FDA Advisory Committee Briefing Document

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

October 23, 2008

Clinical Development of Radionuclide Imaging Products for the Detection of Amyloid to Assist in the Diagnosis of Alzheimer's Disease

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The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division of Office. We have brought this subject (clinical development of radionuclide imaging products for the detection of amyloid to assist in the diagnosis of Alzheimer's Disease) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

EXECUTIVE SUMMARY

INTRODUCTION

Alzheimer's disease (AD) is generally recognized as the most common cause of dementia in the elderly and is estimated to affect more than 4 million people in the United States. At the present time, the pre-mortem diagnosis of AD relies upon expert clinical evaluation and a battery of nonspecific diagnostic tools (such as brain computerized tomography, CT or magnetic resonance imaging, MRI) generally aimed at ruling out other causes for dementia.

A definitive pathological diagnosis of AD is generally established with a post-mortem examination that reveals the pattern of pathology thought typical for AD, including the presence of neurofibrillary tangles (NFT) of the microtubular protein tau and "neuritic" plaques that contain deposits of ß-amyloid.

The detection of ß-amyloid deposition has received considerable attention because several ligands have been developed that purportedly bind specifically to epitopes on the amyloid deposits and, if radiolabeled, may facilitate the *in vivo* detection of amyloid deposition. This *in vivo* detection of amyloid deposition has been proposed as a tool to assist the clinician in the diagnosis of AD. For example, the absence of amyloid-specific radioligand uptake might eliminate AD as a cause for dementia and prompt a more thorough evaluation for non-AD causes of the dementia.

BACKGROUND AND PURPOSE OF THIS ADVISORY COMMITTEE

Over the past many months, the FDA Division of Medical Imaging and Hematology Products was approached by three sponsors who, either formally or informally, requested advice regarding the development of phase 3 clinical studies that would provide clinical data sufficient to support the marketing approval of *in vivo* diagnostic radiopharmaceutical agents useful in the detection of amyloid deposition within the brain. In response to these requests, the Division asked all three sponsors to provide an outline of a proposed "indication" for their product (i.e., a proposed marketing label indication statement) as well as a brief outline of a proposal for a phase 3 clinical study. The outline for the phase 3 study was to serve as a specific discussion proposal that would have applicability to more than one phase 3 clinical study to support market approval of the imaging product.

All three sponsors responded with generally a similar concept regarding a proposed indication. Specifically, the sponsors emphasized the use of the *in vivo* diagnostic radiopharmaceutical agent as a diagnostic tool for the clinician, with the following major concepts:

- the *in vivo* diagnostic radiopharmaceutical would reliably detect (or quantitate) cerebral amyloid deposition;

- the indication statement would relate to the detection of amyloid, not the specific diagnosis of AD;
- an *in vivo* assay for amyloid deposition would provide a useful tool to assist the clinician in the diagnosis of AD, this tool would join other tools in the diagnostic evaluation, such as CT or MRI.

As described below, these proposals are not unreasonable considerations and are relatively consistent with certain regulatory guidance and diagnostic drug approval precedents.

The sponsors somewhat differed with respect to the specific design of phase 3 clinical studies. These proposals are summarized below and provided in greater detail within the sponsors' background materials. Most notably, the study designs varied in the "standard of truth", i.e., the definitive measure of cerebral amyloid against which the radioligand uptake marker would be compared to obtain performance characteristics (sensitivity, specificity, etc).

This advisory committee is convened specifically to advise the Division regarding:

- the clinical utility of a reliable marker for cerebral amyloid detection and, if determined to have clinical utility, then

- comment upon a reasonable "standard of truth" for amyloid deposition, and provide

- additional comments upon the strengths and limitations of the proposed phase 3 study outlines.

REGULATORY BACKGROUND

The FDA has specific regulations regarding the demonstration of effectiveness and safety of diagnostic *in vivo* radiopharmaceutical drugs. These regulations are interpreted in greater detail within specific guidance documents for industry (see appendix).

Regarding the demonstration of effectiveness, the regulations note the following:

- the product may or may not provide disease-specific information;

- instead, the product's indication may refer to a biochemical, physiological, anatomical or pathological process or to more than one disease or condition;

- the effectiveness is evaluated by the product's ability to provide useful clinical information "related to its proposed indications for use;"

- accuracy and clinical usefulness is determined by comparison with a "reliable assessment of actual clinical status;"

- "actual clinical status" may be provided by:
    - a diagnostic standard, or

- standards of demonstrated accuracy, or in the absence of these standards,
- "established in another manner, e.g., patient follow-up."

These regulatory expectations for *in vivo* diagnostic radiopharmaceuticals are similar to those expected for other drugs used as diagnostics. To illustrate the range of potential label claims for diagnostics (from disease-specific to physiologic or non-specific), listed below are indication statements for certain approved drugs indicated for use as diagnostics:

- Fludeoxyglucose F18 Injection; "assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer" (plus other indications);"

- Iobenguane I 123: "indicated for use in the detection of primary or metastatic pheochromocytoma or neuroblastoma as an adjunct to other diagnostic tests;"

- Cosyntropin Injection: "intended for use as a diagnostic agent in the screening of patients presumed to have adrenocortical insufficiency;"

- Methacholine Chloride for inhalation: "indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma."

The 2004 Guidance for Industry “Development of Medical Imaging Drug and Biological Products, Part 2: Clinical Indications” refers to four types of indications:

- Structure delineation
- Disease or pathology detection or assessment
- Functional, physiological, or biochemical assessment
- Diagnostic or therapeutic patient management

The indication for use in relation to the amyloid imaging agents appears generally related to either a type of “pathology detection” indication or a "biochemical assessment" indication. In general, the regulatory expectations are similar for either of these two types of indications.

DRAFT QUESTIONS TO THE ADVISORY COMMITTEE

1. To what extent, if any, would an indication for use of an *in vivo* diagnostic radiopharmaceutical agent for the "detection of cerebral amyloid" provide useful clinical information?

   This indication might not relate specifically to claims of utility in the diagnosis of Alzheimer's Disease or other neurodegenerative conditions, based upon diagnostic imaging performance characteristics.

2. If a drug is clinically useful in the "detection of cerebral amyloid", what measure should be used as a "standard of truth" (ie., the "standard of demonstrated accuracy") in phase 3 clinical studies?

   In addition to any other items, consider:

   - autopsy results

   - the use of "expert panel" determination of the presence/absence of Alzheimer's Disease as a form of "amyloid deposition surrogate"

   - the use of another radioligand (such as the "Pittsburgh Compound B") as a reference standard.

3. Please comment on the strengths and weaknesses of the phase-3 study outlines supplied by the sponsors.

HIGHLIGHTS OF THE PHASE 3 STUDY PROPOSALS

Greater details are provided within the specific sponsor background materials and the appended FDA review documents. These review documents are preliminary summaries and notations.

1. Avid Radiopharmaceuticals: The sponsor seeks an indication "for PET imaging of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment."

   The Phase-3 trial will enroll and image subjects with terminal conditions not related to dementia (e.g., congestive heart failure, chronic obstructive pulmonary disease, cancer). The end of life population will include non-demented subjects, as well as subjects with various stages of AD, mild cognitive impairment (MCI) and other causes of cognitive impairment. The patients will be followed to autopsy. The "standard of truth" relates to pathology detection of amyloid. The primary endpoint: positive predictive value of "low amyloid burden" in ruling out AD; it will be greater than a threshold to be estimated from the results of a Phase-2 study.

   Following potential NDA approval, the sponsor anticipates an NDA supplement to expand the indication. Specifically, the sponsor proposes Phase-3 trials will provide data supporting an indication for "predicting relative risk of clinical progression in patients with mild cognitive complaints". Patients with MCI and high amyloid level will be compared to those with mild cognitive impairment and low amyloid level for a risk of worsening of impairment over a two year period.

2. Bayer HealthCare: The sponsor seeks an indication that "*the PET tracer* can detect amyloid beta plaque in the brain. In the absence of *tracer* uptake (and thus amyloid ß plaque deposition) Alzheimer's disease can be excluded."

   The phase-3 trial will be conducted in patients with probable AD and in healthy volunteers. The standard of truth pertains to the clinical diagnosis (apparently of probable Alzheimer's disease) which appears to serve as a "surrogate" for the presence of cerebral amyloid. The primary endpoints relate to sensitivity and specificity to be measured each above a pre-specified threshold.

3. GE Healthcare: The sponsor seeks an indication relating to "PET imaging of brain beta amyloid deposition."

   The phase-3 trial will be conducted in patients with AD, patients with mild cognitive impairment, and in healthy age-matched volunteers. The standard of truth is related to use of a reference radioligand imaging agent (C-11 PIB Imaging), which appears to serve as a "surrogate" for amyloid, based upon *in vitro*, animal and certain clinical data.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research

Date: September 17, 2008

From: Russell G. Katz, M.D.
Division Director

Subject: ^{18}F-AV-45
IND #79511 (005)
Proposed Indication: Diagnosis of Alzheimer's Disease
Clinical Development Plan Position Paper

To: Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

IND (Serial Number)	**79511 (005)**
Sponsor:	**Avid**
Drug:	**18F-AV-45**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Position Paper**
Correspondence Date:	**4/8/08**
Date Received / Agency:	**7/29/08**
Date Review Completed	**9/17/08**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission, which has been received as a consultation from the Division of Medical Imaging and Hematology Products (DMIHP), consists of a summary of the sponsor's clinical development program for ^{18}F-AV-45. ^{18}F-AV-45 is being developed for *in vivo* imaging of β-amyloid, using positron emission tomography.

The submission is in response to a letter, dated March 14, 2008, from DMIHP to sponsors of imaging agents being developed for the diagnosis of Alzheimer's Disease; that letter stated that an Agency Advisory Committee meeting was being scheduled to provide advice regarding the design of Phase III studies of such imaging agents, and invited sponsors to submit proposals for the design of such studies. The current submission has been prepared as a Position Paper for that meeting. The Advisory Committee meeting has now been scheduled for October 23, 2008.

