18 September 2008

Diem-Kieu Ngo, Pharm.D., BCPS
Advisors and Consultants Staff
FDA, CDER, OEP
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20857-1734

Re:  GE-067
Background Package Supporting October 23, 2008 Peripheral and Central Nervous System
Drugs Advisory Committee
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Dear Dr. Ngo:

Reference is made to the March 14, 2008 letter from the Division of Medical Imaging and Hematology
Products to sponsors of radionuclide imaging agents for use in the diagnosis of Alzheimer’s disease,
announcing plans to convene an Advisory Committee to discuss clinical development plans. GE Healthcare
concurs with the FDA that the development of safe and effective β-amyloid imaging agents presents an
important health contribution and appreciates the opportunity for seeking substantive feedback from a panel
of experts.

Further reference is made to your letter dated July 7, 2008 requesting GE Healthcare’s background package
for GE-067 in support of this Advisory Committee meeting.

Enclosed please find 25 electronic CD copies and 10 paper copies of our “fully releasable” background
package to be disseminated to the Advisory Committee members/consultants, the Division of Information
Disclosure Policy, and to the Division of Medical Imaging and Hematology Products. This package
provides a summary outline of our clinical development program for GE-067, including our proposal for a
suitable truth standard, as well as our perspectives on the clinical utility of β-amyloid imaging agents.

Please call me at (609) 514-6843 or Fred Longenecker at (609) 514-6573 if you have any questions or
comments regarding this submission.

Sincerely,
GE Healthcare

[Signature]

Allison Mueller
Director, Regulatory Affairs
BACKGROUND PACKAGE FOR PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING

Sponsor: GE Healthcare
Product: GE-067

1. EXECUTIVE OVERVIEW

- Dementia is a global illness characterized by progressive degeneration of the brain affecting elements of memory, thinking, behaviour and emotion.

- Dementia affects 1 in 20 people over the age of 65 and 1 in 5 over the age of 80. Affected individuals need care with all aspects of daily life and costs to society in the USA for example are estimated at approximately $100 billion.

- The most common cause of dementia is Alzheimer’s disease which accounts for 50-60% of cases. This disease is pathologically characterized by β-amyloid plaques and neurofibrillary tangles.

- Currently, a diagnosis of definite Alzheimer’s disease is made on DSM-IV clinical criteria along with histopathologic detection of amyloid pathology. Brain biopsy sampling can rarely be justified in life and post-mortem examinations are not commonly performed so assigning the dementing process a definite diagnosis can be problematic.

- The availability of β-amyloid PET imaging now presents an opportunity for the clinical community to include a tool that visualizes the presence of β-amyloid histopathology when assessing dementia phenotypes.

A PET image of β-amyloid pathology would not provide a definite diagnosis of a specific disease state. Amyloid pathology is not only present in Alzheimer’s disease but is often present in Dementia with Lewy bodies and also a feature of amyloid angiopathy and prion diseases. Additionally, around 30% of healthy individuals in their eighth decade show amyloid at subsequent post-mortem. Multiple pathologies often contribute to the symptoms shown by dementia patients and, as the population ages, mixed dementias will be seen more frequently. Therefore, β-amyloid imaging will not confirm or exclude a specific disease state but, when used in combination with a knowledge of clinical signs and symptoms, will increase the confidence of a clinician’s diagnosis and may influence subsequent treatment paradigms.

One goal of these discussions with the FDA will be to explore the opportunity for PET imaging of β-amyloid to be viewed as an in vivo substitute for a histopathologic examination of β-amyloid at post-mortem. Evidence is gathering that there is an excellent correlation between the presence of β-amyloid at pathology and the increased signal
observed in the brain of AD subjects after $^{11}$CPIB imaging. Additionally, there are a significant number of studies showing raised amyloid levels in 90% of clinically probable AD subjects based on NINCDS-ADRDA criteria.

GE Healthcare wishes to present findings for their novel F-18 labeled β-amyloid imaging agent GE-067 and proposes a clinical development plan to support its initial registration for the detection of β-amyloid in the brain. GE-067 has been studied in 3 clinical trials to date with preliminary data showing that it is both safe and efficacious. The trial to support a β-amyloid detection claim would establish metrics for population ranges of β-amyloid load in normals of varying age ranges, probable AD subjects and amnestic MCI subjects. Data from the study would be read blinded by visual inspection; readers would be asked to designate images into β-amyloid negative or β-amyloid positive boxes. A parallel quantitative analysis would also be performed to validate the use of visual inspection methodology.

2. INTRODUCTION

Reference is made to the March 14, 2008 letter from the FDA to sponsors of radionuclide imaging agents to be developed for use in the diagnosis of Alzheimer’s disease (AD), announcing plans to convene an Advisory Committee (AC) for the purpose of discussing the clinical development plans. GE Healthcare concurs with the FDA that the development of safe and effective imaging agents for dementia patients presents an important health contribution and appreciates the opportunity for seeking substantive feedback from a panel of experts.

On April 24, 2008, GE Healthcare submitted a letter to the FDA confirming its interest in participating in the AC meeting and committing to provide a summary of its clinical development plan GE-067, a fluorine-18 labeled imaging agent utilized with positron emission tomography (PET) that GE Healthcare is currently developing for in vivo imaging of β-amyloid.

This document develops the theme of amyloid imaging, discusses clinical utility, introduces the concept that $^{11}$CPIB could be used as a truth standard, and finally describes the clinical experience with GE-067 as well as outlining future studies to support the registration as an agent to image β-amyloid pathology.

3. BACKGROUND TO AMYLOID PATHOLOGY

The disease area target for imaging with GE-067 is dementia, most notably AD, the alarming demographics of which are well known. Alzheimer’s disease and, to a lesser extent, other forms of dementia are characterized by the presence of both β-amyloid deposits and neurofibrillary tangles in the brain. The conventional standard for diagnosing dementias associated with β-amyloid deposits is histological confirmation of their presence in the brain at the time of autopsy. The existence of an in vivo β-amyloid imaging agent such as GE-067, however, means that β-amyloid deposits can be detected
and delineated in living individuals, with obvious advantages over post-mortem confirmation.

The exact role of β-amyloid in the pathophysiology of neurodegenerative disease in general, and AD in particular, remains unknown. A popular, but still unproven, theory called the “amyloid cascade hypothesis” places faulty metabolism of β-amyloid at the start of a sequence of events that includes microglial activation, tau hyperphosphorylation, formation of neurofibrillary tangles, disruption of axonal transport, synapse loss and ultimately neuronal death [1]. The later events are presumed to directly mediate cognitive dysfunction. The separation of β-amyloid deposition and the clinical symptoms by a multitude of cellular events played out over years or even decades is pointed to as the reason why there is only a loose correspondence between the level of amyloid deposition and the severity of clinical symptoms. Other factors that are likely to interfere with such correlations are often not fully appreciated. For example, these correlative studies often utilize β-amyloid load data obtained by immunohistological techniques that are semi-quantitative at best and are acquired from an extremely small volume of total brain tissue. Another confounding factor is that the cognitive data used in the correlative analysis is often gathered years prior to death or is obtained in a peri-morbid state when other diseases may impact cognition. The one published study that compared a quantitative, biochemical measure of β-amyloid load with cognition measured by the Clinical Dementia Rating (CDR) scale during the last 6 months of life showed that levels of β-amyloid peptides were strongly correlated with cognitive decline (p < 0.001) [2]. In familial, autosomal dominant AD, a single mutation in the β-amyloid precursor protein (APP) or in the presenilin-1 component of the gamma-secretase enzyme responsible for cleavage of APP can lead directly to β-amyloid deposition and dementia [3] - providing the strongest evidence that deposition of β-amyloid can cause AD in these rare families. Thus, while the exact significance of β-amyloid deposition is not fully understood, it holds a central role in most current theories of AD pathophysiology.

β-Amyloid is a 40 to 43 amino acid peptide derived from proteolytic cleavage of APP [4]. The segment of APP that accumulates as β-amyloid includes portions of the transmembrane and extracellular domains of APP following cleavage by β- and γ-secretases [5]. These β-amyloid peptides aggregate to form oligomers, which are considered to be the neurotoxic form of β-amyloid [6, 7], and these oligomers progress to form more pronounced fibrils and then senile plaques (see Figure 1). The β-amyloid present in amyloid fibrils and plaques consists of regular peptide repeats in the form of beta sheets that form the structural basis for the interaction of targeted agents (including GE-067) that bind to β-amyloid rich plaques [8]. It is important to note that the GE-067 class of agents binds only to fibrillar β-amyloid so its primary role is to detect plaques rather than soluble β-amyloid elements. Additionally, biochemical and histological studies have shown that the GE-067 class of agents shows no appreciable in vitro binding to intracellular aggregates at post-mortem, such as Lewy bodies or neurofibrillary tangle deposits, at radiotracer doses so there is no evidence that GE-067 detects tangles or Lewy bodies in vivo.
Figure 1  Processing of amyloid precursor protein to generate senile plaques, the molecular target for GE-067 (also known as AH110690).

