs across the top pair of objects (differed in shape or differed in texture) and then they should decide whether the bottom pair of objects also differ along that same dimension (e.g., if the top pair differs in shape, does the bottom pair also differ in shape). In the control matching condition, participants are shown two objects at the top of the screen and one object at the bottom of the screen, and a word in the middle of the screen (either "shape" or "texture"). They are told to decide whether the bottom object matches either of the top two objects on that dimension (e.g., if the word is "shape", is the bottom object the same shape as either of the top two objects. For both conditions, the subject responds yes or no using response buttons. For the relational condition, the stimuli are presented for 3500 ms, with a 500 ms ITI, and there are four trials per block. In the matching condition, stimuli are presented for 2800 ms, with a 400 ms ITI, and there are 5 trials per block. Each type of block (relational or matching) lasts a total of 18 seconds. There are 3 relational blocks, 3 matching blocks and 3 16-second fixation blocks. Total scan time is 2:56.

Local blood-oxygenation level-dependent (BOLD) image intensity signal changes will be analyzed to assess functional activation. SPM12 [Friston 1995] will be used for individual subject data analysis and visualization. Initially, a mean image from the central time-point of each functional run will be created for use in inter- and intra-scan head motion correction for each subject. The mean image will be used as the standard for re-registration of all 192 volumes. All EPI images will then be smoothed with a Gaussian kernel of roughly 8 x 8 x 8 mm. Image intensities will be subsequently regressed to the mean in order to correct for signal drift associated with fluctuations of the B0 magnetic field. Noise outside the area of the brain will be excluded. EPI volumes will then be sorted into appropriate stimulus groups according to the experimental paradigm. To assess the extent of activation within the brain, a whole-brain analysis will be carried out using the full volume data set for both task conditions. Activation will be assessed by application of the General Linear Model as implemented in SPM12. The reference waveform will be composed of a boxcar waveform (essentially the stimulus paradigm) convolved with a Gaussian envelope of the same width. Correlation coefficient maps or statistical parametric maps of the t-statistic will be constructed and converted into Z-maps for subsequent cluster analysis. Clusters of activation will then be identified by considering both the extent and the magnitude of activation. Active voxel clusters will be subsequently thresholded at Family-Wise Error (FWE) corrected significance level of $p < 0.05$ (corresponding to Z-values >approximately 4.7) in order to statistically account for multiple comparisons. Finally, these clusters will be rendered onto the coplanar high-resolution MR images for precise anatomical localization. Significant clusters will be then used to compare activation across stimulus types and across subjects.

Resting State fMRI (rsfMRI)
Acquisition: 8 minutes of BOLD-EPI data will be collected with subjects lying in the scanner and instructed to simply 'lie still with your eyes open and think of nothing in particular'. We will concurrently monitor pulse oximetry and heart rate. These physiologic data serve two purposes: first, they serve as a ‘real-time’ proxy for assessment of subject discomfort and anxiety during the 8 minute data collection run, as subjects will be instructed to try not to talk during the run (unless in distress). Second, these data provide covariates for motion-related assessment and correction at data analysis stages. Additional motion-related signal change will be assessed by averaging time courses for two ROIs in white matter, CSF, soft tissues of the head, face, and scalp, and corrected within SPM using these and six rigid-body motion correction parameters from the ‘Realign’ step, following previously published procedures in our lab (Anderson et al., 2011b). After motion correction, resulting frames will be inspected for significant motion using the “scrubbing” procedure reported by Power et al. (2012), and frames with temporal derivative of root-mean-square variance over voxels (DVARS) or root-mean- square motion parameters >0.2 mm will be removed prior to analysis of connectivity results, with concatenation of remaining frames.

Analysis: 8-minute BOLD EPI scans will be coregistered with high-resolution anatomical volumes, normalized, and bandpass-filtered between 0.01 and 0.1 Hz. Signal fluctuation within 4 mm spherical seed regions of interest (ROI) representing major nodes within RSN hubs (representing sensorimotor, auditory, visual, speech, semantic, salience, executive function, and

default mode networks) will be cross-correlated with all other brain voxels. Correlation matrices will be constructed and significant pairwise correlation values will be represented in normalized brain space using subjects' anatomical MR image volumes. Groupwise network-level analyses will be carried out as above.

9.5 PET Exams

PET exams of [^{18}F]Flutemetamol and [^{18}F]FDG will be acquired in each participant. Two PET/CT scanning sessions will be required. This is due to fact that both [^{18}F]Flutemetamol and FDG are labeled with F-18 that has a 110-minute half-life, which does not allow for same day imaging. The FDG and [^{18}F]Flutemetamol study procedures will be obtained on separate days usually within 10-14 days of each other. Typically these will be obtained over two separate days (consecutive if possible). However, this may not be possible due to scheduling issues, weekends, and other variables. The days of imaging will be scheduled according to scanner and cyclotron availability, and all days of imaging will be obtained within six weeks of each other. The exact order and timing of the two PET imaging sessions will vary according to logistics, scheduling, and tracer availability. Patients who are not postmenopausal for a minimum of one year or surgically sterile must have a serum pregnancy test performed within 48 hours prior to each research PET imaging. The procedures for each PET scan are similar as described below.