2. Contents Of Submission

This submission has the following main headings

- Cover letter
- Position paper and summary outline of proposed Phase III plan (with the following headings)
  - Summary
  - Background
  - Overview of Phase III proposal
  - Synopses of proposed Phase III trials
  - Questions for the Advisory Committee
  - Critiques and responses
  - References
  - List of abbreviations

3. Contents Of Review

This review will address only those aspects of the submission that are relevant to the sponsor's proposed Phase III program (consistent with the consultation request) under the following main headings:

- (Sponsor's) background to Briefing Document
- Support for each element of proposed Phase III plan
- Synopses of proposed Phase III trials
- Sponsor's questions for Advisory Committee
- Sponsor's responses to potential critiques of proposed Phase III program
- Comments.

4. Background To Briefing Document

The following is a summary of the key items highlighted by the sponsor, that are pertinent to this review.

- The clinical diagnosis of Alzheimer's Disease, when based on "consensus criteria" (this term presumably refers to the NINCDS-ADRDA criteria for Probable Alzheimer's Disease), is fairly accurate in expert hands when compared against the pathological diagnosis, the gold standard.

- Given the high prevalence of Alzheimer's Disease, it is not practical to refer all those suspected of that condition to an expert. Thus, a diagnostic aid that could help community physicians distinguish those patients who do not have Alzheimer's Disease from those needing further evaluation would be very useful, as would an aid to the diagnosis of those at high risk of developing Alzheimer's Disease who do not as yet have that condition.

- Aβ plaques (and neurofibrillary tangles) are histopathological hallmarks of Alzheimer's Disease, and play a key role in the pathogenesis of that condition. Thus, imaging techniques that utilize radiolabeled positron emission tomographic tracers that bind to the aggregated Aβ peptides in amyloid plaques also assess a core pathological feature of Alzheimer's Disease. Most Aβ plaques in Alzheimer's Disease are described as dense neuritic plaques.

- The best investigated β-amyloid-binding tracer is [^{11}C] Pittsburgh Compound B (referred to as [^{11}C]PIB). When positron emission tomography is performed using this compound, neocortical image patterns show a higher level of radioactivity in those with Alzheimer's Disease than in healthy subjects; these patterns are consistent with the known histopathological distribution of amyloid plaques.

- Although there is evidence that [^{11}C]PIB is effective at imaging Aβ in the brain, the short half-life of 11-C (20 minutes) limits the use of [^{11}C]PIB to

specialized research centers. A radiopharmaceutical labeled with ^{18}F which has a half-life of 110 minutes is more suited to wide use.

- ^{18}F-AV-45 is an amyloid-binding agent currently under development by this sponsor for imaging of β-amyloid plaques using positron emission tomography of the brain. This agent has undergone pre-clinical safety pharmacology and toxicology studies, as well as two Phase I clinical studies in which it has been well-tolerated.

- The usefulness of demonstrating amyloid plaques in the brain by post-mortem histopathological examination is well-established as a means of diagnosing Alzheimer's Disease; indeed, the presence of amyloid plaques, while not entirely specific, is essential for that diagnosis to be made. More specifically, the absence of amyloid plaque pathology at histopathological examination can be used to eliminate Alzheimer's Disease as a possible diagnosis.

- There is no accurate reference standard for the clinical diagnosis of Alzheimer's Disease. The current consensus criteria have high sensitivity (almost 100%), but relatively poor specificity especially in the hands of non-experts

Based on the Agency's *Guidance for Industry. Developing Medical Imaging Drug and Biological Products, Part 2, June 2004*, and on discussions among experts (including recommendations from an ad hoc committee appointed by the Society of Nuclear Medicine), the sponsor has proposed a two-tiered approach to the Phase III development of ^{18}F-AV-45. This approach is summarized in the next table, which I have taken from the submission.

Phase III Objective	Phase III Design	Proposed Indication	Anticipated Clinical Utility
Tier 1			
Demonstrate that ^{18}F-AV-45 positron emission tomography provides an accurate indication of the presence or absence of amyloid plaque	Image end-of-life subjects with and without evidence of cognitive deficits; test if image results correlate with autopsy results	^{18}F-AV-45 is indicated for positron emission tomographic image of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment	Elimination of Alzheimer's Disease from the differential diagnosis in patients with negative ^{18}F-AV-45 scan
Tier 2			
Demonstrate that presence of amyloid plaque (by ^{18}F-AV-45 positron emission tomography) predicts risk of progression in patients with mild cognitive deficits	Image subjects with mild deficits; assess if test results are prognostic of rates of clinical progression	^{18}F-AV-45 is indicated for predicting relative risk of clinical progression in patients with mild cognitive complaints	Closer clinical follow-up and management of patients with mild deficits who positive ^{18}F-AV-45 scans

The approach described under Tier 1 above will be used to secure the initial approval of ^{18}F-AV-45.

5. Support For Each Element Of Proposed Phase III Plan

5.1 Tier I (Proposed Indication: "18F-AV-45 is indicated for positron emission tomographic image of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment")

The sponsor cites the following existing evidence in support of the proposed approach at Tier 1.

- Aβ amyloid is the major component of neuritic plaques
- ^{18}F-AV-45 selectively binds with high affinity to Aβ plaques as demonstrated in the following:
  - Brain homogenates containing amyloid plaques from patients with Alzheimer's Disease
  - *In vitro* autoradiography studies using brain slices from patients with Alzheimer's Disease and transgenic mice containing Aβ amyloid aggregates
  - *In vivo* imaging studies in transgenic mice
  - Limited *in vivo* imaging in patients with Alzheimer's Disease, with the anatomical distribution of the signal corresponding to the typical distribution of neuritic plaques in postmortem Alzheimer's Disease brains
- Amyloid plaques are a hallmark of Alzheimer's Disease; patients without amyloid plaque cannot have Alzheimer's Disease (this view is supported by 100 years of autopsy data, beginning with the original description of that disease by Alzheimer, and by several professional guidelines).

In addition to the results of the currently proposed Phase III study, the sponsor plans to provide the following to support the indication proposed under Tier 1:

- Clinical studies that demonstrate that the ^{18}F-AV-45 signal in patients with Alzheimer's Disease is consistent with the expected accumulation and distribution of neuritic plaques in Alzheimer's Disease
- Clinical studies in cognitively normal elderly subjects demonstrating the range of ^{18}F-AV-45 signal
- Evidence from the medical literature that Aβ is a major component of neuritic plaques in the brain of patients with Alzheimer's Disease and that these plaques are a key pathological component of Alzheimer's Disease
- Studies that demonstrate test-retest and inter-reader reliability and the upper and lower limits for the demonstration of positive and negative scan results
- Non-clinical data and human post-mortem pathology data that correlate the distribution of amyloid plaques with the distribution of ^{18}F-AV-45 in the brain.

A minimum of about 350 subjects are expected to have participated in all clinical trials of ^{18}F-AV-45 with about 50-100 subjects participating in the Phase III trials.

The sponsor believes that the approval of ^{18}F-AV-45 for the indication proposed in Tier 1 will have utility in clinical settings in which the exclusion of Alzheimer's Disease is desired. The studies listed above, including the proposed Phase III protocol, will be insufficient for a definitive interpretation of a positive imaging finding (i.e., an Aβ+ finding).

5.2 Tier 2 (Proposed Indication: "18F-AV-45 is indicated for predicting relative risk of clinical progression in patients with mild cognitive complaints")

The sponsor views the clinical utility of the proposed Tier 2 study, assuming that the proposed indication is supported, as follows:

- A negative imaging result will provide information that the risk of developing Alzheimer's Disease in that subject is low
- A positive imaging result will indicate that the subject is at risk of cognitive deterioration with or without the development of dementia.

The sponsor does acknowledge that even if the Phase III study supports the proposed indication, it will not be capable of predicting the lifetime risk of developing Alzheimer's Disease, given the study's limited duration of 2 years.

The sponsor further states the following:

- The proposed Phase III study will be conducted in the same clinical setting in which the test is intended to be used after the Tier 2 indication is approved, i.e., among patients presenting with mild cognitive deficits to a general practitioner, general neurologist, neurologist specializing in dementia, or memory clinic.

- Approval for the Tier 2 indication is expected to broaden the potential use of this test.

6. Synopses Of Proposed Phase III Trials

6.1 Tier 1 Study (Imaging/Autopsy Phase III Study)

6.1.1 Title

Autopsy verification of ^{18}F-AV-45 positron emission tomographic imaging of amyloid plaque pathology.

6.1.2 Objectives

- To determine whether patients rated as a having a low amyloid burden as demonstrated by ^{18}F-AV-45 imaging show low levels of β-amyloid in the brain at autopsy ("none" or "sparse" according to the Consortium to Establish a Registry for Alzheimer's Disease [CERAD] criteria).

- To determine the correlation between amyloid levels (cortical to cerebellar standardized uptake value ratio [SUVR]) as demonstrated by ^{18}F-AV-45 positron emission tomographic imaging and the plaque count in corresponding areas on autopsy.

6.1.3 Key Inclusion Criteria

- Male or female; age ≥ 50 years
- Terminal medical condition not related to dementia
- Any cognitive status, but about 50% of patients should have a diagnosis of Alzheimer's Disease or Mild Cognitive Impairment.

6.1.4 Study Design

This is an open-label, single-arm study.

About 50-100 patients with terminal medical conditions unrelated to dementia will be enrolled.

Screening assessments are to include collection of demographic information, diagnostic information, Mini-Mental Status Examination, safety assessment, and an MRI scan.

All patients will undergo positron emission tomography of the brain after a single dose (10 mCi) of ^{18}F-AV-45.