The most common disease associated with an β-amyloid burden in the brain is AD, which has been estimated to have a prevalence of 10% by the age of 75 rising to 20% by age 80. Clinically it is characterized by impairment of short-term recall along with one or more other cognitive functions. The presence of β-amyloid, however, is not unique to AD. Dementia with Lewy bodies (DLB) is a condition that accounts for around 15% of dementia cases. Clinically it is also characterized by impairment of short-term recall along with one or more other cognitive functions but in addition it is associated with parkinsonism, fluctuating confusion, and visual hallucinosis. There is, therefore, a clinical overlap with AD and neuropathologic findings in the majority of DLB cases include β-amyloid plaques along with the intraneuronal Lewy bodies that characterize the condition. Consequently, some authors have preferred the term “Lewy body variant of AD”. “Pure DLB”, with no β-amyloid accumulation, is estimated to occur in approximately 10 to 20% of clinically diagnosed DLB cases.

Another condition associated with brain β-amyloid deposition is Cerebral Amyloid Angiopathy (CAA), which can be seen in AD or in isolation (where it is associated with cerebral hemorrhage). In contrast, frontotemporal dementia (FTD) and its variants semantic dementia (SD) and progressive focal aphasia and apraxia (FA), which account for 15 to 20% of dementia cases, are not usually associated with β-amyloid deposition.

Currently, the standard of truth (SoT) for confirmation of β-amyloid deposition in the brains of patients is made following death using histological techniques. Several modern criteria have been published for the post-mortem diagnosis of AD and all of them require the presence of β-amyloid plaques [9-11]. The NIA-Reagan criteria are most recent and are the only criteria to utilize a combination of β-amyloid plaque and neurofibrillary

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tangle pathology to arrive at a designation of high, intermediate, or low likelihood that a dementia is due to AD [11].

The current absence of an approved pre-mortem β-amyloid assessment has obvious ramifications for the diagnosis and management of patients with dementias and at present there is a strong reliance on a combination of clinical history, physical examination and neurological and neuropsychological examinations. Patients are categorized as having clinically probable or possible AD, for example, based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-Fourth edition (DSM-IV) and the National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS–ADRDA), which are utilized in the diagnostic process. These diagnostic criteria have been validated against neuropathological gold standards and have a sensitivity ranging from 65 to 96% [12-15], but a wide specificity range of 23 to 88% [14,15]. Both these sensitivity and specificity results highlight the problem of using Clinical Diagnosis as a SoT in large multi-center trials for the development of β-amyloid imaging agents.

Diagnostic accuracy and specificity can be improved by the use of suitable diagnostic biomarkers of disease. Such biomarkers include ApoE genotyping, measurement of tau-protein levels or β-amyloid 1-42 in cerebrospinal fluid (CSF), and neuroimaging. X-ray computed tomography (CT) and magnetic resonance imaging (MRI) can help exclude structural lesions and quantify brain atrophy when present. Fluorodeoxyglucose (FDG) PET is also a useful biomarker of the regional reductions in glucose metabolism associated with the different forms of dementia.

4. DEVELOPMENT OF THE AMYLOID IMAGING CONCEPT

PET-based detection of β-amyloid deposits is also rapidly emerging as a particularly important imaging biomarker. Of the β-amyloid targeted imaging agents that have been used in human studies, [$^{11}$C]PIB is the most widely cited. It was the first tracer to show a clear correspondence to the known regional distribution of post-mortem β-amyloid pathology in AD and, to date, more [$^{11}$C]PIB scans (>2,000) have been performed at more PET centers worldwide (>40 sites) than any other β-amyloid imaging tracer.

The principle of detecting β-amyloid pathology in the brain of patients with dementia was based on a straightforward concept: a) radiolabelling of a histological dye that specifically binds to beta-sheet forms of β-amyloid, b) chemical modification so that it rapidly crosses the blood-brain barrier in large amounts, c) ensure high binding affinity and specificity for β-amyloid, and d) ensure rapid and complete clearance from all non-β-amyloid components of the brain.

This was the approach used in the effort led by the Pittsburgh group of Klunk and Mathis, which focused upon improving the brain uptake of amyloid binding dyes while maintaining low nanomolar affinity and brain clearance properties. Further structure-activity related studies led to selection of a 6-hydroxylated benzothiazole (a thioflavin-T derived compound) as the lead candidate to enter into clinical studies.

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A small clinical study, scanning 16 subjects with probable AD, 6 aged controls and 3 young controls, was initiated during 2001 at the Uppsala University PET center in Sweden. It was here that the acronym “PIB” (i.e., ‘Pittsburgh Compound B) was first used. Although there are other β-amyloid imaging agents in development, it is not unusual to hear the acronym PIB and the phrase β-amyloid imaging used interchangeably. The results obtained in Sweden have been reproduced by numerous sites worldwide [16-21].

In 2002, GE Healthcare acquired a license to access the patent rights and know-how behind the thioflavin-T derivatives. The original β-amyloid imaging agent, [11C]PIB, continues to be used widely as a research tool by the University of Pittsburgh, many other academic institutions and by the Alzheimer’s Disease Neuroimaging Initiative (ADNI). As a radioactive isotope for PET imaging, 11C is attractive as a research tool because it can be incorporated into a number of organic molecules. However, 11C-radiolabelled agents are not widely available due to a short half-life of approximately 20 minutes that requires an on-site cyclotron and radiochemistry for production and immediate use.

The licensing agreement between GE Healthcare and the University of Pittsburgh allows free and unconstrained research use of [11C]PIB. Permission from GE Healthcare to use [11C]PIB is only required when commercial interests, such as Pharmaceutical companies, are involved. Consequently, the vast majority of academic studies using [11C]PIB, clinically or nonclinically, have been conducted independent of GE Healthcare.

A development program focused on 18F labelling of thioflavin derivatives was started in 2003 and ultimately led to identification of GE-067 as the lead development candidate. 18F-radiotracers (such as [18F]FDG) are commercially viable and can be made available through regional cyclotron facilities that distribute the radiotracers to local scanners. The half-life of 18F (almost 2 hours) allows its distribution (subject to shelf-life) for up to 10 hours post manufacture. The longer half-life also allows imaging at longer intervals after injection and this can be useful when the optimal signal-to-noise ratio of a tracer is reached more than 90 minutes after injection. In addition, 18F tracers can often be labeled at higher specific activities than 11C tracers and hence extremely low levels (typically <5μg) of unlabelled ligand are injected.

Both GE-067 and [11C]PIB (see Figure 2), are neutral dyes with close structural similarity to thioflavin-T that selectively bind to the beta-sheets of β-amyloid deposits in brain. The primary difference between the 2 compounds is the inclusion of the 18F isotope in GE-067.
Figure 2  Structures of thioflavin-T, GE-067 and PIB. GE-067 and PIB are identical except for the fluorine atom at the 3’ position of the benzene ring.

5. β-AMYLOID IMAGING

Most imaging studies of β-amyloid have been conducted using $[^{11}\text{C}]$PIB. $[^{11}\text{C}]$PIB imaging has been extensively adopted by the scientific community and could be potentially viewed as the gold standard imaging agent for the detection of β-amyloid. Highlights of academic results with $[^{11}\text{C}]$PIB are described throughout the course of this document.

The half-life of the $^{11}$C isotope is 20 minutes which makes the manufacturing and wide-scale distribution to institutions with PET scanning facilities limited and impractical. For this reason GE Healthcare has developed the $^{18}$F labeled compound closely related to PIB, GE-067, in which the isotope has a half-life of 110 minutes. GE-067 was recently used in the ALZ103 study (results described in section 10.4) and Figure 3 below shows an example of scans taken from control and AD subjects.