9.5.1 Day of Research PET Scan(s)

The patient will have the appropriate IV access placed for radiotracer administration. Access for temporal blood sampling, necessary for obtaining the input function for PET kinetic modeling, will be obtained using the heated-hand methodology for obtaining arterialized venous blood (FDG). The patient will be positioned comfortably on the PET imaging table. After positioning the patient in the gantry of the GE Discovery 710 PET/CT system, a topogram of the head will be obtained to confirm the correct positioning and identify the anatomic range for a single PET bed position covering the entire brain. A helical CT scan is then performed over the same anatomic range corresponding to the PET scan in order to perform attenuation correction. Thereafter the PET scans will then be acquired for either the dynamic FDG PET study or the static [^{18}F]Flutemetamol PET study.

9.5.2 PET Tracer Administration Overview

Table 4. PET Tracer Administration: Route, Dosing, and Blood Sampling

Tracer	*Route*	*Manner*	*Injected Dose*	*Scan Mode*	*Blood Sampling*
^{18}F-FDG	IV	~60s push	~10.0 mCi	*Dynamic*	Heated-hand
[^{18}F]Flutemetamol	IV	~30s push	~5.0 mCi	Static	N/A

Each radiopharmaceutical will be prepared by the investigational drug radiochemists in the PET cyclotron facility at HCI on the day of the scanning session. It will be administered to the patient by a physician, nuclear medicine technologist, or trained nurse in the research PET imaging suite. The dynamic imaging procedure will take 70 minutes to complete for FDG.

No adverse events have ever been reported with the use or administration of FDG so reporting is not required.

9.6 Tissue Collection and Analysis

All patients enrolled on this study may have recent surgical pathology or biopsy information available and tissue specimen reports and assessments will be analyzed by the study PI and co-investigators.

10. METHODS FOR EVALUATION OF IMAGING STUDIES/ DATA ANALYSIS AND STATISTICS

Each PET imaging study will be evaluated using qualitative, semi-quantitative, and fully-quantitative analysis techniques that have previously been evaluated by us and other groups[116,139,140] and represent the standard and accepted means of evaluating static- and dynamic-PET images for these tracers. These assessments are described below for each tracer.

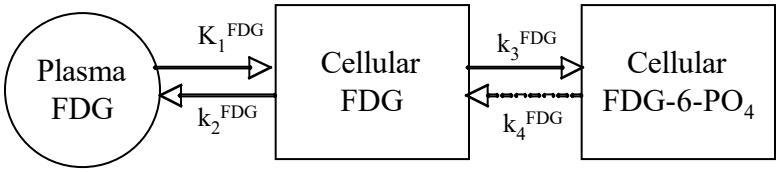
10.1 ^{18}F-FDG-PET Imaging

10.1.1 FDG Semi-Quantitative Assessment

FDG-PET data will be analyzed using CortexID Suite, a software application provided by GE Healthcare. The software has a large group of normal healthy controls of varying ages included as the normal database so the provided Z scores are in comparison to age and sex matched controls. Cortex ID Suite is an FDA approved brain image analysis software designed to quantify FDG uptake measured with PET and PET-CT brain scans. The software aids clinicians in the assessment of FDG-PET scans by providing automated analysis through quantification of the comparison of local peak FDG uptake activity values, at standardized bilateral anatomical locations, compared with the corresponding reference normal peak activity in age- stratified normal control subjects. The resulting quantification is presented through 3D Stereotactic Surface Projection (SSP) maps of the brain as initially described by Minoshima et al.[141] CortexID allows for user generated information on the relative changes in metabolic activity normalized to the pons presented as regional and global Z-scores between a subject's images and age-stratified controls. The regions of interest that will be assessed include: parietal association, temporal association, frontal association, occipital association, posterior cingulate, anterior cingulate, medial frontal, medial parietal, visual, cerebellum, pons, average association, averaged cerebral, global average.

10.1.2 FDG Fully-Quantitative Assessment

Compartment modeling techniques will be applied to the dynamic PET data to obtain estimates of kinetic rate parameters (K_1, k_2-k_4) and FDG net uptake (K_{net}). Individual rate parameters will be computed using full compartment-modeling techniques according to the two-tissue compartment model shown below. The commercially available PET analysis software (e.g. PMOD Technologies LTD., Zurich, Switzerland) will be used. The net uptake parameter will be computed from both full compartment modeling and Patlak graphical analysis[139,140] both of which are standard and accepted methods.



A region-of-interest (ROI) will be drawn over the defined cortical brain region on the summed static FDG PET image. The summed image will be co-registered and fused to the patient's MRI. This will allow for regional determination of brain glucose metabolic rates. For each ROI the metabolic rate obtained can then be correlated with available clinical data, neuropsychological data, and the regional amyloid plaque burden SUV.

10.2 [^{18}F]Flutemetamol-PET Imaging

The primary assessment of amyloid plaque burden will be with visual assessment of abnormal cortical flutemetamol uptake as outlined in the recently approved Vizamyl (flutemetamol F 18 injection) prescribing information (section 2.5).[1] This will be a binary assessment of the images being positive or negative for increased and abnormal flutemetamol uptake and thus increased amyloid plaque burden. A secondary analysis of flutemetamol binding will occur using a regional semi-quantitative technique as described by Vanderberghe et al.[123] In this technique, a semi-quantitative global composite of standardized uptake value ratios (SUVRs) in the cerebral cortex which is obtained and normalized to the cerebellum or pons. The following regions are averaged to yield the global composite: lateral frontal, lateral temporal, lateral parietal, anterior cingulate, and posterior cingulate. This will yield a global composite for [^{18}F]Flutemetamol-PET data. GE proprietary software (CortexID Suite) is available in our laboratory and will be used to determine both regional SUV values and a composite SUVR for [^{18}F]lutemetamol uptake. This database also contains [^{18}F]Flutemetamol scan data from 105 healthy volunteers and has been validated to be over 99% concordant with visual reads using 172 scans from AD, MCI, and healthy controls using a threshold Z score of 2 (which corresponds to a composite SUVR of 0.59). This software will provide the control population to which we will compare our symptomatic CICI patients. Z scores obtained for the study patients using this software will then be correlated with available clinical data, neuropsychological data, and the regional FDG Z scores or metabolic rates.