All patients will be followed to autopsy and only those patients who undergo autopsy within 6 months following imaging will be included in the statistical analysis.

Autopsy will be performed according to the CERAD guidelines for brain sampling and staining. The frequency of neuritic plaques will be evaluated and scored in 3 categories: sparse, moderate, or frequent; the score will then be correlated with age to derive an age-related score. The number of neuritic plaques per high-powered field will be counted for each slide.

Brain images will be examined both quantitatively and qualitatively:

- Qualitative evaluation: Imaging specialists, blinded to the clinical data, will rate individual image sets as Aβ+ (amyloid positive, Alzheimer's Disease-like) or Aβ- (amyloid negative, not Alzheimer's Disease-like). Limited sequential unblinding may explore the impact of additional information such as age, Mini-Mental Status Examination score, and clinical MRI report on the qualitative interpretation of the images obtained with ^{18}F-AV-45

- Quantitative evaluation: Standardized uptake values will be calculated for the cerebellum, for the sponsor's standard cortical target areas (frontal cortex, temporal cortex, parietal cortex, and precuneus) and for 4 target areas drawn to correspond closely with the regions of interest for CERAD autopsy sampling (superior-middle temporal gyrus, middle frontal gyrus, inferior parietal lobule and anterior cingulate gyrus). Standardized uptake value ratios for cortical target areas relative to the cerebellum will be calculated; a global mean standard uptake value ratio will be calculated from the average across the sponsor's standard cortical target areas and the 4 target areas for autopsy verification.

6.1.5 Methods Of Analysis

The primary analysis will test the hypothesis that the positive predictive value of a low amyloid burden (Aβ-) by ^{18}F-AV-45 imaging and autopsy evaluation (none/sparse) is high.

Secondary analyses will:

- Determine the overall agreement (kappa statistic) between the classification of amyloid burden by ^{18}F-AV-45 imaging (i.e., Aβ+ or Aβ-) and autopsy evaluation (none-sparse/moderate-frequent)

- Test the degree of correlation between plaque burden as measured by cortical to cerebellar standard uptake value ratio and counts per high powered filed in the 4 cortical regions of interest.

6.2 Tier 2 Study (Prognostic Phase III Study)

6.2.1 Title

Evaluation of ^{18}F-AV-45 in subjects with mild cognitive deficits.

6.2.2 Objective

To determine whether patients with mild cognitive deficits and high levels of amyloid, as assessed by ^{18}F-AV-45 imaging, have a significantly higher risk of short-term worsening of impairment than patients with mild cognitive deficits and low levels of amyloid.

6.2.3 Key Inclusion Criteria

- Male or female; age ≥ 50 years

- Complaints of memory or cognitive changes corroborated by an informant

- Clinical Dementia Rating (CDR) of 0.5

- Objective cognitive impairment or marginally normal cognition in a person with a documented history of high cognitive performance
- Normal activities of daily living
- Not demented
- Mini-Mental Status Examination score > 24
- Presenting for initial diagnosis or have been seen for initial diagnosis within the past year

6.2.4 Study Design

This is an open-label, single-arm study.

About 250 patients with mild cognitive deficits will be enrolled in the study.

Screening assessments are to include demographics, diagnostic interview, cognitive testing (a battery of tests is proposed and is listed in the submission: Clinical Dementia Rating, Mini-Mental Status Examination, Alzheimer's Disease Assessment Scale, Wechsler Logical Memory I and II, Digit Symbol Substitution, Category Verbal Fluency, Geriatric Depression Scale and the Alzheimer's Disease Cooperative Study – Activities of Daily Living scale), safety assessment, and MRI scan of the brain.

All patients will undergo positron emission tomography of the brain after a single dose (10 mCi) of ^{18}F-AV-45.

Patients will be evaluated every 6 months for 2 years. At the follow-up visits, the following will be evaluated: adverse events, concomitant medications, cognitive test battery (the same as at screening), and safety.

The presence of clinically significant progression (the primary outcome variable) will be determined by an expert clinician (who will review the results of all psychometric tests and the investigator's progress notes, including diagnosis and concomitant medications). Clinically significant progression will be considered present if one of the following is true:

- The investigator has initiated treatment with an acetylcholinesterase or memantine
- The subject has received a diagnosis of Alzheimer's Disease, confirmed by the expert
- The expert believes that the patient has experienced clinically significant progression whether or not a formal diagnosis of Alzheimer's Disease is given,

based on the notes of the investigator or consistent changes in psychometric or activities of daily living scales.

Brain images (which will be obtained only once at study entry) will be examined both quantitatively and qualitatively:

- Qualitative evaluation: Imaging specialists, blinded to the clinical data, will rate individual image sets as Aβ+ (amyloid positive, Alzheimer's Disease-like) or Aβ- (amyloid negative, not Alzheimer's Disease-like). Limited sequential unblinding may explore the impact of additional information such as age, Mini-Mental Status Examination score, and clinical MRI report.

- Quantitative evaluation: Standardized uptake values will be calculated for the cerebellum, for the sponsor's standard cortical target areas (frontal cortex, temporal cortex, parietal cortex, and precuneus) and for 4 target areas drawn to correspond closely with the regions of interest for CERAD autopsy sampling (superior-middle temporal gyrus, middle frontal gyrus, inferior parietal lobule and anterior cingulate gyrus). Standardized uptake value ratios for cortical target areas relative to the cerebellum will be calculated; a global mean standard uptake value ratio will be calculated from the average across the sponsor's standard cortical target areas and the 4 target areas for autopsy verification.

6.2.5 Methods Of Analysis

The primary analysis will be a comparison of probability of clinically significant progression at 2 years in Aβ+ versus Aβ- subjects (Chi-Square test of proportions, H0: odd ratio = 1).

The sample size estimates under various assumptions for the primary efficacy analysis are summarized in the table below which I have copied from the submission.

Hypothetical proportion of Aβ+ / Aβ- scans in subjects enrolled	1/1		2/1	
Assumed two-year progression rate of total population	7%	12.5%	8.7%	15%
Assumed two-year progression rate of Aβ+ and Aβ- populations	12%, 2%	20%, 5%	12%, 2%	20%, 5%
Calculated Odds Ratio for Progression of Aβ+ / Aβ- subjects	6.7 : 1	4.8 : 1	6.7 : 1	4.8 : 1
Sample size required to reach $p<0.05$ (80% power)	204	152	245	180

Secondary analyses will:

- Further analyze the factors within the above composite outcome and will determine whether the probability of 2-year conversion to Alzheimer's Disease or any other type of dementia is different from Aβ+ versus Aβ-subjects
- Determine whether quantitative measures derived from the ^{18}F-AV-45 imaging signal with receiver operating characteristics (ROC) type cutoffs yield an increased sensitivity to predict conversion
- Determine whether qualitative or quantitative image analysis predicts and correlates with the rate of cognitive decline

7. Sponsor's Questions For Advisory Committee

These are copied below.

1. Do the experts concur that evaluation of amyloid plaques (e.g. at autopsy) is well validated as *sine qua non* for the definitive diagnosis of AD?
    a. Do the experts concur that the proposed development plan would validate ^{18}F-AV-45 as an in vivo marker for amyloid plaque pathology?
    b. If not, how should amyloid plaque-binding PET agents be validated as markers for amyloid plaque pathology?
2. Is there sufficient evidence to conclude that knowledge of a patient's amyloid plaque pathology would be clinically useful in certain defined clinical settings? e.g.
    a. Patients with dementia of uncertain etiology?
        i. Elimination of AD as a potential diagnosis in patients who are plaque negative?
        ii. Increasing consideration of AD as a potential diagnosis in patients who are plaque positive?
    b. Patients with mild memory deficits?
        i. Providing prognostic value in patients who are plaque negative (lower risk of progression to dementia)?
        ii. Providing prognostic value in patients who are plaque positive (higher risk of progression to dementia)?
3. Should a safe and effective amyloid plaque-avid PET agent be approvable as a tool for imaging amyloid plaques?

8. Sponsor's Responses To Potential Critiques Of Proposed Phase III Program

The sponsor has anticipated a number of potential critiques of the development program.

The individual potential critiques of the development program and the sponsor's response to each are summarized below.

Item #1	Potential Critique	Sponsor's Response (summarized)
1	The Tier 1 plan does not assess ^{18}F-AV-45 in the population of intended use	The patients enrolled in the Tier 1 study do not have end-stage Alzheimer's Disease, merely end-stage co-morbidities The intended use population is to be studied in Phases I and II. The images seen in the intended use population will be compared with those in the end-of-life population enrolled in the Phase III study and the significance of any differences will be evaluated There is no other practical means of correlating imaging data with the gold standard (i.e., pathological confirmation of the disease)
2	^{18}F-AV-45 may detect different types of amyloid some of which may not be related to Alzheimer's Disease	The diagnostic value of a negative scan is therefore to be emphasized: a patient negative for all amyloid pathology cannot have neuritic plaques and therefore cannot have Alzheimer's Disease. The true diagnostic value of a positive scan cannot be addressed in the context of the Tier 1 trial. The utility of a positive scan as a risk stratification tool will be addressed in the Tier 2 trial
3	Fibrillary amyloid aggregates can be detected in different types of amyloid plaque and in cerebral amyloid angiopathy	The diagnostic value of a negative scan has thus been emphasized. The diagnostic value of a positive scan is a subject for further investigation
4	A patient with a negative scan who lacks neuritic plaques may still get Alzheimer's Disease in the future	The imaging test can only provide information about current brain pathology and current diagnosis
5	The Tier 2 study is likely to have relatively low risks of conversion to Alzheimer's Disease. For example, in those with a mild cognitive deficit, a positive scan may predict a ~ 20% conversion rate and a negative scan may predict a ~ 5% conversion rate, not a major difference	Relative risk is to be emphasized in the analysis of the Tier 2 study results. "In a short duration trial of an insidiously progressive disease, any significant separation between conversion rates in the two groups indicates prognostic values for the test."