In order to ensure consistency when comparing scans, the images are scaled to provide equivalent brightness levels in a reference region (the cerebellum – labelled $d$ in Figure 3). With this scaling, healthy volunteers show moderate, non-specific uptake in the mylinated fibers that interconnect various regions of the brain (i.e., the white matter) and low uptake in the outer cellular layers of the brain (i.e., the grey matter). AD patients have scans which predominantly show enhanced signal due to β-amyloid loading in the
grey matter, specifically in the frontal cortex (a & a’ in Figure 3) and posterior cingulate (c) in the figure below (as with all of the images presented in this document the darker / blue shading represents areas of low radiolabelled drug substance uptake whereas red/orange shading represents areas of high uptake).

![Figure 3](image-url)

**Figure 3** GE-067 imaging of a healthy volunteer (HV) - upper row and an Alzheimer’s disease (AD) patient - lower row. A HV GE-067 negative scan is characterized by white matter retention, low signal in the grey matter and a “gap” in the cortex signal above the corpus callosum (as indicated by arrow b). A positive AD GE-067 scan shows enhanced signal in the grey matter, specifically in the frontal cortex (a & a’), and posterior cingulate (c). The images are scaled such that the uptake is the same in the cerebellum reference region (d).

When studied in the same subjects, GE-067 and [11C]PIB scans show similar enhancement to the grey matter cortical regions of the brain due to increased β-amyloid plaque loading. The main difference in the distribution between the two compounds is the relative amount of binding between the grey and white matter. A comparison of [11C]PIB and GE-067 imaging on the same AD patient is shown in Figure 4. The [11C]PIB images show lower binding in the white matter and pons (wm and p in the

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figure, respectively) than the GE-067 images. However, most importantly, the images show similar enhancement to the grey matter cortical regions due to β-amyloid loading.

Figure 4 GE-067 (upper row) and $^{11}$CPIB (lower row) images of the same AD patient. The images show similar enhancement to the grey matter cortical regions of the brain due to β-amyloid plaque loading, with the main differences being that the GE-067 has a higher signal in the white matter (wm) and the pons (p) than the $^{11}$CPIB images.

6. CLINICAL UTILITY OF AMYLOID IMAGING AGENTS

GE Healthcare believes detection imaging of β-amyloid deposits can provide useful information for evaluation and assessment of neurodegenerative diseases. Extensive literature evidence supports the association of β-amyloid deposition with cognitive decline (particularly in AD). However, until five years ago or so, β-amyloid deposition in the form of senile plaques could only be confirmed post-mortem. β-amyloid deposition detected at autopsy serves as a pathologic marker and is useful in refining or confirming diagnoses based on clinical observations and testing.

Today, however, based largely on work with $^{11}$CPIB, β-amyloid can be exploited as a useful biomarker in living patients to complement other methods for diagnostic evaluation of neurodegenerative diseases. Research on β-amyloid imaging using $^{11}$CPIB suggests that approximately 90% of cases with clinically probable AD as defined by NINCDS-ADRDA criteria are β-amyloid positive. This detection rate is comparable to the detection rate of neuropathological examination for the post-mortem detection of β-amyloid deposits in clinically probable AD, even when diagnosed in the most experienced clinical settings. Therefore, the availability of a β-amyloid diagnostic tool to distinguish β-amyloid free patients from those with a β-amyloid burden can
benefit clinicians. The use of β-amyloid imaging agents should be viewed as part of a diagnostic algorithm and not as the sole determinant of a particular disease state. A robust in vivo assay would provide an essential tool for aiding diagnosis of many patients, however, the complete assessment and ultimate diagnosis of the patient will be by the clinician who utilizes this information. The clinical utility of the test should be judged on the weight of the evidence - whether the benefit of the knowledge gained outweighs the cost, the risk of an incorrect result, and the potential safety issue for the patient. GE-067 would not be a stand-alone diagnostic test for one neurodegenerative disease or another but rather provides relevant information on the pathological status of a patient, which contributes to the overall clinical assessment. As with all biomarker information, what the presence of β-amyloid means requires judgment and coordination with other facts and observations.

The proposed indication for GE-067 is relatively circumscribed - detection of β-amyloid deposits in the brain. If cognitive and/or memory testing confirms that a cognitive complaint is serious, detection (or failure of detection) of β-amyloid with GE-067 could provide useful information bearing on the underlying pathology. It is likely that MRI evaluation would also be a significant element in such a workup, to rule in or out the presence of structural pathology such as stroke or tumor. Other tests, including evaluation of regional brain metabolism with FDG, might also prove useful or necessary to make a diagnosis, particularly in difficult or atypical cases. The point is that we propose the use of GE-067 imaging as one possible clinical test, among several existing tests (i.e., not as a replacement), that would be available to the clinician faced with the evaluation of complaints of cognitive impairment.

The test should have low intra-subject variability and a validated manufacturing process. Overall PET is a very safe procedure (with less than 1 serious adverse event reported per 1,000 patients), so the benefit:risk analysis should be readily apparent to the clinician when ordering the test. Whilst GE Healthcare believes there is sufficient knowledge at present to support registration of the β-amyloid detection claim additional utility will be apparent once follow up studies have been performed. Clinicians will also want to know the long-term prognosis of each patient based on the scan and therefore a much larger database of patients, married to clinical history, will be required over time. Requiring this long-term data prior to the routine use of a β-amyloid in-vivo assay however, will significantly delay, and may halt, development.

The clinical utility of β-amyloid imaging at the present time may, therefore, be particularly useful in the evaluation of complicated or atypical cases of neurodegenerative diseases. For example, a patient with a clinical history of progressive cognitive impairment who is found not to have evidence of β-amyloid deposition would be very unlikely to be designated a diagnosis of AD. In this situation, the likelihood of an alternative pathologic basis for their neurodegeneration (such as frontotemporal lobar degeneration) would be considerably raised, and this would be an example of clinical utility. In the future, the life cycle plan for broader application of β-amyloid imaging will likely include sufficient data to permit thoroughly examining its potential utility in the differential diagnosis of neurodegenerative diseases, in monitoring disease progression,
in therapy monitoring (and for tailoring therapy to individual patients) and in predicting at risk patient populations.

With respect to the latter, for example, research has shown that 60% of amnestic patients with mild cognitive impairment (MCI) show brain \( \beta \)-amyloid deposition approaching AD levels. Four separate studies [22-25] have shown that 30-80% of “amyloid-positive” MCI patients convert to AD over a brief, 2-year follow-up compared to 0-10% of MCI patients without evidence of \( \beta \)-amyloid deposition on PET imaging with \([^{11}C]\)PIB. A \( \beta \)-amyloid imaging agent could therefore be used to stratify patient management decisions based upon imaging pathology in-life and could be especially useful when \( \beta \)-amyloid targeted therapies become available.

It is also well described in the scientific literature e.g. Mintun et al. [26] that there is a 10-30% prevalence of \( \beta \)-amyloid positivity in elderly patients that do not display reduced cognitive performance or other evidence of neurodegenerative impairment. A new report suggests that this figure may be as high as 50% [27]. Further work is needed however to understand whether these subjects progress to AD and if GE-067 could have utility to detect ‘at risk’ normals for whom early intervention may be beneficial.

These specific indications, however, are outside the scope of the discussion on the \( \beta \)-amyloid detection claim. GE Healthcare plans to develop separate clinical development plans supporting these indications in consultation with FDA.

7. **REQUIREMENTS FOR DEVELOPMENT OF RADIOPHARMACEUTICAL IMAGING AGENTS**

In general, the goal of any confirmatory clinical trial is to produce clinically relevant information that is valid and reproducible. In the specific case of clinical trials intended to assess the efficacy of pharmaceuticals, specific sub-goals are to ensure that any apparent drug effect is free from bias, spontaneous change in the course of a disease, chance, or the placebo effect. These goals are generally pursued through the inclusion of key design elements such as a control group (e.g., a placebo), randomized assignment of subjects to either the active or control agent, the inclusion of a sufficient number of subjects to reduce the effects of chance, and blinding of patients, observers and analysts to information that might result in biased results. Replication of studies is another tool by which to minimize the effects of chance. These principles are reflected in both the US Code of Federal Regulations (CFR) and in several International Conference on Harmonization (ICH) guidance documents, including ICH E8. Along with other criteria regarding protocols and study reports, the CFR lists 5 key design elements that are expected in an adequate and well-controlled study:

1. A design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (5 types of controls are defined: placebo concurrent, dose-comparison concurrent, no-treatment concurrent, active-treatment concurrent and historical).
2. A method of assigning patients to treatment and control groups (ordinarily, randomization) that minimizes bias and that is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug.

3. A method of selecting subjects that provides adequate assurance that they have the disease or condition being studied.