10.3 Magnetic Resonance Imaging

Participants will be imaged using a Siemens Trio 3T MRI scanner with 32 channel head coil using a magnetization prepared rapid gradient echo (MPRAGE) acquisition with isotropic image resolution of 1.0 mm and full head field of view. Imaging will be performed in the sagittal plane with repetition of sequences deemed at the time of acquisition to exhibit patient head motion or other artifacts. Images will be analyzed using SPM12 toolbox for MATLAB, with linear normalization to Montreal Neurological Institute (MNI) template brain space, segmentation of gray matter, white matter, CSF, and volumetric quantitation of gray matter voxels and gray matter density compared to previously acquired control cohorts using the same sequence, with age-matched normative database. Regions of abnormal volume and density will be identified in 116 regions of the automated anatomical labeling (AAL) brain atlas.

10.4 Data Analysis

The primary hypothesis is that individuals with chemotherapy induced cognitive impairment (CICI) will have a greater than expected amyloid plaque burden when compared to a control group of individuals who are not experiencing cognitive complaints. It is hypothesized that increased and abnormal [^{18}F]Flutemetamol uptake will be present in individuals with CICI. The primary analysis will be an exact one sample binomial test based on a composite SUVR of 0.59 (Z-score =2) provided by the CortexID software from GE Healthcare. A Z-score greater than or equal to 2.0 (composite SUVR greater than or equal to 0.59) will be coded as a positive amyloid scan and a Z score less than 2.0 (composite SUVR less than 0.59)[134] will be coded as negative. In clinical practice visual analysis is the standard approach for assessing amyloid positivity. This provides a simple binary positive or negative visual assessment of flutemetamol uptake. Since the visual approach is the standard used in clinical interpretation (Vizamyl prescribing information - section 2.5)[1] we will also perform a secondary visual analysis to compare with the more quantitative SUVR approach to assess for correlation between the composite SUVR and visual binary analysis methods. This is an exploratory analysis independent from the primary binary determination of amyloid positivity based on the composite SUVR. The prevalence of amyloid plaque burden in cognitively normal elderly individuals is up to 33% depending on the amyloid imaging agent used, patient age, and criteria used for evaluation.[1,142-145] However, using [^{18}F]Flutemetamol in a slightly younger population, Vandenberghe al. found that in a group of fifteen cognitively intact healthy volunteers over 55 (mean age 68.7) only one healthy volunteer had a positive amyloid scan.[123]

The following exploratory endpoints will also be also evaluated:

I. Objective cognitive impairment correlated with subjective reports of cognitive impairment as measured by administered questionnaires.
II. Amyloid plaque burden using regional semi-quantitative determinations is associated with greater objective cognitive impairment.
III. Those individuals with the most profound cognitive impairment may have associated regional FDG metabolic changes consistent with neuronal loss or damage.

The imaging parameters will include the Z score values from Cortex ID for FDG and Z scores, regional SUV values and the composite SUVR for [^{18}F]lutemetamol from CortexID.[146] For FDG these particular values are in comparison to an age-matched cohort so by definition they define a degree of FDG uptake reduction from normal. For [^{18}F]Flutemetamol there is no specific age-related deposition in the database to assess age-matched normality so the study images will be compared the database control group as a whole to determine the Z scores compared to clinically negative amyloid scans. Z score values both regional and global for FDG and composite ([^{18}F]Flutemetamol) can then be correlated with the various neuropsychological variables and clinical variables obtained to assess for differences and trends. The data will be analyzed descriptively using summary statistics and paired t-tests. Means, standard deviations and confidence intervals will also be reported. Scatterplots and bivariate summaries such as Pearson correlation coefficient and scatterplots will be used to characterize pairs of imaging parameters.

10.5 Justification of Sample Size

Twelve evaluable patients (defined as having complete imaging and blood data available) will be enrolled in this study. By definition, 100% of evaluable patients enrolled will receive the complete set of PET studies [^{18}F]Flutemetamol, FDG, and MRI. Due to blood drawing issues the total enrollment will need to be approximately 15 subjects to assure that complete blood and imaging data sets in 12 participants will be available for analysis. The data from Vandenberghe al. found that in a group of fifteen cognitively intact healthy volunteers over 55 (mean age 68.7) only one healthy volunteer had a positive amyloid scan.[123] Based on this data using a population similar in age to the expected experimental cohort, our null hypothesis ($H_{0)}$ is that 12% of study participants will have amyloid positivity. With 12 patients we will have 80% power to reject H_0 at the nominal 0.05 one-sided significance level provided the true proportion of subjects with amyloid positivity is 42%. The null hypothesis will be rejected if 4 or more out of 12 patients show amyloid positivity. We will not image a separate control population in this study. The CortexID software contains a database of [^{18}F]Flutemetamol scan data from 105 healthy volunteers[134] and will serve the function of a control group for the purposes of this exploratory study. The CortexID database has been validated in a subsequent study using [^{18}F]Flutemetamol scans from 345 AD, MCI, or cognitively normal individuals.[134]