9. Comments

9.1 Summary Of Submission

This submission, which has been received as a consultation from the Division of Medical Imaging and Hematology Products (DMIHP), and consists of a summary of the sponsor's clinical development program for ^{18}F-AV-45, an agent that is being developed for imaging of β-amyloid, using positron emission tomography.

The sponsor's current submission has been prepared as a Position Paper for an Advisory Committee meeting convened by this Agency to discuss the design of Phase III studies of imaging agents that are under development for the diagnosis of Alzheimer's Disease.

In this submission, the sponsor has drawn attention to the following:

- The diagnosis of Alzheimer's Disease based on the consensus criteria is fairly accurate in expert hands when compared against the pathological diagnosis, the gold standard. However, given the high prevalence of Alzheimer's Disease, it is not practical to refer all those suspected of that condition to an expert; thus, a diagnostic aid that could help community physicians distinguish those patients who do not have

Alzheimer's Disease from those needing further evaluation would be very useful, as would an aid to the diagnosis of those at high risk of developing Alzheimer's Disease who do not actually have that condition.

- Aβ plaques are a histopathological hallmark of Alzheimer's Disease, and play a key role in the pathogenesis of that condition. Thus, imaging techniques that utilize radiolabeled positron emission tomographic tracers that bind to the aggregated Aβ peptides in amyloid plaques also assess a core pathological feature of Alzheimer's Disease.

- The best investigated β-amyloid-binding tracer is [^{11}C] Pittsburgh Compound B (referred to as [^{11}C]PIB); positron emission tomography of the brain with this agent reveals an uptake pattern that is consistent with the known distribution of amyloid plaques on histopathological examination. However, 11-C has a short half-life, therefore limiting its use to specialized facilities; a β-amyloid imaging agent labeled with 18-F which has a longer half-life, such as ^{18}F-AV-45, is thus likely to have wider clinical application

- The presence of amyloid plaques is essential, albeit not entirely specific for making a histopathological diagnosis of Alzheimer's Disease. The corollary of that statement is that the absence of amyloid plaques on histopathological examination can rule out the presence of Alzheimer's Disease; that concept is to form the basis for the initial segment (Tier 1) of the sponsor's Phase III development program. As a second step (Tier 2) in Phase III development, the sponsor is to attempt to determine whether the presence of amyloid plaques on imaging in individuals with cognitive impairment short of overt dementia is predictive of subsequent deterioration. The overall Phase III program, including its clinical utility and the indications that it is expected to lead to, is summarized in the following table

Phase III Objective	**Phase III Design**	**Proposed Indication**	**Anticipated Clinical Utility**
Tier 1			
Demonstrate that ^{18}F-AV-45 positron emission tomography provides an accurate indication of the presence or absence of amyloid plaque	Image end of life subjects with and without evidence of cognitive deficits; test if image results correlate with autopsy results	^{18}F-AV-45 is indicated for positron emission tomographic image of amyloid plaque pathology in the brain to aid in the evaluation of patients with signs or symptoms of cognitive impairment	Elimination of Alzheimer's Disease from the differential diagnosis in patients with negative ^{18}F-AV-45 scan
Tier 2			
Demonstrate that presence of amyloid plaque (by ^{18}F-AV-45 positron emission tomography) predicts risk of progression in patients with mild cognitive deficits	Image subjects with mild deficits; assess if test results are prognostic of rates of clinical progression	^{18}F-AV-45 is indicated for predicting relative risk of clinical progression in patients with mild cognitive complaints	Closer clinical follow-up and management of patients with mild deficits who have positive ^{18}F-AV-45 scans

- Possible critiques of the sponsor's development program have been addressed in the submission.

9.2 Additional Comments

The concepts underlying the sponsor's proposed Phase III studies appear on their face to be valid ones, but do merit further detailed discussion at the Advisory Committee meeting.

It is noteworthy that the Tier 1 Phase III study is to be conducted in patients with terminal illnesses unrelated to dementia, and not those in whom the test is intended to be used; if the results of that study support the sponsor's primary hypothesis, imaging with ^{18}F-AV-45 is to be used to exclude a diagnosis of Alzheimer's Disease in those presenting primarily to a community-level physician with symptoms or signs of cognitive impairment. While there appears to be no alternative to the proposed study design if establishing a correlation between imaging and histopathological findings is the purpose of the study, the implications of that discrepancy between the population in whom the efficacy of imaging with ^{18}F-AV-45 is to be assessed and the population to whom the test is to be clinically applicable warrant detailed discussion; currently, the sponsor proposes to address that discrepancy by comparing images obtained in Phase I and II studies conducted in the population of intended use with those obtained in the Phase III study.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 9/17/08
cc:
HFD-120
IND 79511 (005)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research

Date: September 15, 2008

From: Russell G. Katz, M.D.
Division Director

Subject: [F–18] AV1/ZK
IND #78868 (007)
Proposed Indication: Diagnosis of Alzheimer's Disease
Outline of Clinical Development Plan

To: Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

IND (Serial Number)	**78868 (007)**
Sponsor:	**Bayer HealthCare**
Drug:	**[F-18] AV1/ZK**
Proposed Indication:	**Alzheimer's Disease**
Material Submitted:	**Briefing Document**
Correspondence Date:	**5/15/08**
Date Received By Reviewer:	**7/29/08**
Date Review Completed	**9/15/08**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission, which has been received as a consultation from the Division of Medical Imaging and Hematology Products (DMIHP), consists of a summary of the sponsor's proposed clinical development program for [F-18] AV1/ZK.

[F-18] AV1/ZK is being developed for the *in vivo* imaging of β-amyloid in the brain and is also referred to as BAY 94-9172. The sponsor considers the program proposed in this submission to be applicable to putative β-amyloid imaging agents as a class.

This submission is in response to a letter, dated March 14, 2008, from DMIHP to sponsors of imaging agents being developed for the diagnosis of Alzheimer's Disease; that letter stated that an Agency Advisory Committee meeting was being scheduled to provide advice regarding the design of Phase III studies of such imaging agents, and invited sponsors to submit proposals for the design of such studies. The current submission has been prepared as a Briefing Document for that meeting. The Advisory Committee meeting has now been scheduled for October 23, 2008.

2. Contents Of Submission

This submission contains 3 main items:

- Cover letter
- Outline of Clinical Development Plan
  - Background
  - Neuropathological features of Alzheimer's Disease
  - Clinical diagnosis – methodology and the importance of early and accurate diagnosis
  - Biomarkers, structural and functional imaging studies
  - Positron emission tomographic amyloid-targeted imaging

  - F-18 labeled positron emission tomography tracers
  - Possible indications to be studied with amyloid-targeted positron emission tomographic tracers
  - General approach to be followed in the development of positron emission tomographic amyloid tracers

- Outline of Phase III Study Protocol.

3. Contents Of Review

The contents of this submission will be reviewed under the following main headings:

- Sponsor's outline of clinical development plan for [F-18] AV1/ZK
- Protocol for Phase III study
- Comments.

4. Sponsor's Outline Of Clinical Development Plan For [F-18] AV1/ZK

The sponsor's outline has been summarized using headings that are similar to those used by the sponsor.

4.1 Background

In this section, the sponsor draws attention to the high prevalence of Alzheimer's Disease, and to the considerable medical and other costs associated with that condition.

4.2 Neuropathological Features Of Alzheimer's Disease

The following is a summary of what is stated by the sponsor under this heading:

- The definitive diagnosis of Alzheimer's Disease is based on histopathological examination of the brain
- The distinctive neuropathological features of Alzheimer's Disease are the presence of neurofibrillary tangles and amyloid plaques, and the occurrence of neocortical neuronal degeneration.
- Amyloid plaques may sometimes be seen in dementias that are less frequent than Alzheimer's Disease, such as Dementia with Lewy Bodies, and in a small proportion of non-demented subjects > 75 years old
- In patients with frontotemporal dementia, the deposition of β-amyloid in the brain is rare.

4.3 Clinical Diagnosis – Methodology And The Importance Of Early Diagnosis

The sponsor states the following:

- The diagnosis of Alzheimer's Disease in a living patient requires thorough clinical assessment by a clinician experienced in dementia
- The most-widely accepted and established diagnostic criteria for Alzheimer's Disease are the NINCDS-ADRDA criteria
- If the NINCDS-ADRDA and DSM IV-TR criteria are applied together, Alzheimer's Disease can be diagnosed with "reasonably" high accuracy, even in mildly impaired patients
- The process for diagnosing Alzheimer's Disease can, however, be time-consuming and difficult, especially if confounded by the presence of entities such as depression or a high intelligence quotient
- Alzheimer's Disease may not be recognized, even by specialists, particularly if it is in its early stages or if mixed pathology is present
- The timely and accurate diagnosis of Alzheimer's Disease is important in alleviating uncertainty, avoiding further unnecessary investigation, and in alleviating symptoms; it has now become particularly important with the development of (putative) disease-modifying agents.

4.4 Biomarkers, And Structural And Functional Imaging Studies

The use of the following diagnostic modalities is discussed:

- Cerebrospinal fluid examination for $A\beta_{1-42}$, total tau, and phosphorylated tau
- Qualitative and quantitative magnetic resonance imaging of the brain
- Single photon emission computed tomography of the brain using [^{99}Tc] HMPAO
- Positron emission tomography of the brain using [F-18] fluorodeoxyglucose

The results of the above tests in patients with Alzheimer's Disease, as described in the medical literature, including their sensitivity and specificity, when available are outlined.

As also outlined by the sponsor, the tests listed above have:

- Not yet been validated in prospective clinical trials
- Major limitations.