4. Adequate measures to minimize bias on the part of the subjects, observers, and analysts of the data.

5. The methods of assessment of subjects’ response are well defined and reliable.

ICH E8 also expects these design elements. In addition, ICH E8 mentions measurement of patient compliance with the drug regimen as a means to assess potential bias.

The design of clinical trials of medical imaging modalities and agents present some unique challenges. Medical imaging results in objective, often quantifiable, image data, and placebo effects are virtually unknown. Therefore, the administration of a control agent is generally not utilized, and consequently masking of the identity of the imaging agent is not possible. Rather, these studies may use a no-treatment concurrent control design, with the subject being imaged first without the investigational agent (this image then serves as the control), and then with the investigational agent (this image depicts the objective effects of the investigational agent). However, in some cases no control is feasible, based on the known mechanism of image formation.

For example, in imaging with PET radiopharmaceuticals (RP), the radioactive agent is administered to a patient and distributes to body tissues, where it emits positrons through radioactive decay followed by the production of 2 gamma rays per positron. The gamma rays generated within the body penetrate body tissues and are detected outside the body using a PET camera. In the absence of the RP, the only radiation that would be detected would be background radiation, and no diagnostically useful image could result. Thus, because there can be no image without the PET radiopharmaceutical, clinical trials of RP intended for imaging generally do not use any control.

Because it is generally not feasible to administer a control agent in imaging studies, it is not possible to provide a randomized assignment to active or control agent (every subject receives the active agent). Further, each subject usually receives a single dose of the imaging agent intravenously, under the direct supervision of study personnel, ensuring very high compliance rates. Therefore, key design elements numbers 1 and 2 and the ICH E8 requirement for compliance are generally not interpreted the same for clinical trials of RP, including those with GE-067. The drug effect stated in element 1 for a RP is the ability to provide accurate and diagnostically relevant information, and the validity of images in providing information of clinical value is assessed by comparison of the image-derived information with the same information derived from an SoT (an independent test that is believed to be the most accurate method available). It is also useful in defining summary test statistics, sensitivity, specificity, and positive and negative predictive value.
In the case of GE-067, sensitivity indicates the proportion of patients for whom GE-067 images show a positive β-amyloid burden, among patients known (or believed) to have this pathology based on the SoT. Similarly, specificity indicates the proportion of patients for whom GE-067 images show no appreciable β-amyloid burden among patients known (or believed) to not have the pathology based on the SoT.

Since images must be interpreted by physicians to extract clinically relevant information, it is important to avoid potential bias in image reading. A number of studies have demonstrated that image interpretation is affected by, and is often more accurate with, the availability of clinical information about the patient. For example, knowing that a patient had colon cancer may bias a reviewer toward calling a liver mass a metastasis. Blinding of image reviewers to clinical information about the patient is thus important to reduce this potential source of bias in compliance with key element 4 above.

8. $^{11}$C-PIB AS A STANDARD OF TRUTH FOR THE PRESENCE OF CEREBRAL AMYLOID

As discussed above, an SoT would be needed to demonstrate the accuracy and validity of GE-067 for registration purposes. Based largely on work with $[^{11}\text{C}]$PIB, it is evident that β-amyloid can be exploited as a useful biomarker in living dementia patients. GE Healthcare believes $[^{11}\text{C}]$PIB could serve as a practical standard against which to compare GE-067 to evaluate it for detection of cerebral amyloidosis.

The ideal SoT would be correlation of regional brain GE-067 uptake and autopsy findings of β-amyloid deposition in the same subjects. Unfortunately, this is not practical nor particularly efficient in this clinical setting. Alternative standards include clinical diagnosis and long term outcomes, which may be more practical but are associated with considerable uncertainty.

PIB has undergone detailed characterization to determine its binding to β-amyloid pathology in post mortem brain sections from human donors. In such studies, PIB shows excellent specificity for the target (>94%) [28-30], with 10 times the binding to β-amyloid plaque rich areas in AD brains compared to corresponding plaque-free areas of control brains. Furthermore, binding could not be detected in pathology-free white matter or to areas rich in neurofibrillary tangles that have a similar tertiary beta sheet structure to that presented by β-amyloid plaques.

The use of post-mortem AD tissue sections has confirmed that PIB co-localizes with β-amyloid as measured by immunohistochemistry [31,32]. The specificity of PIB for the β-amyloid target was further characterized by studies using post-mortem neocortical samples from diseased brains that do not have β-amyloid pathology as a hallmark (pure DLB, Huntington’s disease, Pick’s disease, motor neuron disease-inclusion dementia or dementia lacking distinctive histological features) which revealed no significant PIB binding [30].
Binding studies using β-amyloid -rich human AD brain homogenates show that PIB uptake reflects the amount of β-amyloid present [33] and therefore predict that the PET signal will increase with β-amyloid burden. This has in fact been demonstrated using $[^{11}C]$PIB in a β-amyloid overexpressing transgenic mouse model [34] and the clinical case described below.

Particularly notable is the autopsy-based report by Ikonomovic et al [35], in which it was demonstrated that radioactive or fluorescent PIB analogues are highly selective for β-amyloid deposits in AD brain. In this study, the pattern of fluorescent CN-PIB and tritiated PIB in 25 regions of post-mortem brain tissue from an AD subject was studied and corresponded with β-amyloid distribution/intensity determined by immunohistochemistry. Furthermore, PIB binding to AD brain homogenates correlated with the β-amyloid peptide levels and PIB binding was most pronounced in compact/cored β-amyloid plaques in the prefrontal and temporal cortices. Less pronounced PIB retention was seen in diffuse plaques and background levels were seen in the cerebellum.

This study also showed that PIB did not bind to any appreciable extent to other pathologic structures (neurofibrillary tangles, dystrophic neurites, or neutrophil threads) or to tissue treated with formic acid, which disrupts the β-pleated sheets in β-amyloid plaques.

In one AD patient included in the Ikonomovic study, an $[^{11}C]$PIB scan (obtained 10 months prior to the patient’s death) was compared with region-matched post-mortem quantitative analyses for the same subject. The retention of $[^{11}C]$PIB in the pre-mortem PET scan correlated directly with the post-mortem region-matched localization of a) fluorescent PIB positive β-amyloid plaques, b) $[^{3}H]$PIB binding to homogenates of the patients brain, and c) β-amyloid levels determined by ELISA (see Figure 5).
Figure 5  Colocalization of 25 regions of interest (ROI) in a $^{11}$CPIB-PET scan (left) and matching post-mortem formalin fixed tissue (center) from the same AD subject. Representative images of fluorescent PIB positive plaques in ROIs from different brain regions are shown on the right, illustrating the range from low (e.g., hippocampus, ROI 25) to high (frontal cortex, ROI 15).

Additional studies with $^{11}$CPIB [36] used statistical parametric mapping (SPM) to show β-amyloid deposition in patients with AD (n=17), relative to healthy subjects (n=11). For AD patients, localized increases of $^{11}$CPIB retention were seen in the frontal, parietal and lateral temporal cortices, as well as in the posterior cingulate and striatum.

No differences were found in the primary sensory and motor cortices, primary visual cortex, thalamus and medial temporal lobe. These results were corroborated by a quantitative region-of-interest (ROI) analysis which showed that the most prominent retention in AD patients was in the frontal cortex where $^{11}$CPIB uptake was 163% of the mean in healthy control subjects. Posterior cingulate (146% increase in AD), parietal (146% increase in AD) and temporal (145% increase in AD) cortices and striatum (133% increase in AD) also showed significant increases. Smaller increases were seen in the occipital cortex (117% increase in AD) and thalamus (115% increase in AD). The high increases in uptake seen in the frontal cortex and cingulate of patients with AD correlates with previously published PET results where increased $^{11}$CPIB retention was seen in AD patients relative to controls [21,28,36].

The retention of $^{11}$CPIB by β-amyloid in the brain has also been demonstrated in a case involving a 76-year-old man who had been clinically diagnosed with DLB [37,38].
He had an FDG scan 2 years prior to death and an $^{11}$CPIB scan 3 months prior to death. The FDG scan revealed a pattern of temporo-parietal glucose hypometabolism that was consistent with both a diagnosis of DLB and AD. The $^{11}$CPIB scan showed an increased β-amyloid load while post-mortem revealed severe CAA with a moderate number of parenchymal β-amyloid plaques. Biochemical analyses showed a positive regional correlation between β-amyloid levels determined post-mortem and $^{11}$CPIB retention seen with PET.