11. REGULATORY AND REPORTING REQUIREMENTS

This study involves exposure to radiation and is appropriate for Human Use Subcommittee Review. FDG-PET is a clinically approved procedure for patients with cancer. However, for this research study, FDG is being performed under IND# 113,858 and [^{18}F]Flutemetamol is being performed under IND#109,760 (Yap is IND holder for both INDs), as such the following FDA reporting of unexpected fatal or life threatening events, serious adverse events, and serious and unexpected adverse events will occur: (1) reporting any unexpected fatal or life threatening adverse experience associated with the use of [^{18}F]Flutemetamol by telephone or fax no later than 7 calendar days after initial receipt of the information. (2) Reporting any adverse experience associated with the use of [^{18}F]Flutemetamol, that is both serious (SAE) and unexpected in writing

no later than 15 calendar days after initial receipt of the information. (3) Submitting annual reports. The reportable events will also be submitted to the IRB using the University of Utah ERICA online system:
https://erica.research.utah.edu/erica/Rooms/DisplayPages/LayoutInitial?Container=com.webridge.entity.Entity%5BOID%5B5FD2DA60262617429607E459C0E09D92%5D%5D

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting (http://ctep.cancer.gov/reporting/index.html).

All appropriate research areas will have access to a copy of the CTCAE version 4.03 with modifications. A list of adverse events that have occurred or might occur (Reported Adverse Events and Potential Risks) can be found in Section 6 (Imaging Studies Information).

The reportable events will also be submitted to the IRB using the University of Utah ERICA online system:
https://erica.research.utah.edu/erica/Rooms/DisplayPages/LayoutInitial?Container=com.webridge.entity.Entity%5BOID%5B5FD2DA60262617429607E459C0E09D92%5D%5D

Adverse events will be assessed for [^{18}F]Flutemetamol immediately following the imaging scan. Additionally, a follow-up telephone call will be made to each participant within 1 day following their imaging scan. If the participant cannot be contacted at 1 day post-scanning, then we will continue trying to contact them for up to 7 days post-scanning.

11.1 Expedited Adverse Event Reporting

Those adverse events which are not associated with [^{18}F]Flutemetamol do not require expedited reporting and will be reported in the routine manner to the IRB. Adverse event reporting is only required for events within 24 hours from the time of the injection of the experimental imaging agents [^{18}F]Flutemetamol.

11.2 Expedited Reporting Guidelines – Phase 1/2 studies with Investigational Agents

The guidelines given in **Table 5** below will be followed. Any unexpected fatal or life threatening adverse experience associated with the use of [^{18}F]Flutemetamol will be reported to the FDA by telephone or fax no later than 7 calendar days after initial receipt of the information. All reportable adverse events will be submitted to the FDA & IRB within the required timeframe by as mandated by the FDA and IRB. Hospitalization will be defined as any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitated hospitalization (or prolongation of existing hospitalization). Adverse event reporting is only required for events within 24 hours from the time of the injection of the experimental imaging agent [^{18}F]Flutemetamol.

Table 5.

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 3 Attribution of Possible, Probable or Definite	**GRADES 4 and 5 Regardless of Attribution**	**GRADES 1 - 3**	**GRADES 4 and 5 Regardless of Attribution**
Expedited report within 10 working days. (Grade 1or 2 Adverse Event Expedited Reporting NOT required.) Report to FDA Report to HCI DSMC	Expedited report to follow within 7 working days. Any late death attributed to the agent (possible, probable, or definite) should be reported within 7 working days. Report to FDA Report to HCI DSMC	Adverse Event Expedited Reporting NOT required.	Expedited report within 7 working days. Any late death attributed to the agent (possible, probable, or definite) should be reported within 7 working days. Report to FDA Report to HCI DSMC

For **Hospitalization** only – Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution.

11.3 Expedited Expected Adverse Event Reporting Exclusions

For this protocol, the following adverse events are specifically excluded from expedited AE reporting: **None**

Note: All deaths on study will be reported using expedited reporting regardless of causality. Attribution to treatment or other cause will be provided.

Fatal and life-threatening events will be reported to the IRB within 24 hours of notification of the event, indicating that a full report will follow. Any unexpected fatal or life threatening adverse experience associated with the use of [^{18}F]Flutemetamol will be reported to the FDA by telephone or fax no later than 7 calendar days after initial receipt of the information. All reportable adverse

events will be submitted to the FDA & IRB within the required timeframe by as mandated by the FDA and IRB.

11.4 Data Reporting

A Data and Safety Monitoring (DSMC) is established at Huntsman Cancer Institute (HCI) and approved by the NCI to assure the wellbeing of patients enrolled on Investigator Initiated Trials that do not have an outside monitoring review. Roles and responsibilities of the DSMC are set forth in the NCI approved plan. The activities of this committee include a quarterly review of adverse events including SAEs, important medical events, significant revisions or amendments to the protocol, and approval of cohort/dose escalations. If the DSMC and/or the PI have concerns about unexpected safety issues, the study will be stopped and will not be resumed until the issues are resolved. The DSMC also reviews and approves audit reports generated by the Research Compliance Office.