4.5 Amyloid-Targeted Positron Emission Tomography

As stated by the sponsor:

- Since the extracellular deposition of β-amyloid is an important and early event in the pathogenesis of Alzheimer's Disease, an imaging marker that can detect β-amyloid in the brain will help in the early (and accurate) detection of that condition.
- The best investigated β-amyloid-binding tracer is [^{11}C] Pittsburgh Compound B (referred to as [^{11}C]PIB). When positron emission tomography is performed using this compound, neocortical image patterns in those with Alzheimer's Disease differ significantly from those in healthy subjects; in patients with Alzheimer's Disease, there was a higher retention of the compound in those areas known, on

the basis of histopathology, to have amyloid plaques in patients with Alzheimer's Disease than in healthy subjects, while in other areas of the brain, retention patterns were similar in those with Alzheimer's Disease and in healthy subjects.

- Although there is evidence that [^{11}C]PIB is effective at imaging Aβ in the brain, the short half-life of 11-C (20 minutes) limits the use of [^{11}C]PIB to centers with an on-site cyclotron. A radiopharmaceutical with a longer half-life than [^{11}C]PIB is therefore required. Such an agent is best labeled with ^{18}F which has a half-life of 2 hours, and can therefore be used more widely.

4.6 ^{18}F-Labeled Positron Emission Tomography Tracers

The sponsor's summary is as follows:

- Several ^{18}F-labeled tracers have been shown to have a high *in vitro* affinity for β-amyloid.

- Limited clinical studies have also demonstrated significant differences in the neocortical uptake pattern of these tracers between patients with Alzheimer's Disease and healthy subjects, with the patterns between similar to those seen with [^{11}C]PIB. It is possible to reliably distinguish images from subjects with Alzheimer's Disease from those from healthy subjects and those with frontotemporal dementia by visual inspection alone.

- The validity of imaging with ^{18}F-labeled tracers that bind to β-amyloid in enabling an earlier and more accurate diagnosis of Alzheimer's Disease needs to be established as follows (and in the same sequence?):

  - Effectiveness at different stages of Alzheimer's Disease
  - Distinguishing well-manifest Alzheimer's Disease from normal non-demented subjects
  - Distinguishing early Alzheimer's Disease from normal ageing
  - Distinguishing Alzheimer's Disease from non-Alzheimer's dementia

4.7 Possible Indication To Be Studied With Amyloid-Targeted Positron Emission Tomographic Tracers

The sponsor points out that while Aβ plaques are sometimes seen pathologically in dementias other than Alzheimer's Disease, and even in non-demented elderly subjects, Alzheimer's Disease is the only dementia consistently associated with plaque deposition. The sponsor therefore suggests that the following indication may be appropriate for [F-18] AV1/ZK.

"The tracer can detect β-amyloid plaque deposition in the brain. In the absence of uptake (and thus β-amyloid deposition), Alzheimer's Disease can be excluded."

Note that elsewhere in this submission the sponsor has stated that the detection of this pathology must be determined to be clinically useful.

4.8 General Approach To Be Followed In The Development Of Positron Emission Tomographic Amyloid Tracers

The sponsor proposes that after initial verification of the efficacy and safety of [F-18] AV1/ZK in one or more clinical trials, the further development program should follow the recommendations made in the *Agency's Guidance for Industry. Developing Medical Imaging Drug and Biological Products, Parts 1, 2, and 3, June 2004*.

The proposed aims of Phase I, II and III trials are outlined by the sponsor. Those aims that are related to the safety and pharmacokinetics of the product and to the methods of image acquisition are not listed in this review. The objectives that are related to the evaluation of efficacy are summarized below

Study Phase	Populations to be Studied and Aims Pertinent to this Review
II	The populations to be studied are those with Alzheimer's Disease and healthy non-demented subjects The aim of this phase is to provide further evidence of efficacy The sensitivity of imaging with the amyloid-binding agent will be derived from patients with Alzheimer's Disease The specificity of imaging with the amyloid-binding agent will be derived from healthy subjects
III	The populations to be studied are those with Alzheimer's Disease and healthy non-demented subjects ("subjects included in these studies should be representative of the population in which the imaging agent is intended to be used") The aim of this phase is to confirm efficacy (i.e., the hypotheses developed in earlier studies)

5. Protocol For Phase III Study

A synopsis of a protocol for a Phase III efficacy study for a generic β-amyloid imaging agent has been provided by the sponsor, and is further summarized below.

5.1 Title

An open-label, non-randomized, multi-center Phase III study to evaluate the efficacy and safety of the positron emission tomographic amyloid-targeted tracer for detection/exclusion of amyloid in subjects with Probable Alzheimer's Disease and other forms of dementia compared to cognitively-normal healthy volunteers.

5.2 Objectives

5.2.1 Primary

To determine the sensitivity and specificity of the independent visual assessment of tracer uptake pattern in detecting/excluding cerebral amyloid in subjects with Probable Alzheimer's Disease as compared with cognitively-normal healthy subjects.

5.2.2 Secondary

To determine the accuracy, positive predictive value, and negative predictive value of the visual assessment of tracer uptake pattern in detecting/excluding cerebral amyloid when compared to the clinical diagnosis as the standard of truth.

Descriptive analysis of the distribution of normal versus abnormal uptake pattern and/or quantitative data obtained in dementia "subtypes" (e.g., Dementia with Lewy Bodies, frontotemporal dementia).

To assess the on-site dementia expert's ability to establish a diagnosis with and without knowledge of the scan results, the respective confidence of diagnosis thereof, and the impact of scan findings on (clinical?) management decisions.

To confirm the safety of a single dose of imaging tracer.

5.3 Design

This is an open-label, non-randomized, single-dose study.

5.4 Key Inclusion Criteria

(The list of criteria below does NOT include all those listed by the sponsor).

- Male or female
- Age: 55 to 90 years
- Patients with dementia must fulfill the DSM-IV criteria for that diagnosis, and must satisfy at least one of the following sets of diagnostic criteria
    - The NINCDS-ADRDA criteria for Probable Alzheimer's Disease
    - The International Consensus Criteria for Dementia with Lewy Bodies
    - The NINDS-AIREN criteria for <u>possible</u> vascular dementia
    - The Neary criteria for frontotemporal dementia
- Mini-Mental Status Examination score within a range to be determined (presumably only for those with dementia)

- Clinical Dementia Rating scale score within an unspecified range for patients with dementia. Clinical Dementia Rating scale score of zero for healthy subjects.

5.5 Key Exclusion Criteria

(The list of criteria below does NOT include all those listed by the sponsor).

- Evidence of major cerebrovascular disease on imaging and/or probable vascular dementia by the NINDS-AIREN criteria
- Persistent severe depression
- Normal pressure hydrocephalus.

5.6 Outcome Measures And Analysis Methods

For all patients with dementia and for healthy subjects enrolled in the trial, the results of the independent assessment of the positron emission tomographic images will be compared with the clinical diagnosis as the standard of truth.

The primary efficacy parameters for the study are the sensitivity and specificity of the "visual assessment" (qualitative visual impression as opposed to quantitative analysis?) of the positron emission tomographic images in enabling the correct differentiation between subjects with Alzheimer's Disease and healthy subjects (based on the presence or absence of uptake of radiopharmaceutical) when compared to the clinical diagnosis as the standard of truth.

<u>The diagnosis of Probable Alzheimer's Disease is to be used as the standard of truth for calculating sensitivity. The presence of a cognitively-normal healthy state (by clinical assessment) is to be used as the standard of truth for calculating specificity.</u>

The clinical determination of the presence of Probable Alzheimer's Disease and the cognitively-normal healthy state is to be based on the consensus opinion of a panel of experts. The positron emission tomographic scans will be read by (other) experts who will be blinded to clinical data.

Sample size estimates are to be based on hypothesis testing where both the sensitivity and specificity of the imaging tracer in the detection of Alzheimer's Disease and healthy subjects (respectively) are greater than the specified thresholds.

The null hypothesis tests for both sensitivity and specificity are each designated as:

H_0: $p \leq p_0$ (where p_0, the specified threshold, is the sensitivity or specificity corresponding to the clinical diagnosis without access to imaging).

The alternative hypothesis tests for both sensitivity and specificity are designated as:

H_1: $p > p_0$

6. Comments

6.1 Summary Of Submission

This submission, which has been received as a consultation from the Division of Medical Imaging and Hematology Products (DMIHP), consists of a summary of the sponsor's proposed clinical development program for [F-18] AV1/ZK, an agent that is being developed for imaging of β-amyloid using positron emission tomography. The sponsor considers the program proposed in this submission to be applicable to putative β-amyloid imaging agents as a class.

The sponsor's current summary has been prepared as a Briefing Document for an Advisory Committee meeting convened by this Agency to discuss the design of Phase III studies of imaging agents that are under development for the diagnosis of Alzheimer's Disease.

In this submission, the sponsor has drawn attention to the following:

- Alzheimer's Disease has a high prevalence and is linked to significant medical and other costs
- The definitive diagnosis of Alzheimer's Disease is based on histopathological examination of the brain
- Amyloid plaques are an essential (and early) pathological feature of Alzheimer's Disease, although they may also be seen with lesser frequency in other clinical settings
- The most widely-accepted means of diagnosing Alzheimer's Disease, short of histopathological examination of the brain, is through application of the NINCDS-ADRDA criteria which when combined with the DSM IV-TR criteria have a high degree of accuracy, but are not without their limitations. An accurate means of diagnosing Alzheimer's Disease, particularly in its early stages is needed
- Currently used brain imaging and biochemical tests for Alzheimer's Disease have not been clinically validated and have major limitations
- An imaging technique that can detect β-amyloid in the brain can provide both an early and an accurate means of diagnosing Alzheimer's Disease

- The best investigated β-amyloid-binding tracer is [^{11}C] Pittsburgh Compound B (referred to as [^{11}C]PIB); positron emission tomography of the brain with this agent reveals an uptake pattern that is consistent with the known distribution of amyloid plaques on histopathological examination. However, 11-C has a short half-life, therefore limiting its use to facilities with an on-site cyclotron; a β-amyloid imaging agent labeled with 18-F, which has a longer half-life, is thus likely to have wider commercial application

The sponsor has proposed that β-amyloid imaging agents be developed for the following indication

> *"The tracer can detect β-amyloid plaque deposition in the brain. In the absence of uptake (and thus β-amyloid deposition), Alzheimer's Disease can be excluded."*

A general approach to developing β-amyloid imaging radiopharmaceuticals through Phases I, II, and III has been suggested by the sponsor.