The finding of extensive CAA at autopsy by Bacskai et al [38], suggests that $^{11}$CPIB uptake can reflect vascular as well as brain parenchymal β-amyloid deposition. If this is the case, it indicates that while $^{11}$CPIB is a marker of β-amyloid, it is not specific for the nature of the β-amyloid pathology. It is also important to note that the presence of an β-amyloid burden is not exclusive to AD and other dementias are known to be associated with β-amyloid deposits that could be detected by $^{11}$CPIB (e.g., CAA, DLB with co-existent β-amyloid pathology). Additionally, ~25% of normal elderly patients [26], 20% of FTD patients [39] and ~50-60% of MCI cases [20,21] show β-amyloid deposition in the brain. The clear demonstration that β-amyloid deposition in the brain occurs across a number of different clinical presentations illustrates that $^{11}$CPIB and GE-067 PET imaging is not restricted to AD, but that utility could be more accurately defined as an agent to detect increased deposition of fibrillar β-amyloid deposits.

Biopsy studies correlating the presence of amyloid seen in histology to a signal observed in clinical $^{11}$CPIB imaging have also been performed by the Finnish group of Leinonen et al [40]. In this study, 10 surgical biopsies were obtained from patients who had undergone intraventricular pressure monitoring for a suspected normal pressure hydrocephalus. Of the 10 subjects sampled, 5 had clear cortical amyloid deposits as measured by immunohistochemistry, 4 were clearly negative and one had trace amounts of diffuse amyloid. All subjects were scanned with $^{11}$CPIB. In the 5 amyloid positive cases, 4 were shown to have increased $^{11}$CPIB signals, there was concordance between lack of histology and imaging in all 4 clearly negative cases and the case with traces of diffuse amyloid was PIB negative.

GE Healthcare believes that β-amyloid imaging may be particularly useful in the setting of MCI which is characterized by either isolated memory impairment (amnestic MCI), or impairment in other cognitive domains without memory impairment. These subjects do not meet the diagnostic NINCDS-ADRDA or DSM-IV criteria for AD. Amnestic MCI can have many causes (including AD, other forms of dementia, depression and physical causes). Patients have been imaged with $^{11}$CPIB and initial findings suggest that those with raised amyloid levels are more likely to progress to AD. Again it is expected that GE-067 would have an equivalent utility.

In a study described by Kemppainen et al [20], 13 patients with amnestic MCI and 14 control patients were imaged with $^{11}$CPIB. SPM localised significantly higher $^{11}$CPIB retention in patients with MCI compared to control subjects in the frontal, parietal and lateral temporal cortices and the posterior cingulate. ROI analysis confirmed that increased $^{11}$CPIB retention was localized in the frontal cortex, posterior cingulate,
parietal and lateral temporal cortices, putamen and caudate. Overall, the pattern of increased $[^{11}\text{C}]$PIB retention in patients with MCI was similar to that seen in AD and on an individual level, approximately half of the MCI patients showed increased $[^{11}\text{C}]$PIB retention that was typical of AD (increased retention values above 2 standard deviations from the control mean) and suggestive of early dementia.

Detection of increased $[^{11}\text{C}]$PIB retention in a subgroup of amnestic MCI patients was also reported in another study [22]. Here, 21 patients with MCI underwent $[^{11}\text{C}]$PIB PET and $[^{18}\text{F}]$FDG PET, cognitive function assessment and CSF sampling. Data from these patients were compared to data obtained from 27 AD patients and 6 healthy controls. $[^{11}\text{C}]$PIB retention in patients with MCI spanned the range from controls to AD patients, again with about half of the MCI patients having $[^{11}\text{C}]$PIB retention in the range of the AD patients. Seven of the ten MCI patients with raised $[^{11}\text{C}]$PIB retention converted to clinically probable AD 2 to 16 months later. None of the 11 MCI patients with levels of $[^{11}\text{C}]$PIB retention in the control range converted to AD over this same period. These subjects differed from non-converters in having a higher proportion of apolipoprotein E4 gene carriers, and lower CSF β-amyloid1-42 levels.

Further evidence for increased β-amyloid in a subset of MCI patients has been presented with cohorts of 5 subjects with AD, 5 subjects with amnestic MCI and 5 control subjects which revealed similar findings following $[^{11}\text{C}]$PIB imaging [23]. $[^{11}\text{C}]$PIB retention in individual MCI subjects was either AD-like (60%) or control-like (40%), which is consistent with the clinical observation that 40 to 50% of patients with MCI do not develop AD over a 10-year follow-up period. In yet another study of MCI using $[^{11}\text{C}]$PIB, MCI patients were found to have either an AD-like (60%) or normal (40%) binding pattern [21].

These findings are in keeping with post-mortem findings from the Mayo Clinic group that have shown that 8 of 15 (53%) of amnestic MCI patients had neuropathological evidence of cored β-amyloid plaques at autopsy. The key issues raised by all of these studies of MCI patients are the following: 1) Not all MCI progress to AD as in some cases their cognitive complaints are caused by a non-degenerative disorder. 2) Not all MCI patients show in vivo β-amyloid deposition when studied with $[^{11}\text{C}]$PIB PET. 3) Those MCI patients with increased $[^{11}\text{C}]$PIB retention have a higher rate of conversion to clinical AD than those without $[^{11}\text{C}]$PIB retention. The challenge will be to determine the tightness of the association between increased β-amyloid deposition determined in vivo and clinical conversion to AD. The implications of this are clear as the prevalence of MCI is similar to that of AD and clinical diagnosis is only about 50% accurate in predicting the prognosis for clinical AD. This, in turn, has great implications for decisions to start currently available therapies and will have even greater implications if therapies are developed to specifically target β-amyloid deposition in the brain.
**11C-PIB uptake in MCI**

PIB +ve MCI:  
- Uppsala: 7 out of 21 converted to AD over 8 months  
- Hammersmith: 4 out of 5 converted to AD over 2 years  
- Pittsburgh: 5 out of 13 converted to AD over 2 years

6/17/2008  

Figure 6 Summary of MCI data from Forsberg et al (2007) indicating the conversion of MCI subjects to AD (shown in filled circles in the MCI group). These subjects are all classified as amyloid positive.

9. STUDIES TO SUPPORT GE-067 EQUIVALENCE TO [11C]PIB

9.1 In Vitro Binding Studies

Affinity of GE-067 for β-amyloid has been tested using a number of different assessments, confirming that GE-067 has high affinity for this target consistent with our contention that GE-067 and PIB have very similar binding characteristics to β-amyloid. The affinity of GE-067 for synthetic β-amyloid 1-40 fibrils is high, with a Kd of 1.5 nM, and compares favorably to PIB, which has a comparable Kd value of 4.7 nM (lower values of Kd indicate better affinity) [41].

Localization of [3H]GE-067 binding to senile plaques in areas of AD brain that would be expected to show signs of Alzheimer’s pathology (e.g., cingulate and association cortex) has also been demonstrated on frozen human AD brain sections (GE Healthcare internal data). Binding is clearly restricted to senile plaques as demonstrated by co-localization with anti-β-amyloid antibodies in adjacent sections (see Figure 7).

Furthermore, the binding of the [3H]GE-067 to AD sections can be prevented by incubating with an excess of cold PIB ligand (i.e., the binding is saturable and specific). Binding was not observed in control brain sections or those that did not contain senile plaques.
Figure 7  Co-localization of [³H]GE-067 and [³H]PIB with immunocytochemistry (ICC) in senile plaques from human AD brain sections. ICC was used on the same tissue sections as the two tracers and is a reference standard known to bind and identify β-amyloid rich senile plaques.

A series of binding studies using AD brain homogenates from fourteen different brain regions isolated from post-mortem tissue demonstrated near equivalence of GE-067 with PIB. The brain homogenates used in these experiments were from the Ikonomovic study described above in Figure 5.

When the binding of [³H]GE-067 to the 14 different brain area homogenates was compared to that of [³H]PIB to the same homogenate samples, (Figure 8), the Pearson’s R² value (coefficient of determination) obtained was 0.98 confirming that the two compounds have nearly identical binding specificity for the human pathology isolated from the same patient donor. Furthermore, the correlation of [³H]GE-067 binding with the β-amyloid content of the tissue (R² = 0.85) compared favorably with that of [³H]PIB (R² = 0.89), again supporting the conclusion that GE-067 and PIB provided similar information.
Figure 8  Equivalence of $^3$H|GE-067 (also known as AH110690) and $^3$H|PIB binding to 14 different brain area homogenates isolated from the brain of a single AD brain donor. The brain samples were taken from the donor used for the histology-imaging co-registration study described in Ikonomovic et al [35].