This study is considered a low risk trial per the DSMC plan. All low risk studies are audited no less than annually by the Research Compliance Office and audit reports will be reviewed and approved by the full DSMC. The DSMC will also review all Serious Adverse Events for patients on this study.

11.5 Reporting Protocol Violations/Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the prompt reporting of the following protocol deviations:

- Exceptions to eligibility criteria
- Intended to eliminate apparent immediate hazard to a research participant or
- Harmful (caused harm to participants or others, or place them at increased risk of harm - including physical, psychological, economic, or social harm) or
- Possible serious or continued noncompliance

Annual progress reports will be submitted to the FDA within 60 days of the date that the IND was effective/or approved.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Informed consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

12.2 Institutional Review

This study will be reviewed and approved by the Institutional Review Board of University of Utah prior to any participants being enrolled on the study.

12.3 Reported Adverse Events and Potential Risks

Blood sampling entails the risks of minor discomfort, infection, bruising and bleeding. Radiation risk accompanies the use of radioisotopes in PET imaging. FDG-PET imaging is considered to be generally safe and effective. It has been approved by the Centers for Medicare and Medicaid for several clinical indications, using procedures identical to those used in this study. FDG is administered in trace doses and adverse effects have not been reported during it's more than 20 years of use. Nevertheless the possibility exists for a rare allergic reaction.

The current use of [^{18}F]Flutemetamol is investigational although it did receive FDA approval in October 2013. To date, it has been given to numerous individuals world-wide at the doses proposed here without significant adverse effect.[122] Subjects scanned with PET are exposed to radiation. The amount of radiation exposure will be well within limits permitted to radiation workers by federal regulations. There is no known minimum level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects (cellular abnormalities) or cancer. However the risk associated with the amount of radiation exposure that the subject will receive from this study is considered to be low.

Radioisotope injection requires the use of an intravenous catheter. There is a minimal risk of infection and bruising associated with the venipuncture required for the indwelling catheter. There can be discomfort from the requirement from lying quietly during imaging. Research data includes personal health information that can be inadvertently revealed to others. All of these risks are similar to those encountered during usual clinical care.
For the MRI, the risks are expected to be minimal. There is a protocol to follow prior to imaging, which includes a rigorous screening by specially trained MR personnel to avoid the risks listed below. All MR imaging will occur in the Imaging and Neurosciences Center at the University of Utah under the supervision of a Neuroradiologist. If individuals have any MRI incompatible metal pieces in their body, these metal pieces could potentially move during the scan and damage nearby tissues or organs. Transdermal patches also may contain metal and may cause burns if they are not removed from the skin before the scan. There can be a feeling of claustrophobia associated with the procedure; if participants experience anxiety from a feeling of claustrophobia, they can tell the researcher. Individuals can be removed from the scanner and given the option to terminate the study, if they become uncomfortable for any reason.
We will strive to maintain confidentiality of all participants enrolled in the study. All paper research data will be stored in a locked file cabinet. All electronic data will be stored on password-protected computers. All research data will be de-identified. Finally, all participants will be assigned a unique identification number to use in place of their name on all study data.

12.4 Agent Accountability

Each radiosynthesis is done by University of Utah cyclotron and radiochemistry staff and the product [^{18}F]Flutemetamol in a dose calibrated syringe will be released after passing all required quality control assays to the physician who will be responsible for administering the appropriate amount (John M. Hoffman, MD or his designee). The quality control tests that must be passed prior to release of the product [^{18}F]Flutemetamol for injection include the radioactive purity, the radiochemical purity, sterilizing filter integrity, pyrogens, and particulates. The [^{18}F]Flutemetamol dose is drawn up into a syringe, assayed for mCi at the time of injection, and administered to the research subject. Any remaining compound from the synthesis will be allowed to decay and destroyed per our facilities standard operating procedures.

12.4.1 [^{18}F]Flutemetamol

Flutemetamol is a radiopharmaceutical that is produced in the cyclotron facility at the Huntsman Cancer Institute. The agent is investigational and approved by the FDA under IND #109,760.

12.4.2 [^{18}F]FDG

FDG is a radiopharmaceutical that is produced in the cyclotron facility at the Huntsman Cancer Institute. The agent is investigational and approved by the FDA under IND # 113,858.

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14. APPENDICES

APPENDIX A
Eligibility Check List and Current Drug Use and Potential Toxicities

APPENDIX B
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GE Healthcare Supplemental Safety Reporting Form

APPENDIX A: Eligibility Check List and Current Drug Use and Potential Toxicities

Patient Name: _____ **Date:** _____

MRN: _____ **Person Confirming Eligibility** _____

_____ (Yes/No) Patient is female.

_____ (Yes/No) Patient is ≥ 18 years old.

_____ (Yes/No) Patient is ≤ 70 years old.

_____ (Yes/No) Patient has a histologically proven diagnosis of Stage I through III C breast cancer

_____ (Yes/No) Patient has been previously treated with chemotherapy at least 6 months prior, but no more than 36 months prior to initial study scan.

Dates: _____

Type of Chemotherapy:_____

_____ (Yes/No) Patient must be postmenopausal for a minimum of one year, surgically sterile, or has been confirmed not to be pregnant by serum pregnancy test performed within 48 hours prior to research PET imaging.