A proposal for a Phase III protocol to evaluate the efficacy of a generic β-amyloid imaging agent, using positron emission tomography, has also been outlined by the sponsor. This is an open-label, non-randomized, single-dose study whose primary objective is to determine the sensitivity and specificity of the uptake pattern of the imaging agent in detecting/excluding the presence of cerebral amyloid in subjects with Probable Alzheimer's Disease and in healthy subjects respectively. The diagnosis of Probable Alzheimer's Disease is to be used as the standard of truth for calculating sensitivity; the presence of a cognitively-normal healthy state (by clinical assessment) is to be used as the standard of truth for calculating specificity. In addition to patients with Probable Alzheimer's Disease and healthy subjects, those with Dementia with Lewy Bodies, frontotemporal dementia, and possible vascular dementia are to be enrolled; the performance of brain imaging with the β-amyloid imaging agent in the latter groups is to be evaluated in this study on an exploratory basis only.

6.2 Additional Comments

A primary objective of the Phase III study proposed in this submission is to evaluate the efficacy of brain imaging (using positron emission tomography) with a β-amyloid imaging agent by determining the sensitivity and specificity of blinded visual assessment of the uptake pattern for that agent using the clinical diagnosis of Probable Alzheimer's Disease from the NINCDS-ADRDA criteria as the standard of truth for calculating sensitivity, and the determination of a cognitively-normal state for calculating specificity. Unless it can be established that the clinical diagnosis of Probable Alzheimer's Disease is equivalent to the presence of β-amyloid plaques in the brain (i.e., the clinical diagnosis of Probable Alzheimer's Disease represents the same standard of truth as the presence of β-amyloid plaques), and the presence of a cognitively-normal state as the standard of truth for the absence of β-amyloid plaques, it is unclear how the planned study

will be adequate to support the approval of that agent for the purpose intended by the sponsor

Under the Phase III protocol proposed by the sponsor, the sensitivity and specificity of brain imaging with the β-amyloid imaging agent can at best be demonstrated to be no better than the current clinical diagnosis, albeit one made by experts. Under those circumstances, the clinical utility of imaging with such an agent as a more accurate means of diagnosing Alzheimer's Disease or excluding the presence of that disorder are questionable.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 9/15/08
cc:
HFD-120
IND 78868 (007)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Division of Neurology Products (HFD – 120)
Center for Drug Evaluation and Research

Date: September 11, 2008

From: Russell G. Katz, M.D.
Division Director

Subject: GE-067 ([^{18}F]AH110690) Injection
Pre-IND #101866 (004)
Proposed Indication: Diagnosis of Alzheimer's Disease
Outline of Clinical Development Plan

To: Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Document Type: Consult

Enclosed is the Division's response to your request

Review and Evaluation of Clinical Data

Pre-IND (Serial Number)	**101866 (004)**
Sponsor:	**GE Healthcare**
Drug:	**GE-067 ([^{18}F]AH110690)**
Proposed Indication:	**Diagnosis Of Alzheimer's Disease**
Material Submitted:	**Consult**
Correspondence Date:	**6/27/08**
Date Received By Reviewer:	**7/29/08**
Date Review Completed	**9/11/08**
Reviewer:	**Ranjit B. Mani, M.D.**

1. Background

This submission, which has been received as a consultation from the Division of Medical Imaging and Hematology Products (DMIHP), and consists of a summary of the sponsor's clinical development program for [^{18}F]AH110690. [^{18}F]AH110690 is being developed for *in vivo* imaging of β-amyloid, as a single-dose injection.

AH110690 is now also referred to as GE-067 by the sponsor.

The submission is in response to a letter, dated March 14, 2008, from DMIHP to sponsors of imaging agents being developed for the diagnosis of Alzheimer's Disease; that letter stated that an Agency Advisory Committee meeting was being scheduled to provide advice regarding the design of Phase III studies of such imaging agents. The current submission has been prepared as a Briefing Document for that meeting. The Advisory Committee meeting has now been scheduled for October 23, 2008.

An earlier consultation on a Briefing Package for a Pre-IND meeting on the same product was completed by this Division on May 13, 2008. Please see that consultation for further details. A representative of this Division also attended the Pre-IND (Type C) meeting between DMIHP and the sponsor on May 19, 2008.

In this review, the names "AH110690 / [^{18}F]AH110690" and "GE-067" are used interchangeably. The names "Aβ" and "β-amyloid" are also used interchangeably.

2. Contents Of Submission

The main contents of this submission are as follows:

- Cover letter

- FDA Advisory Committee Meeting Briefing Document (with the following main headings)

  - Introduction
  - Background to Amyloid Pathology
  - Development of the Amyloid Imaging Concept
  - Clinical Utility of Amyloid Imaging Agents
  - Requirements for Development of Radiopharmaceutical Imaging Agents
  - Pittsburgh Compound B as a Standard of Truth for the Presence of Cerebral Amyloid
  - Clinical Development Plan

3. Contents Of Review

The contents of this submission will be reviewed under the following headings and in the same order as below. The headings are similar to those used in the Briefing Document.

- Introduction (in Briefing Document)
- Background to amyloid pathology
- Development of amyloid imaging concept
- Clinical utility of amyloid imaging agents
- Requirements for development of radiopharmaceuticals
- Pittsburgh Compound B imaging as the standard of truth for the presence of cerebral amyloid
- Clinical development plan
- Comments.

4. Introduction (In Briefing Document)

In this section of the Briefing Document, the sponsor refers to:

- The letter, dated March 14, 2008, from DMIHP to sponsors of imaging agents being developed for the diagnosis of Alzheimer's Disease stating that an Agency Advisory Committee meeting was being scheduled to provide advice regarding the design of Phase III studies for the same indication
- A letter from the sponsor, dated April 24, 2008, confirming its intention of participating in the planned Advisory Committee meeting and in providing a summary of the clinical development plan for [^{18}F]AH110690

- Discussions at the Pre-IND (Type C) meeting held on May 19, 2008.

5. Background To Amyloid Pathology

The contents of this section of the Briefing Document may be summarized as follows:

- Beta-amyloid deposition is one of several characteristic pathological features of Alzheimer's Disease, but is not unique to that condition; it may be seen, for example, in Dementia with Lewy Bodies, and cerebral amyloid angiopathy. β -amyloid deposition is not, however, associated with frontotemporal dementia or its variants.

- While the exact role of β-amyloid deposition in the pathogenesis of Alzheimer's Disease is unclear, most current theories about the pathophysiology of Alzheimer's Disease hold that the role of β-amyloid deposition is central. The structure of β-amyloid and its potential role in the pathogenesis of Alzheimer's Disease are further described.

- [^{18}F]AH110690 binds to extracellular insoluble Aβ so that it primarily detects plaques and not soluble Aβ elements. [^{18}F]AH110690 shows no binding to tau, and thus does not image neurofibrillary tangles.

- Currently, the standard of truth for confirming brain amyloid deposition in patients is through post-mortem histological examination of the brain. Several sets of criteria have been proposed for the post-mortem diagnosis of Alzheimer's Disease, among which the National Institute of Aging – Reagan criteria are the most recent.

- In current clinical practice, the diagnosis of Alzheimer's Disease is based on a combination of the clinical history, physical examination, neurological and neuropsychological assessments and standard imaging, followed by categorization as either Probable or Possible Alzheimer's Disease based on the NINCDS-ADRDA criteria. These criteria have been evaluated against neuropathological standards and have a sensitivity ranging from 65% to 96% and a specificity ranging from 23% to 88%.

- The accuracy and specificity of the above diagnosis can be improved by the use of diagnostic tests such as ApoE ε4 genotyping, measurement of cerebrospinal fluid tau or $A\beta_{1-42}$ levels, and imaging techniques such as computed tomography, magnetic resonance, and fluorodeoxyglucose positron emission tomography.

6. Development Of Amyloid Imaging Concept

The sponsor's description may be summarized as follows:

- Most studies directed at imaging β-amyloid in the brain have been conducted using positron emission tomography with ^{11}C-labeled Pittsburgh Compound B, also referred to as [^{11}C]PIB.

- The development of [^{11}C] PIB as an agent for imaging β-amyloid in the brain is described (see the submission for further details).

- While ^{11}C is advantageous as a research tool for positron emission tomographic imaging since it can incorporated into a number of organic molecules, the half-life of ^{11}C is 20 minutes which renders its manufacture and distribution to institutions with facilities for positron emission tomography impractical (an on-site cyclotron is required). Therefore, an ^{18}F-labeled compound, [^{18}F]AH110690, which is closely related in structure and binding properties to Pittsburgh Compound B), and has a half-life of 110 minutes, has been developed.

7. Clinical Utility Of Amyloid Imaging Agents

I have interpreted the sponsor's view of the potential utility of cerebral amyloid imaging (in summary) as follows. Cerebral amyloid imaging may have value in:

- Diagnosing disorders of cognitive impairment in which amyloid deposition occurs in the brain and characterizing their natural history; here the sponsor believes that amyloid imaging should be part of a diagnostic algorithm, not the sole basis of diagnosis.

- Evaluating the effects of treatment in conditions in which amyloid deposition occurs in the brain.