The slope does not equal 1.0 due to the fact that $^3$H|GE-067 has a lower Kd (1.5 nM) compared to $^3$H|PiB (4.7 nM) and both the concentrations of the two ligands (1.0 nM) and the amount of β-amyloid (i.e., the amount of tissue homogenate) were identical in the two assays.

In the second series of brain homogenate equivalence binding studies, a frontal cortex AD brain homogenate with a high β-amyloid rich plaque load (determined by ELISA) was used to assess the ability of unlabelled PIB to inhibit the binding of either $^3$H|PIB or $^3$H|GE-067. The results obtained (Figure 9a) highlighted two important outcomes that again point to the near equivalence of these two compounds in terms of binding affinity and selectivity for the human β-amyloid:

a) The Ki for inhibition for $^3$H|PIB (4.9 nM) was nearly identical to the Ki for inhibition of $^3$H|GE-067 (4.1 nM).

b) The fitted curves are nearly superimposable and cold PIB can completely block the binding of either $^3$H|PIB or $^3$H|GE-067 to the brain homogenates.

Shown in Figure 9b are results from a third series of brain homogenate equivalence binding experiments in which unlabelled GE-067 was used to compete with either $^3$H|PIB or $^3$H|GE-067 for binding. Similar findings were obtained, the displacement...
binding curves were superimposable, and the Ki values for GE-067 competition with \(^{3}\text{H}\)GE-067 and \(^{3}\text{H}\)PIB binding to the homogenate were 2.4 nM and 1.9 nM, respectively.

![Graph A](image)

![Graph B](image)

**Figure 9**  (A) PIB competition with \(^{3}\text{H}\)GE-067 (also known as AH110690) and \(^{3}\text{H}\)PIB for binding to human AD brain homogenate.  (B) Cold GE-067 (AH110690) competition with \(^{3}\text{H}\)GE-067 (AH110690) and \(^{3}\text{H}\)PIB for binding to human AD brain homogenate.

The results from this series of experiments using human AD brain homogenates revealed the affinity of \(^{3}\text{H}\)GE-067 to be 1.7 nM, with a Bmax of 2.8 pmol compound bound per mg AD brain homogenate.  The corresponding \(^{3}\text{H}\)PIB affinity data yielded a Kd of 3.0 nM and a Bmax of 3.1 pmol compound bound per mg AD brain homogenate. Together, the results shown in figures 9a and 9b indicate identical specific binding sites for the two compounds in the AD tissue samples (i.e., equivalent binding specificities). GE Healthcare is, therefore, confident that GE-067 and PIB have a comparable affinity for the \(\beta\)-amyloid target.

### 9.2 Pittsburgh Study to Compare Intrasubject Uptake of \(^{11}\text{C}\)PIB and \(^{18}\text{F}\)GE-067 in AD and Control Subjects (RDRC Study)

A small clinical study (n=5) was performed in Pittsburgh to compare the intrasubject uptake of \(^{11}\text{C}\)PIB and \(^{18}\text{F}\)GE-067 in control and AD subjects. The study is described in more detail in the clinical section below but demonstrated a) that GE-067 was capable of discriminating \(\beta\)-amyloid uptake in AD subjects compared to controls and b) that the uptake of GE-067 was comparable to \(^{11}\text{C}\)PIB in the same subjects. Representative images from this study are shown in Figure 4.
10. CLINICAL EXPERIENCE WITH GE-067

10.1 GE Healthcare Study ALZ101

This was the first human study of GE-067 conducted by GE Healthcare. A carbon-11 labelled version of GE-067 was administered to young healthy volunteers (HV) (n=3), older HV (n=10) and probable AD patients (n=10). Each subject received a single intravenous dose of $[^{11}\text{C}]$GE-067 containing approximately 5 µg drug substance and a radioactivity dose of maximum 550 MBq. In this study, PET imaging with $[^{11}\text{C}]$GE-067 was able to differentiate subjects with probable AD from HV, both visually and using uptake ratios (derived from SUVs) and distribution volume ratios (DVRs) relative to a cerebellar reference region. In all examined areas of the brain except the medial temporal cortex, subcortical white matter, and pons, higher uptake ratios with $[^{11}\text{C}]$GE-067 were seen in eight of the ten subjects with probable AD than with HV. A statistical comparison supported these observations. In particular, the frontal region (left and right), parietal cortex (left), anterior cingular cortex (left and right) and posterior cingular cortex (left) demonstrated significantly raised $[^{11}\text{C}]$GE-067 uptake ratios and DVRs in AD. $[^{11}\text{C}]$GE-067 was well tolerated in this study; there were no deaths, serious adverse events (SAE) or withdrawals due to adverse events (AE). The few AEs that occurred were primarily mild in intensity, resolved during the study, and were deemed unrelated to $[^{11}\text{C}]$GE-067. Assessment of laboratory parameters (hematology, serum biochemistry and urinalyses), vital signs and electrocardiograms (ECG) showed no clinically important trends or safety signals.

10.2 GE Healthcare Study ALZ102

The second human study with $[^{11}\text{C}]$GE-067 was designed as a clinical and imaging longitudinal study to measure and compare the regional cerebral uptake of $[^{11}\text{C}]$GE-067 over an interval of one year follow-up in the subject population evaluated at baseline in study ALZ101. Safety and efficacy analyses were similar in both studies. The target population for the study consisted of adult subjects who were at least 50 years old and had already participated in study ALZ101. Nineteen subjects (10 HV and 9 probable AD patients) were dosed and evaluable for the safety analysis, and 18 subjects were evaluable for the efficacy analysis. At follow-up, all subjects retained their clinical diagnosis from study ALZ101 including the two probable AD subjects who showed no $[^{11}\text{C}]$GE-067 retention during study ALZ101. $[^{11}\text{C}]$GE-067 continued to show the potential to differentiate between subjects with probable AD and HV using uptake ratios (UR) or DVRs with a mean higher ratio being observed in subjects with probable AD. When compared with the ALZ101 study results, ALZ102 showed no significant changes in $[^{11}\text{C}]$GE-067 brain uptake in AD subjects or HV over the one year follow-up (see Figure 10).
Figure 10 ALZ102 One year follow up study: Example of results from the Parietal Cortex showing uptake ratios of \([^{11}\text{C}]\)GE-067 compared to cerebellum as the reference region. Subjects 1-9 are the AD cases and subjects 10 -19 are the aged control subjects. The blue bars represent the original scan data from study ALZ101 and the red bars represent uptake after a one year follow up period. There were no significant changes over this period and the data showed less than 10% (typically 5-7%) variability.

From a safety perspective, \([^{11}\text{C}]\)GE-067 was again well tolerated. No deaths, SAEs, or withdrawals due to AEs occurred during the study. The few AEs that occurred were primarily mild in intensity, resolved during the study, and were deemed unrelated to \([^{11}\text{C}]\)GE-067. Assessment of laboratory parameters (hematology, serum biochemistry and urinalyses), vital signs and ECGs showed no clinically important trends or safety signals. The study showed no significant change in the deposition of \(\beta\)-amyloid over a one year period and hence demonstrates by default that the test-retest variability of this agent is comparable to that seen with \([^{11}\text{C}]\)PIB.

10.3 Pittsburgh Study to Compare Intrasubject Uptake of \([^{11}\text{C}]\)PIB and GE-067 in AD and Control Subjects (RDRC Study)

As described above in ALZ101 and ALZ102, the preliminary clinical studies were performed using an \(^{11}\text{C}\) labeled version of the fluorinated lead candidate GE-067. Once this molecule had shown promise in the clinic a method was developed to \(^{18}\text{F}\) label GE-067 and a clinical study performed by the Pittsburgh group to demonstrate that changing the position of the radiolabel did not cause the \(\beta\)-amyloid signal in AD brain to be lost. Additionally both the normal and AD subjects were scanned with \([^{11}\text{C}]\)PIB to demonstrate the potential comparability of these two \(\beta\)-amyloid imaging agents. \([^{11}\text{C}]\)PIB and GE-067 were imaged in 3 control (75 y/o F, MMSE=30; 55 y/o F, MMSE=30; 74 y/o F, MMSE=29) and two AD subjects (78 y/o F, MMSE = 28; 78 y/o F, MMSE=26). For \([^{11}\text{C}]\)PIB, dynamic emission data were collected for 90 min after injection. For GE-067, dynamic emission data were collected over 250 min after...
injection. Both $^{11}$CPIB and GE-067 images were co-registered to SPGR MRIs for region of interest (ROI) definition and atrophy correction. ROIs included precuneus (PRC), frontal cortex (FRC), cerebellum (CER), and subcortical white matter (SWM), and ratios of regional to CER standardized uptake values (SUVR) were determined. GE-067 readily entered human brain, with uptake at 2 min in all subjects similar to $^{11}$CPIB (3.1-4.5 SUV units). Following injection of GE-067, approximately 2-fold greater retention of radioactivity was observed in AD cortical areas known to contain $\alpha$ plaques (eg, PRC and FRC) relative to that in control subjects. GE-067 SUVR (90-120’) in PRC and FRC were similar (within 10%) to $^{11}$CPIB SUVR (40-90’) in all subjects, while higher non-specific binding was observed (approximately 20%) in SWM for GE-067 than for $^{11}$CPIB. GE-067 shows uptake and retention characteristics comparable to those of $^{11}$CPIB in cortical brain regions. Somewhat higher non-specific retention in white matter was observed for GE-067 relative to $^{11}$CPIB, but this likely will not negatively impact the ability of GE-067 to identify and quantify cortical $\alpha$ deposits as evidenced in Figures 4 and 5.