If patient is postmenopausal, how far out are they from menopause: _____

If patient is of childbearing potential, date of negative pregnancy test: _____

_____ (Yes/No) Patient is not lactating.

_____ (Yes/No) Patient has no history of previous stroke, seizures, or other neurological disorders.

_____ (Yes/No) Patient agrees to have clinical and radiographic endpoints and results of histopathologic tissue analysis and other laboratory information entered into a research database, as evidenced by signing the informed consent form.

_____ (Yes/No) Patient does not have allergic or hypersensitivity reactions to previously administered radiopharmaceuticals.

_____ (Yes/No) Patient does not require monitored anesthesia for PET scanning or MRI imaging.

_____ (Yes/No) Patient is not too claustrophobic to undergo MRI or PET imaging.

_____ (Yes/No) Patients is able to lie still for 60 minutes.

_____ (Yes/No) Patient does not have any MRI incompatible metal implants or clips.

_____ (Yes/No) Patient has not been diagnosed with dementia or any other cognitive deteriorating conditions.

_____ (Yes/No) Does patient have a family history of dementia? (Does not preclude participation in study)

_____ (Yes/No) Is the patient right handed? (Informational for set up of fMRI study)

_____ (Yes/No) Patient is not moderately or severely depressed as measured on the Beck Depression Inventory (BDI) –Short Form.

_____ (Yes/No) Patient must report persistent cognitive problems following the initiation of chemotherapy, defined as being one or more standard deviations above normative data on our two scales of subjective cognitive dysfunction

- Cognitive Failure Questionnaire Score: _____ (Total score 45 or higher)___
- Frontal System Behavioral Scale Score: _____ (T-score of 60 or higher)

_____ (Yes/No) Patient is not currently using gabapentin or venlafaxine for hot flashes.

_____ (Yes/No) Patient is not currently using cholinesterase inhibitors, other cognitive enhancers, antipsychotics, antidepressants or anticonvulsant medications.

_____ (Yes/No) Patient is not color blind.

_____ (Yes/No) Patient has no history of radiation therapy to the brain, any current or past major psychiatric illness, or a history of alcoholism or other substance abuse.

_____ (Yes/No) Patient does not have a current or past major psychiatric illness such as schizophrenia or bipolar affective disorder.

Comments:

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

_____	_____	_____
Investigator Signature	**Date**	**Time**

Appendix B: Current Drug Use and Potential Toxicities

Current Drug Use and Potential Toxicities

Drug	Neuropathy	Hematologic	Hepatic	Other prominent toxicity (note it)

Completed by _____ Date: _____

APPENDIX C: MRI Patient History and Safety Screening

MRI PATIENT HISTORY & SAFETY SCREENING
Please print

Date _____ *Patient MRN*_____

Name _____

Patient Height_____Weight_____

Date of Birth _____ Age _____ ReferringPhysician_____

DO YOU HAVE AN APPOINTMENT WITH YOUR DOCTOR TODAY? _____If yes, at what time?_____

IMPORTANT INSTRUCTIONS*: You may be asked to change into hospital clothing for purposes of MRI safety. A locker will be provided. Please remove ALL metallic objects such as hearing aids, dentures, partial plates, keys, cell phone, eyeglasses, hair pins/clips , jewelry, body piercing jewelry, watch, safety pins, magnetic strip cards and clothing with metallic fasteners, threads or fibers including some sportswear tech fabrics. If you have any questions, please ask a technologist BEFORE entering the MRI scan room.*

□ Yes □ No Cardiac Pacemaker ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Implanted Cardiac Defibrillator (ICD) ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Breast Tissue Expanders ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Spinal cord stimulator ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Swan-Ganz Thermo Dilution catheter ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Acticoat Silver Wound Dressing ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Cochlear Inner Ear Implant ***(If yes, Stop** and inquire with MRI personnel)*
□ Yes □ No Stapes Inner Ear Implant
□ Yes □ No Brain Aneurysm Stents, Clips or Coils *Type* _____
□ Yes □ No Electronic or Magnetic Implant, Neurostimulator (tens unit, bone growth, etc.)
□ Yes □ No Internal electrodes or wires
□ Yes □ No Aortic or Carotid Artery Clips
□ Yes □ No Hearing Aid *(Remove before entering MRI scan room)*
□ Yes □ No Insulin pump or Implanted Infusion device *Type* _____
□ Yes □ No Heart Valve or Cardiac Stent
□ Yes □ No Shunt, intraventricular or spinal
□ Yes □ No Vascular Coil, Umbrella Filter, or other Stent
□ Yes □ No Vascular Access Port or I.V. Catheter
□ Yes □ No Prosthetic device (Limb, Joint, Eye, etc.) *Type* _____
□ Yes □ No Joint replacements (Hip, Knee, etc.) *Location* _____
□ Yes □ No Metal (circle) Rods, Plates, Screws, Nails, Pins, Clips, Other *Location*_____
□ Yes □ No Shrapnel (Metal Fragments) or Gunshot Injury *Location* _____
□ Yes □ No Metal Fragments in eye past or present (History as Grinder, Welder, Machinist, etc.)
□ Yes □ No IUD, Diaphragm, Penile Implant
□ Yes □ No Eyelid Spring, Wire, Gold Weight
□ Yes □ No Medication Patch *(Remove before entering MRI scan room)*
□ Yes □ No Wire Mesh Implant
□ Yes □ No Removable Denture or Retainer
□ Yes □ No Tattoos (Cosmetic, Body)
□ Yes □ No Body Piercings *Location* _____