8. Requirements For Development Of Radiopharmaceuticals,

The sponsor first draws attention to the usual key features of the design of studies intended to evaluate the efficacy of pharmaceutical agents. These elements include the following:

- The use of a control agent
- Randomization
- A sufficiently large sample size
- Blinding of patients, observers, and analysts
- Replication of study results.

The basis for requiring that the above be part of the design of key efficacy studies in Alzheimer's Disease has been explained by the sponsor, who also points out that the same elements are incorporated into the US Code of Federal

Regulations, and into various International Committee on Harmonization Guidance documents.

For medical imaging agents and modalities, however, other considerations apply, as per the sponsor:

- Imaging generates quantifiable data and placebo effects are generally unknown. Control agents are therefore not generally used, although a no-treatment concurrent control may be incorporated into the study design if feasible (for radiopharmaceuticals, that is not feasible). In the absence of a control arm, randomization and masking of the identity of the administered agent are not possible.

- The ability of imaging to provide clinically valuable information is assessed by comparison of data derived from imaging with that derived from a standard of truth (defined as an independent test believed to be the most accurate available). Summary test statistics, sensitivity, specificity, positive predictive value, and negative predictive value are derived from that comparison.

For [^{18}F]AH110690, based on the second consideration above:

- Sensitivity will indicate the proportion of patients for whom that agent shows a positive Aβ burden, among those known (or believed) to have the same pathology based on the standard of truth
- Specificity will indicate the proportion of patients for whom the agent shows no appreciable Aβ burden among patients known (or believed) to not have the same pathology based on the standard of truth

The sponsor believes that it is important for those interpreting images to be blinded to clinical data about each study subject.

9. Pittsburgh Compound B Imaging As The Standard Of Truth For The Presence Of Cerebral Amyloid

The sponsor proposes that imaging with [^{11}C]PIB be used as the standard of truth for evaluating the utility of [^{18}F]AH110690 in detecting brain amyloid. The basis for this proposal may be summarized as follows.

- *In vitro* studies using post-mortem brain slices and brain homogenates from patients with Alzheimer's Disease, as well as post-mortem brain tissues from patients with other diseases not associated with β-amyloid deposition and from healthy controls indicate the high specificity with which [^{11}C]PIB binds to β-amyloid. Studies using brain homogenates, and a study of a transgenic mouse model that over-expresses Aβ also indicate that the extent of [^{11}C]PIB binding reflects the amount of brain amyloid present.

- Published individual cases and case series of patients with Alzheimer's Disease who have undergone imaging with [^{11}C]PIB and subsequent examination of the brain at autopsy also indicate that the binding of that radiopharmaceutical is

highly specific for the presence of plaques. A correlation has also been demonstrated between the presence of amyloid on brain biopsy and a positive signal on [^{11}C]PIB in another case series

- In case series of patients with amnestic Mild Cognitive Impairment, [^{11}C]PIB retention was higher than in controls. The regional pattern of [^{11}C]PIB retention resembled that of Alzheimer's Disease in a substantial proportion of patients. In some studies, the regional pattern of [^{11}C]PIB retention in patients with amnestic Mild Cognitive Impairment, when it resembled that of Alzheimer's Disease, correlated with the later development of overt Alzheimer's Disease.

Evidence supporting the validity of [^{11}C]PIB as a standard of truth is to be obtained by the sponsor from the following sources:

- A summary of 65 peer-reviewed studies of the medical literature
- A "meta-analysis" of the clinical literature to demonstrate concordance of the amyloid signal in both patients and controls
- The interpretation of multiple [^{11}C]PIB scans pooled from academic sites by readers blinded to clinical data (to demonstrate the ability to blinded readers to term a [^{11}C]PIB scan either "positive" or "negative" for amyloid retention)
- Correlations between autopsy data and results of antemortem [^{11}C]PIB scans.

10. Clinical Development Plan

The following is an outline of the clinical development plan for [^{18}F]AH110690 as proposed by the sponsor.

[Note that limited clinical studies with both [^{11}C]AH110690 and [^{18}F]AH110690 that had been conducted earlier by the sponsor were summarized in the Pre-IND Briefing Package whose review was completed by this Division in consultation on May 13, 2008. Please see that review for further details. None of these investigations could be considered by design to be a major study directed at the objectives of the current development program for [^{18}F]AH110690]

10.1 Background

The sponsor has outlined 3 elements of the development of [^{18}F]AH110690 that it considers critical, based on advice provided earlier by the Agency.

10.1.1 Standard Of Truth

While the ultimate standard of truth for confirming deposition of Aβ is at autopsy, the use of such a standard is impractical in a product development program. Instead the sponsor proposes that demonstration of amyloid deposition with [^{11}C]PIB imaging serve as the standard of truth.

The sponsor hopes that the Advisory Committee will answer the following questions:

- Can [^{11}C]PIB serve as the standard of truth for registration of Aβ imaging agents such as [^{18}F]AH110690?
- What information would be needed to establish [^{11}C]PIB as a suitable standard of truth?

10.1.2 Clinical Utility

The sponsor seeks to have [^{18}F]AH110690 (GE-067) approved on the basis that it detects Aβ in the brain, believing that such an indication is consistent with the Guidance for Industry entitled *Developing Medical Imaging Drug and Biological Products, Part 2: Clinical Indications* which refers to "Disease or Pathology Detection;" the sponsor points out that Aβ deposits are pathological structures.

The sponsor believes that if [^{18}F]AH110690 is (initially) approved as a product that can detect cerebral amyloid, the product will have utility in clinical settings where the other available diagnostic data are inconclusive, but only in combination with the other available data.

The sponsor further believes that in the longer term, other areas in which [^{18}F]AH110690 may have utility are as follows:

- Screening patients at high risk for Alzheimer's Disease
- Predicting which patients with amnestic Mild Cognitive Impairment are likely to progress to having overt Alzheimer's Disease
- Monitoring the therapeutic effect of anti-amyloid drugs

The sponsor intends to pursue the indications immediately above in the future and has, in fact, submitted a proposal in the current submission as to how it might be determined that [^{18}F]AH110690 is of value in monitoring the effect of anti-amyloid drugs.

In accordance with the above, the sponsor proposes that the Advisory Committee consider the following questions.

- Is detection of cerebral amyloidosis by [^{18}F]AH110690, an indication that could justify initial US approval?
- If so, is the proposed Phase III protocol outline an acceptable approach?
- Does the Advisory Committee agree with the Phase III protocol design supporting a therapy monitoring indication?

10.1.3 Imaging Metrics

The study to support initial registration is intended to compare the detection of Aβ deposits in healthy individuals, those with amnestic Mild Cognitive Impairment, and those with probable Alzheimer's Disease, using both [^{11}C]PIB and [^{18}F]AH110690. Some patients with Alzheimer's Disease will receive [^{18}F]AH110690 twice rather than single administrations of both [^{18}F]AH110690 and [^{11}C]PIB in an effort to demonstrate that imaging with [^{18}F]AH110690 is reproducible.

The sponsor plans to use previous data for [^{11}C]PIB and data from ongoing studies with [^{18}F]AH110690 to specify cut-off ratios for binding values in specific areas of the brain that will determine what is normal and what is abnormal for a specific patient population. An approach to image analysis and imaging metrics is to be presented by the sponsor at the Advisory Committee meeting.

A response by the Advisory Committee to the following question has been sought by the sponsor.

- Is the approach GE Healthcare presents for image analysis and metrics satisfactory?

10.2 Proposed Registration Study

This study which is intended to demonstrate the utility of detecting Aβ in the brain. The main elements of the protocol are summarized below.

10.2.1 Title

An open-label study to assess the imaging comparability of GE-067 with [^{11}C]PIB, reproducibility of imaging with GE-067, and safety in healthy volunteers

10.2.2 Specific Objectives

- Establish the metrics of GE-067 uptake both visually and quantitatively in healthy volunteers, subjects with amnestic Mild Cognitive Impairment, and subjects with possible Alzheimer's Disease
- Demonstrate that Aβ imaging with GE-067 is comparable to Aβ imaging with [^{11}C]PIB
- Demonstrate that Aβ imaging with GE-067 is associated with an acceptable degree or reproducibility
- Demonstrate that the use of GE-067 is safe and well-tolerated, posing minimal risk to individuals exposed to the agent.

10.2.3 Design

This will be a two-dose, open-label trial.

3 groups of subjects will receive one dose each of GE-067 and [^{11}C]PIB, with brain imaging performed after each dose; these groups are:

1. Healthy age-matched subjects (about 25% of these subjects are anticipated to display evidence of abnormal Aβ deposition)
2. Patients with a clinical diagnosis of Mild Cognitive Impairment (about 60% of these patients are anticipated to display evidence of abnormal Aβ deposition)
3. Patients with a clinical diagnosis of Alzheimer's Disease (about 90% of these patients are anticipated to display evidence of abnormal Aβ deposition).

A fourth group, consisting of patients with Alzheimer's Disease will be imaged twice with GE-067 to examine the reproducibility of imaging with that product.

There will be a gap of 1 to 4 weeks between the first and second injections. For the 3 groups of subjects who will receive both [^{11}C]PIB and GE-067, the order of injection will be randomized.

Imaging evaluation will be blinded and randomized; that evaluation will be performed by 3 central independent physicians experienced in amyloid imaging using positron emission tomography.

10.2.4 Main Endpoint

The main study endpoint will be based on a comparability of findings from GE-067-derived imaging with those from [^{11}C]PIB-derived images.

The sponsor proposes that the above comparisons be made in 5 areas of the brain in which a higher load of amyloid has been seen on [^{11}C]PIB scans (these areas are listed in the table below). The sponsor further proposes that in each area, a Standard Uptake Value Ratio (SUVR) above that in the table below (measured at 60 to 90 minutes after injection for [^{11}C]PIB and at 85-105 minutes after injection for GE-067) be considered abnormal (these values are currently considered provisional).