10.4 GE Healthcare Study ALZ103

The objectives of this study were to evaluate the safety of GE-067 in cognitively intact HV and in subjects with early-stage clinically probable AD and to compare GE-067 brain retention in HV versus AD.

A multi-step, single-center study was conducted. **Step 1**: evaluation of whole-body biodistribution and radiation dosimetry (n = 6 HV, 4 men/2 women, age 51-73 yr). Three HV (1 men/2 women, age 56-71 yrs, education 18-20 yrs, MMSE 28-30 out of 30, CDR 0) and 3 AD patients (3 men, age 55-68 yrs, education 18-30 yrs, MMSE 22-24, CDR 0.5, time-to-AD-diagnosis 1-1.5 yrs) were dynamically scanned on a Siemens Biograph PET-CT scanner during 0-90, 150-180 and 220-250 minutes post-injection with arterial sampling. **Step 2**: Logan graphical analysis with cerebellar cortex as reference region was performed and metabolite-corrected time-activity curves of GE-067 retained in the brain were generated to compare time-dependent brain distribution between HV and AD (distribution volume ratios, DVR). **Step 3**: (n = 5 HV, 5 AD) Confirmation that an 80-170’ scanning window provides good visual discrimination of GE-067 uptake in AD compared to normal controls and that a 5-10 minute snapshot may provide adequate counts.

From a safety perspective, GE-067 was well tolerated. No deaths, SAEs, or withdrawals due to AEs occurred during the study. The few AEs that occurred were primarily mild in intensity, resolved during the study, and were deemed unrelated to GE-067. Assessment of laboratory parameters (hematology, serum biochemistry and urinalyses), vital signs and ECGs showed no clinically important trends or safety signals. On the basis of Step 1 the injected dose in Step 2 and 3 was set at approximately 185MBq.

Results from Steps 2 and 3 indicated that good discrimination between early stage probable AD patients and healthy elderly volunteers can be seen using simple target to reference region rations using cerebellum as the reference region. Statistical differences in uptake in frontal, parietal, temporal lateral and posterior cingulate areas were observed.
at both 85-105 minutes and 120-140 minutes. One of the eight healthy volunteers showed increased uptake rations in frontal regions which is consistent with findings from many studies using $[^{11}\text{C}]$PIB where a proportion of healthy elderly volunteers showed increased PIB retention. Two of the AD scans were visually and quantitatively similar to the HV scans possibly indicating that these subjects, although meeting the clinical criteria for probably AD, may lack the Aβ plaque pathology necessary for a neuropathological diagnosis of ‘definite AD’

Discrimination between AD and HV subjects was only marginally affected by the scanning start time in the 85-140 minute interval tested and short scanning times of 5-10 minutes have been found to be adequate even with the suggested dose of 185MBq.

Figure 11 Images from GE Healthcare ALZ103 study. Top panel shows GE-067 images from a HV and the bottom panel shows corresponding images from an AD patient. Images were normalized to cerebellum activity.
11. CLINICAL DEVELOPMENT PLAN

Three critical elements have been identified in the future development and approval of GE-067. These are SoT, clinical utility, and appropriate imaging metrics.

1. SoT: Ultimately, the SoT for β-amyloid deposition is histological confirmation at the time of autopsy. Using autopsy findings as the SoT in a product development program, however, is not practical and we are proposing a different approach. Since the field of \textit{in vivo} β-amyloid imaging was largely created by research with $[^{11}\text{C}]$PIB for which pathological validation is available, we propose that $[^{11}\text{C}]$PIB could represent a viable SoT for evaluation of Aβ imaging agents such as GE-067.

Accordingly, we hope the AC will consider the following questions: a) Can $[^{11}\text{C}]$PIB serve as an SoT for registration of β-amyloid imaging agents such as GE-067, and b) What information would be needed to establish $[^{11}\text{C}]$PIB as a suitable SoT?

2. Clinical Utility: GE Healthcare is seeking initial registration of GE-067 based on its ability to detect Aβ in the brain. In terms of the Guidance for Industry, entitled \textit{Developing Medical Imaging Drug and Biological Products, Part 2: Clinical Indications}, we believe this corresponds to Pathology Detection, since β-amyloid deposits are pathologic structures, detection of which conveys potentially important information for clinical evaluation of neurodegenerative disease.

The proposed utility associated with the initial registration of GE-067 is detection of abnormal pathology (specifically, cerebral amyloidosis) in the brains of individuals with suspected neurodegenerative disorders. In the short term, we contend there is value and utility in identification and detection of cerebral amyloidosis. GE-067 would be able to detect the presence or absence of amyloid pathology in cases where diagnostic uncertainty exists and to rationalize the use (or not) of current treatments when the underlying pathology cannot be confidently predicted on the basis of clinical evaluation. GE-067 would be used in combination with other tools and diagnostic features to guide a clinician’s diagnosis.

The most obvious clinical utility prospects for GE-067 include screening high-risk patients, predicting progression of disease in patients with amnestic MCI, and monitoring therapeutic effects of anti-amyloid drugs. GE Healthcare intends to pursue these types of indications and others in the future with appropriate clinical studies.

3. Imaging Metrics: The registration study to support approval of a detection claim is designed to compare detection of β-amyloid deposits in healthy, normal individuals, individuals with amnestic MCI, and individuals with clinically probable AD using both $[^{11}\text{C}]$PIB and GE-067. Based on previous work with $[^{11}\text{C}]$PIB and ongoing work with GE-067, we will define and present cutoff ratios for binding values in specified regions of the brain to delineate what is abnormal and normal for a particular patient population.
GE Healthcare will be prepared to present our approach to image analysis and imaging metrics at the AC meeting for review and discussion.

11.1 Summary of Clinical Development Program to Support the Detection of β-Amyloid in the Brain

**Background**

The registration study to support approval of a detection claim is designed to compare detection and population ranges of β-amyloid deposits in healthy volunteers, individuals with amnestic MCI, and individuals with probable AD on NINCDS-ADRDA criteria using both [$^{11}$C]PIB and GE-067. Some of the subjects will receive a repeat administration of GE-067 rather than [$^{11}$C]PIB in order to demonstrate the degree of reproducibility associated with GE-067. Based on work with [$^{11}$C]PIB and GE-067, we will define cutoff ratios for binding values in specified regions of the brain to delineate what is abnormal and normal.

Additionally considerable evidence has accumulated supporting the validity of [$^{11}$C]PIB as a potential standard of truth. Evidence to support this claim will be derived from a number of sources and will include:

1. Summary of approximately 65 peer reviewed literature studies
2. A “Meta-analysis” of the clinical literature results to demonstrate concordance between the prevalence of raised amyloid signal in clinically probable AD cases and absent amyloid signal in controls.
3. Blinded read of [$^{11}$C]PIB scans pooled from academic sites to demonstrate the ability of readers blinded to clinical information to call the scan either positive or negative

**Clinical Trial Outline**

**Title of Study:**
An open-label study to assess imaging comparability of GE-067 with [$^{11}$C]PIB, reproducibility of imaging with GE-067 and safety in healthy volunteers, subjects with suspected MCI, and subjects with probable AD.

**Objectives:**
This trial is designed to support the initial registration for GE-067 based on detection of β-amyloid in the brain. The primary objective is to:

1. Establish the metrics of GE-067 uptake both visually and quantitatively in healthy volunteers, subjects with amnestic MCI, and subjects with probable AD.
Secondary Objectives are to:

2. Demonstrate that β-amyloid imaging with GE-067 is comparable to β-amyloid imaging with \([^{11}\text{C}]\text{PIB}\) (used as the SoT for this study).