□ Yes □ No Biopsy Markers or Breast Implants: Type_____
□ Yes □ No Hair Pins or Hair Piece / Wig *(Will need to be removed before entering MRI scan room)*
□ Yes □ No Bronzing / Tanning Lotions
□ Yes □ No Other Implants (Pill Camera, Tooth, etc.) *Type* _____

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form:_____

Print Name:_____ Date:____/_____/_____

Form Completed By: □ Patient □ Guardian □ Relative □ Nurse/Physician

APPENDIX D: Schedule of Events

Test / Procedure	Screen	Research MRI study and Neuro-psychological Testing	PET Imaging Visit 1 First PET Exam Will depend on whether [^{18}F]-Flutemetamol or FDG study is performed	PET Imaging Visit 2 Second PET Exam Will depend on whether [^{18}F]-Flutemetamol or FDG study is performed
Inclusion / Exclusion Criteria	X			
Informed Consent	X			
Research MRI study		X		
Infusion of [^{18}F]Flutemetamol			X	X
[^{18}F]Flutemetamol PET Imaging			X	X
Adverse Event Questionnaire After [^{18}F]Flutemetamol study			X (3)*	X (3)*
^{18}F-FDG PET Imaging			X	X
Neuropsychological Testing		X		
Pregnancy Test (1)			X (2)	X (2)

* Performed immediately after ^{1}[^{18}F]Flutemetamol study

1 Patient must be postmenopausal for a minimum of one year, surgically sterile, or has been confirmed not to be pregnant by serum pregnancy test performed within 48 hours prior to research PET imaging.

2 GE requires all pregnancies that occur within 30 days of exposure to the investigational product be submitted to their institution. Patients will be contacted approximately 30 days post [^{18}F]Flutemetamol scanning to collect information from the patient regarding pregnancy status.

3 A follow-up telephone call will be made to each participant within 1 day following their imaging scan with [^{18}F]Flutemetamol. If the participant cannot be contacted at 1 day post-scanning, then we will continue trying to contact them for up to 7 days post-scanning.

4 The research MRI study and neuropsychological testing can be completed depending on staff availability and can be done before, after, or in between PET/CT imaging sessions.

Research MRI study

The research MRI study will include the following imaging sequences/studies. This is our current clinical brain tumor imaging protocol.
Scout
T1–weighted SE (pre injection)
T2
FLAIR;
Dynamic contrast enhanced images with associated T1 mapping
Diffusion- weighted imaging
Post T1–weighted SE

PET Imaging Visits 1 & 2:

Imaging of the PET tracers will be performed on two separate days with FDG imaging occurring on one day and [^{18}F]Flutemetamol occurring on another day. The imaging will be performed on separate days depending on scheduling with the cyclotron. The days of imaging will be scheduled according to scanner and cyclotron availability, and all days of imaging will be obtained within six weeks of each other.

APPENDIX E: [^{18}F]Flutemetamol Patient Adverse Event Questionnaire

Completed at conclusion of [^{18}F]Flutemetamol infusion.

Subject Name and MRN: _____ Subject Study ID (if enrolled) _____

Projected Study Start Date_____ Referring MD_____

Possible Adverse Event	**Y =Yes N = No** **Comment on possible AE**
Body as a Whole:	
Pain (Abdominal)	
Pain (Chest/Breast)	
Pain (Other site)	
Fever	
Injection site reaction	
Cardiovascular System:	
Vasodilation (flushing)	
Digestive System:	
Nausea	
Diarrhea	
Vomiting	
Respiratory System:	
Dyspnea (Shortness of breath)	
Skin and Appendages:	
Rash	
Pruritus (Itching)	
Urticaria (Hives)	
Sweating	
Cyanosis (discoloration of fingers/toes)	
Central Nervous System	
Visual disturbances	
Numbness of feet	
Numbness of fingers/hands	
Weakness of feet	
Weakness of fingers	
Burning sensation in feet	
Burning sensation of fingers	

Performed by _____ **Date** _____ **Time** _____

PI Oversight _____ **Date**_____**Time**_____

APPENDIX F: NCI Common Toxicity Criteria

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX G: GE Healthcare Pregnancy Reporting Form

GE HEALTHCARE **Pregnancy Reporting Form**

ISS NO.	SUBJECT NO.	Investigational Product	

Please report to GEHC MDx all reported pregnancies that occur within 30 days of exposure to the investigational product.
Please send this form within 24 hours of a positive pregnancy test, to the GEHC MDx Pharmacovigilance Department,
In the Americas : Fax: 609-514-6575
Rest of World: Fax: + 47 23 18 60 29

Date of last menstrual period (first day): D D M M M 2 0 Y Y

Date of verified pregnancy: D D M M M 2 0 Y Y

Date of expected birth: D D M M M 2 0 Y Y

Has the pregnancy proceeded normally so far? ☐ Yes ☐ No

If No, please specify:_____

_____

_____

Investigator's Signature:

_____ D D M M M 2 0 Y Y

APPENDIX H: GE Healthcare SAE Reporting Form

GE Healthcare

Fax Cover for SAE Reporting

To: GE Healthcare Pharmacovigilance/Drug Safety
Fax number: Americas: +1 609 514-6575
+1 609 514-6550 (alternate)
All other sites: +47 23 18 6029

Re: Protocol number: _____

Subject number: _____

From (name): _____

Site number: _____

Investigator: _____

Site contact phone number: _____

Site fax number: _____

Comments:

_____

_____

_____

_____

_____

Sponsor-Investigator Name:	Initial Report ☐ Follow-up Report ☐
Blinded trial - Investigational Products tested: Open trial - Investigational Product administered:	
ISS ID number: ☐☐☐☐	Subject Number ☐☐☐☐☐
Gender:	Female ☐ Male ☐
Subject age:	Height /units: Weight /units:
Race: Caucasian ☐ Black ☐ Hispanic ☐ Asian ☐ Other ☐ (specify): _____	
Therapy start date/time: ____/____/____; ____:____ dd/mmm/yyyy; hh:mm (military time)	Therapy end date/time: ____/____/____; ____:____ dd/mmm/yyyy; hh:mm (military time)
Dose/units:	Route of administration:
Type of examination: if applicable	Indication for examination: if applicable
Event term:	
Onset date/time: ____/____/____; ____:____ dd/mmm/yyyy; hh:mm (military time)	Resolution date/time: ____/____/____; ____:____ dd/mmm/yyyy; hh:mm (military time)
Relationship to Investigational Product: 1 = Before IP admin 2 = After IP admin - relationship to IP **NOT Suspected** 3 = After IP admin - relationship to IP **IS Suspected** ☐	Intensity: 1 = Mild 2 = Moderate ☐ 3 = Severe
Outcome: 1 = Resolved 2 = Not resolved ☐ 3 = Death	
Which of the following criteria were met (check all that apply): Death ☐ Life-threatening ☐ Hospitalization ☐ Disability ☐ Congenital anomaly ☐ Other important medical condition ☐ describe why	
Did event abate/stop when IP stopped? Yes ☐ No ☐ Not applicable ☐	
Did event reappear/worsen when IP restarted? Yes ☐ No ☐ Not applicable ☐	
Death date/time: ____/____/____; ____:____ dd/mmm/yyyy; hh:mm (military time)	Cause(s):
Was the subject withdrawn due to this event? Yes ☐ No ☐	

Relevant medical/surgical history:

Describe course of event:

Continuation page number: ☐

Sponsor-Investigator signature: _____
Date:_____

APPENDIX I: GE Healthcare Supplemental Safety Reporting Form

SUPPLEMENTAL SAFETY CRF

ISS ID ☐☐☐☐ SUBJECT NO. ☐☐☐☐ GEHC MDx Product:

Date of Birth ☐☐/☐☐/☐☐☐☐ (D D M M Y Y Y Y)

Height ☐☐☐.☐ in / ☐☐☐ cm

Weight ☐☐☐.☐ lb / ☐☐☐.☐ kg

Gender: 1 ☐ Male 2 ☐ Female

Race (check one): 1 ☐ White 2 ☐ Black or African American 3 ☐ Asian 4 ☐ American Indian or Alaska Native 5 ☐ Native Hawaiian or Other Pacific Islander 99 ☐ Other, specify: _____

Ethnicity (check one): 1 ☐ Not Hispanic or Latino 2 ☐ Hispanic or Latino

PRE-TREATMENT EVENTS AND TREATMENT-EMERGENT EVENTS

Record AEs outcomes or attribution to agent. Serious AEs should be reported to GE within 24hrs using the SAE form provided in your ISS Site Manual.

Event No.	Event (Record diagnosis in Standard Medical Terminology) (Record One Event Per Line) Be as specific as possible, for example: Infection = NOT SPECIFIC Upper respiratory infection = SPECIFIC	Date / Time of Dose Administration	Date / Time of Onset / Date / Time of Resolution	Intensity 1=Mild 2=Moderate 3=Severe	Relationship to IMP 1=Not Related 2=Related	Treatment Given 1=Yes** 2=No	Action Taken With Study Treatment (check one only): Dose Not Changed; Drug Withdrawn; Not Applicable; Drug Interrupted	Outcome of Adverse Event 1=Resolved 2= Not Resolved 3=Fatal 4=Unknown
1.		☐☐/☐☐/20☐☐ (D D M M Y Y Y Y) ☐☐:☐☐ (H H M M)	☐☐/☐☐/20☐☐ ☐☐:☐☐ ☐☐/☐☐/20☐☐ ☐☐:☐☐				1 ☐ 2 ☐ 3 ☐ 4 ☐	
	**If treatment given, specify:							
2.		☐☐/☐☐/20☐☐ ☐☐:☐☐	☐☐/☐☐/20☐☐ ☐☐:☐☐ ☐☐/☐☐/20☐☐ ☐☐:☐☐				1 ☐ 2 ☐ 3 ☐ 4 ☐	
	**If treatment given, specify:							
3.		☐☐/☐☐/20☐☐ ☐☐:☐☐	☐☐/☐☐/20☐☐ ☐☐:☐☐ ☐☐/☐☐/20☐☐ ☐☐:☐☐				1 ☐ 2 ☐ 3 ☐ 4 ☐	
	**If treatment given, specify:							

SAE defined as: Any event that resulted in death; was immediately life-threatening, required inpatient hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; or other medically significant events which when based on appropriate medical judgement may jeopardize the subject and may require medical/surgical intervention to prevent one of the outcomes listed above.
Serious Adverse Events should be reported on the SAE form provided by your GEHC ISS Contact.

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Primary Investigator/Designee's Signature: _____ Date: ☐☐/☐☐/20☐☐ (D D M M Y Y Y Y)