Brain Region	SUVR Cut-off Value
Prefrontal	1.4
Anterior cingulate	1.6
Posterior cingulate	1.7
Parietal	1.4
Lateral temporal	1.4

10.3 Proposed Study To Support A Therapy-Monitoring Claim

The sponsor proposes that after the initial approval of GE-067 as an agent for imaging cerebral amyloid, the same compound be investigated as a means of

monitoring the effects of anti-amyloid agents on brain Aβ burden. The outlines of the protocol as presented in this submission are below.

The sponsor notes that such a study will need to be conducted in conjunction with a pharmaceutical company that is developing an anti-amyloid agent.

10.3.1 Title

Study using positron emission tomography with the β-amyloid marker GE-067 to assess changes in β-amyloid load over time in patients with mild to moderate Alzheimer's Disease who are treated with repeat doses of a human anti-Aβ antibody or with placebo

10.3.2 Design

This will a randomized, double-blind, placebo-controlled, repeated-dose study.

A proportion of patients enrolled in the study will undergo imaging with GE-067 at baseline and after the last dose of study medication.

Images are to be co-registered to each patient's MRI and differences in Aβ uptake between baseline and the end of treatment will be monitored by methods such as statistical parametric mapping or other subtraction techniques.

11. Reviewer's Comments

11.1 Summary Of Submission

This submission has been received as a consultation from DMIHP, and consists of a summary of the sponsor's clinical development program for [^{18}F]AH110690, which also referred to as GE-067. [^{18}F]AH110690 has been developed for imaging β-amyloid and is to be administered by injection in a single dose.

The sponsor's current summary has been prepared as a Briefing Document for an Advisory Committee meeting convened by this Agency to discuss the design of Phase III studies of imaging agents that are under development for the diagnosis of Alzheimer's Disease.

The sponsor's clinical development program for [^{18}F]AH110690 has already been the subject of a Pre-IND meeting between DMIHP and the sponsor. This Division had reviewed the Briefing Package for that meeting in consultation.

In this submission, the sponsor has drawn attention to the following:

- Beta-amyloid deposition is one of several characteristic pathological features of Alzheimer's Disease, but is not unique to that condition.

- [^{18}F]AH110690 is being developed an agent for the detection of β-amyloid deposits by positron emission tomography *in vivo* in patients with Alzheimer's Disease and other neurodegenerative disorders. The indication that the sponsor intends to initially seek for [^{18}F]AH110690 does not extend beyond the detection of β-amyloid deposits in the brain.

- The sponsor anticipates that in future [^{18}F]AH110690 will be used in conjunction with other diagnostic procedures, (presumably) in patients with dementia and with lesser degrees of cognitive impairment in whom the diagnosis is otherwise inconclusive, as well for other purposes such as screening patients at high risk for Alzheimer's Disease, predicting which patients with amnestic Mild Cognitive Impairment are likely to progress to having overt Alzheimer's Disease and in monitoring the therapeutic effects of anti-amyloid drugs.

- Currently, the most widely-studied amyloid-binding radiopharmaceutical is [^{11}C]PIB which is also being developed by the same sponsor. *In vitro* studies using both human and animal brain tissue have confirmed that [^{11}C]PIB binds specifically to β-amyloid and *in vivo* studies in patients with Alzheimer's Disease and other neurodegenerative disorders suggest the same. However, the short half-life of [^{11}C]PIB makes it inconvenient for use at imaging facilities that lack a cyclotron on-site; thus [^{18}F]AH110690 which is similar in structure and binding properties to [^{11}C]PIB, but has a longer half-life, has been developed as an alternative imaging agent for the same purpose.

- Currently, the ultimate standard of truth for confirming brain amyloid deposition in patients is through post-mortem histological examination of the brain; however, the use of that standard is impractical in a clinical development program.

Since the demonstration of brain amyloid deposition by histological examination is not practical in a clinical development program, the sponsor proposes that, instead, the presence or absence of amyloid as demonstrated by imaging with [^{11}C]PIB be used as the standard of truth in supporting the efficacy of [^{18}F]AH110690 for the proposed initial indication. Therefore, it is proposed that in the planned registration study of [^{18}F]AH110690, the ability of [^{18}F]AH110690 to image amyloid deposits in the brain in comparison with [^{11}C]PIB in an open-label trial in which patients with Alzheimer's Disease and Mild Cognitive Impairment as well as healthy age-matched controls will each receive a single dose of both [^{18}F]AH110690 and [^{11}C]PIB in random order separated by an interval of 1 to 4 weeks. A fourth group, consisting of patients with Alzheimer's Disease will be imaged twice with [^{18}F]AH110690 to examine the reproducibility of imaging with that product. Comparisons between the two products are to be based on radioisotope uptake in 5 areas of the brain where a higher load of amyloid has been seen on [^{11}C]PIB scans. Brain images are to be read by physicians familiar with the technique and blinded to other clinical information for each study subject.

The sponsor proposes that after the initial approval of [^{18}F]AH110690 (GE-067) as an agent for imaging cerebral amyloid, the efficacy of [^{18}F]AH110690 as an agent for monitoring the effects of anti-amyloid agents on brain Aβ burden be

evaluated in a randomized, double-blind, placebo-controlled, parallel-arm study in which imaging with [^{18}F]AH110690 is performed at the beginning and end of the study.

The sponsor has a number of questions for the Advisory Committee based on the contents of the Briefing Document.

11.2 Additional Comments

11.2.1 Development Of [^{18}F]AH110690 As A Means Of Detecting Cerebral B-Amyloid

The sponsor currently seeks to initially develop [^{18}F]AH110690 as a means of detecting cerebral β-amyloid. The question of whether the detection of cerebral β-amyloid can by itself constitute a regulatory indication (i.e., diagnostic claim) is a matter to be primarily addressed by DMIHP and is also to be discussed further at the forthcoming Advisory Committee meeting.

Assuming that the detection of β-amyloid in the brain is indeed a valid regulatory indication, the question of whether the detection of β-amyloid by [^{11}C]PIB can serve as the standard of truth for evaluating the effectiveness of [^{18}F]AH110690 for the same indication is an item for detailed discussion (at the forthcoming Advisory Committee meeting) with those considered to have expertise in the area.

If the detection of β-amyloid by [^{11}C]PIB can indeed serve as the standard of truth for evaluating the efficacy of [^{18}F]AH110690 for the same purpose, the registration study presented in outline in this submission may possibly be appropriate in design; however the submission of a full protocol, including a statistical analysis plan, and further discussion will be needed before more definite conclusions can be drawn in that regard.

11.2.2 Development Of [^{18}F]AH110690 As A Means Of Monitoring Anti-Amyloid Treatment

The sponsor has also asked whether a subsequent Phase III randomized, double-blind, placebo-controlled, parallel-arm study of a putative anti-amyloid agent in patients with mild to moderate Alzheimer's Disease that will include serial brain imaging with [^{18}F]AH110690 will be sufficient to support a "therapy-monitoring" claim for [^{18}F]AH110690. The answer to this question will appear to depend in part on whether it can first be established that [^{18}F]AH110690 does indeed detect cerebral β-amyloid. However, it would also appear to depend in part on the meaning and full implications of the term "therapy monitoring" and whether such a term would constitute a valid regulatory indication, a subject that will need to be addressed by DMIHP and at the Advisory Committee meeting.

Of particular significance from this Division's perspective in regard to a "therapy monitoring" indication is whether a putative effect of a therapeutic

agent on β-amyloid as demonstrated by [^{18}F]AH110690 imaging can be interpreted as supporting the use of that effect as a surrogate marker of a disease-modifying effect of that treatment.

The subject of using brain imaging instruments, or biochemical measures derived, for example, from peripheral blood or cerebrospinal fluid, as surrogate markers for a disease-modifying effect of a treatment for Alzheimer's Disease has been under consideration by this Division for a number of years and has been extensively discussed with sponsors, at public meetings (including an Advisory Committee meeting), and in publications by staff of this Division. The generic approach to surrogate markers that we have proposed is to first attempt to address the following questions.

- What clinical outcome is the imaging marker a surrogate for?
- Does the imaging marker reliably predict the clinical outcome?
- Is the desired clinical outcome based on the drug effect on the surrogate?
- Assuming that one uses the imaging marker to support a claim that a drug has a disease-modifying effect, to what extent does the drug effect on the marker reflect a drug effect on the pathology and/or pathophysiology of the disease?
- Is the effect of the drug on the imaging marker clinically meaningful, and of sufficient importance to outweigh the risks of treatment?

While addressing the above questions, we believe that the following should be kept in mind

- Correlation with a concurrent clinical outcome is insufficient, by itself, to establish the "surrogacy" of the imaging modality, and/or that a drug-induced effect on the imaging modality is indicative of disease-modification.
- The biological basis for the drug-induced change in the surrogate marker should also be understood.

A practical approach to validating a surrogate marker might consist of

- Comparing the imaging surrogate marker with the desired clinical outcome across multiple drugs and clinical trials
- Explaining the biological basis for the intervention-induced change in the surrogate marker

This Division does not currently endorse any specific entities as being appropriate surrogate markers for disease-modifying activity in Alzheimer's Disease. Furthermore, thise Division does not currently know what criteria will be applied in determining that a drug has a disease-modifying effect in Alzheimer's

Disease when an application seeking such a claim is submitted. Imaging measures alone, as opposed to imaging measures in combination with clinical instruments, would be unlikely to suffice as a means of establishing a disease modifying effect. As a means of further clarifying what should be the basis for granting a claim for a disease-modifying effect in Alzheimer's Disease, the initial New Drug Application or Biologic License Application that seeks such a claim will be discussed at a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee.

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rbm 9/11/08
cc:
HFD-120
Pre-IND 101866 (004)

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