3. Demonstrate that β-amyloid imaging with GE-067 is associated with low test-retest variability.

4. Demonstrate that use of GE-067 is safe and well tolerated, posing minimal risk to individuals exposed to the agent.

**Study Design:**
The study is designed as a multi-center, open-label, double-dose clinical trial to evaluate the ability of GE-067 to image β-amyloid deposits compared with \([^{11}\text{C}]\text{PIB}\) imaging in healthy volunteers and subjects with suspected neurodegenerative disease (amnestic MCI or AD). In a specific group of patients with suspected neurodegenerative disease, repeat administrations of GE-067 will be performed to evaluate reproducibility of β-amyloid imaging.

Four groups of subjects will be studied with GE-067 and two of these groups also with \([^{11}\text{C}]\text{PIB}\):

1. Normal, healthy, age-matched (>55 years) and younger volunteers (<55 years). It is anticipated that approximately 25% of older subjects may display evidence of abnormal β-amyloid deposition. These volunteers will only have GE-067.

2. Patients clinically diagnosed with MCI (>55 years). It is anticipated that approximately 60% of these patients will display evidence of abnormal β-amyloid deposition. These patients will receive both GE-067 and \([^{11}\text{C}]\text{PIB}\).

3. Patients clinically diagnosed with AD (>55 years). It is anticipated that approximately 90% of these patients will display evidence of abnormal β-amyloid deposition. These patients will receive both GE-067 and \([^{11}\text{C}]\text{PIB}\).

4. A fourth group of subjects with AD will be scanned twice with GE-067 to examine the reproducibility of imaging (i.e., test retest).

The key endpoint for the detection claim is the comparability of imaging findings between GE-067 and \([^{11}\text{C}]\text{PIB}\) derived images in AD and MCI cases. The percentage of positive β-amyloid findings in a particular group is actually not relevant for endpoint evaluation but would potentially represent a useful means of assessing how well the groups are representative of conventional thinking regarding frequencies of positive Aβ observations (e.g., in the probable AD group).

In the 2 groups receiving GE-067 and \([^{11}\text{C}]\text{PIB}\), the order of injection will be randomized. Either \([^{11}\text{C}]\text{PIB}\) or GE-067 will be administered on the day of the baseline
visit and imaging will take place at approximately 60 minutes after dosing with $^{[1]}C$PIB or 85 minutes after dosing with GE-067. All subjects will be contacted 24 hours after GE-067 or $^{[1]}C$PIB administration and asked a non-leading question to determine whether any adverse events (AEs) have occurred. Safety data will be collected at 24 hours only if abnormal observations were obtained during the post-injection safety recordings (ie injection site monitoring, ECG, vital signs, standard blood and serum clinical chemistry to be taken up until the end of PET scanning at approximately 2 hours post injection). The second injection (GE-067 or $^{[1]}C$PIB as appropriate) will be administered 1 to 4 weeks later following the appropriate protocol and repeating the safety follow-up.

In the fourth group (subjects with AD receiving 2 administrations of GE-067), a second GE-067 injection will be administered and scan performed 1 to 4 weeks after the first injection in order to evaluate reproducibility and consistency of images in the same subjects.

Subject allocation to the study will be non-randomized and blinded image evaluation (BIE) will be randomized. The efficacy evaluation of GE-067 brain PET imaging data will be based on a BIE that will be performed by 3 central independent physicians experienced in the evaluation of PET amyloid imaging. All subjects will attend screening and baseline visits.

**Metrics:**

The brain image evaluation and comparisons could be made by focusing on 5 brain areas which have shown a consistently higher load of amyloid in AD subjects on $^{[1]}C$PIB scans. To define what is abnormal, Standard Uptake Value Ratios (SUVR; at 60-90 minutes for $^{[1]}C$PIB and at 85-105 minutes for GE-067) above the following cutoffs are suggested at present.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>SUVR cutoff value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal:</td>
<td>1.4</td>
</tr>
<tr>
<td>Anterior Cingulate:</td>
<td>1.6</td>
</tr>
<tr>
<td>Posterior Cingulate:</td>
<td>1.7</td>
</tr>
<tr>
<td>Parietal:</td>
<td>1.4</td>
</tr>
<tr>
<td>Lateral Temporal:</td>
<td>1.4</td>
</tr>
</tbody>
</table>

These SUVR cutoff values are provisional. Additional work is being conducted with the University of Pittsburgh to refine the values and procedures for interpreting the images, therefore final values may be different.

Examples of images obtained with GE-067 (study ALZ103) are shown in Figure 12.
Figure 12 Images from GE Healthcare ALZ103 study to illustrate how SUVR values could be used as metrics for differentiating patients. The 2 top images are from AD subjects and the lower one is from a healthy volunteer. Note that the values for 2 specific regions in the brain, frontal cortex and posterior cinguli, are generally below 1.5 for healthy volunteers and above 1.5 for AD subjects. The high uptake of GE-067 evident in the white matter of the healthy volunteer images is characteristic and represents the high nonspecific binding observed in white matter, emphasizing the importance of defining metrics by specific regions of the gray matter in the brain.

12. LIFE CYCLE PLANNING

Today, however, based largely on work with $[^{11}\text{C}]$PIB, β-amyloid can be exploited as a useful biomarker in living patients to complement other methods for diagnostic evaluation of neurodegenerative diseases. GE-067 would not be a stand-alone diagnostic test for one neurodegenerative disease or another but rather provides relevant information on the pathological status of a patient, which contributes to the overall clinical assessment. In the future, the life cycle plan for broader application of β-amyloid imaging will likely include examining its potential utility in establishing the pathology underlying neurodegenerative diseases, in monitoring disease progression, in therapy monitoring and in predicting progression of at risk patient populations. Research has shown that 50-60% of amnestic patients with MCI show brain β-amyloid deposition approaching AD levels,
of which 30-80% convert to AD over a 2-year follow-up. The agent could therefore be used to stratify patient management decisions based upon imaging pathology in-life and could be especially useful when β-amyloid targeted therapies become available. It is also well described in the scientific literature that there is a 10 to 25% prevalence of β-amyloid positivity in elderly patients that do not display reduced cognitive performance or other evidence of neurodegenerative impairment. Further work is needed however to understand whether these subjects progress to AD and if GE-067 could have utility to detect ‘at risk’ normals for whom early intervention may be beneficial.

These specific indications, however, are outside the scope of the discussion on the β-amyloid detection claim. GE Healthcare plans to develop separate clinical development plans supporting these indications in consultation with FDA.

13. SUMMARY

GE Healthcare believes that imaging of β-amyloid deposits could provide useful information for evaluation and assessment of neurodegenerative diseases. Until 2003, β-amyloid deposition in the form of senile plaques could only be confirmed post-mortem.

Today, based largely on work with [11C]PIB, β-amyloid can be exploited as a useful biomarker in living patients to complement other methods for diagnostic evaluation of neurodegenerative diseases.

GE Healthcare believes that a detection claim is the most efficient way to make an approved product available to clinicians working on neurodegenerative disorders. We contend that a case can be made in the short term for approval based on detection and hope the AC proceedings will help to resolve the requirements of a detection claim for imaging cerebral Aβ deposits.

Three critical elements have been highlighted: SoT, clinical utility, and appropriate imaging metrics. GE Healthcare proposes that [11C]PIB could be used as the SoT for amyloid imaging, that clinical utility could be defined by detection of cerebral amyloidosis in individuals with suspected neurodegenerative disorders without the requirement of long term clinical trials, and that imaging metrics can be refined to facilitate interpretation of amyloid imaging scans.

We suggest that the AC consider the following questions to evaluate what we acknowledge is a new approach to the approval of diagnostic imaging agents:

1) Is detection of cerebral amyloidosis by GE-067 an indication that could justify initial US approval?

2) Could [11C]PIB serve as a truth standard for registration of Aβ imaging agents such as GE-067? What information would be needed to establish [11C]PIB as a standard? If so, is the proposed phase 3 protocol outline an acceptable approach?
3) Is the approach GE Healthcare presents for image analysis and metrics satisfactory?

14. REFERENCES

14. Varma AR, Snowden JS, Lloyd JJ, Talbot PR, Mann DM and Neary D Evaluation of the NINCDS–ADRDA criteria in the differentiation of Alzheimer’s disease and

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