

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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**MEDICAL REVIEW(S)**

**Clinical Review Memorandum**  
**Division of Medical Imaging Products**

September 17th, 2013

**NDA:** 203137  
**Product:** Vizamyl  
**Sponsor:** GE Healthcare  
**Submission Date:** 8/14/2013  
**Reviewer:** Phillip Davis, MD

**Summary**

This submission contains the sponsor's formal response to FDA's 6/28/2013 comments regarding the Vizamyl labeling. These same documents were sent to FDA via email on July 9 and July 11 2013.

FDA is currently working to finalize the Vizamyl labeling and this submission contains previously reviewed labeling documents, which have since been revised by both FDA and GE.

**Assessment and Plan**

This submission contains previously reviewed Vizamyl labeling documents; no action is necessary. Note, the Agency is currently working to finalize the Vizamyl labeling documents.

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/s/  
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PHILLIP B DAVIS  
09/17/2013

## CLINICAL REVIEW

Application Type New Molecular Entity  
Application Number(s) 203137  
Priority or Standard Standard

Submit Date(s) 10/26/2012  
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Reviewer Name(s) Phillip B. Davis, MD  
Review Completion Date 6/28/2013

Established Name Flutemetamol F 18 Injection  
(Proposed) Trade Name Vizamyl  
Therapeutic Class Diagnostic  
Radiopharmaceutical  
Applicant GE Healthcare

Formulation(s) Solution  
Dosing Regimen A single 185 MBq (5 mCi)  
dose by intravenous injection  
Indication(s) To estimate  $\beta$  amyloid neuritic  
plaque density in adult patients  
with cognitive impairment who  
are being evaluated for  
Alzheimer's disease (AD) or  
other causes of cognitive

Intended Population(s) decline  
Patients with cognitive  
impairment being evaluated for  
Alzheimer's disease

Template Version: March 6, 2009

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

The clinical reviewer recommends approval of the Vizamyl NDA for the indication of visual detection of  $\beta$  amyloid neuritic plaques in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other cognitive complaints.

This recommendation is based on review of the clinical data evaluating the effectiveness of Vizamyl PET imaging for detecting amyloid in patients with cognitive impairment, combined with the review of safety data submitted from the sponsor's clinical development program.

### **1.2 Risk Benefit Assessment**

Vizamyl has an acceptable risk benefit assessment based on the following qualities:

- Acceptable sensitivity and specificity of blinded interpretation of Vizamyl images
- Single dose (5 millicuries, 20 micrograms) by intravenous administration
- Limited indication (subjects with cognitive impairment)
- Limited patient population (adult patients)
- Adequate safety database with no significant safety concerns

### **1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies**

None recommended.

### **1.4 Recommendations for Post-market Requirements and Commitments**

None recommended.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Vizamyl (Flutemetamol F 18 Injection) is a diagnostic radiopharmaceutical product developed for use with positron emission tomography (PET) imaging for the visual detection of fibrillar amyloid  $\beta$  in the form of neuritic plaques in the brain.

The current proposed indication statement is:

Vizamyl is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate  $\beta$  amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations. (1)

Limitations of Use:

- A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of Vizamyl have not been established for:
  - Predicting the development of dementia or other neurological condition;
  - Monitoring responses to therapies (1).

**Reviewer's Comment**

Section 6.1 contains the sponsor's original proposed indication statement, as well as a brief discussion of changes made by FDA in drafting the current, revised version.

Dosing and administration:

The recommended dose is 185 MBq (5 mCi), administered intravenously in a maximum volume of 10 mL. The total amount of flutemetamol at the 185 MBq dose is 20 micrograms or less.

**Amyloid and Alzheimer's Disease**

Amyloid is an abnormal extracellular aggregate of insoluble protein fibrils in body tissues or organs. It has a  $\beta$  pleated sheet pattern on X-ray diffraction analysis, as well as unique staining properties and appearance on electron microscopy. There are numerous types of proteins that can form amyloid and it can accumulate in the body as plaques, which are visible upon pathologic examination. These misfolded protein structures interact with cellular components and are known to be associated with the pathology of at least 20 human diseases. Alzheimer's disease (AD) is a chronic neurodegenerative disorder which has *beta* amyloid accumulation in the brain as a disease hallmark.

AD usually arising in middle or late life characterized by progressive development of:

(1)

- cognitive dysfunction - memory loss, language difficulty, and executive dysfunction
- psychiatric and behavioral symptoms - such as depression, hallucinations, delusions, agitation
- difficulty performing activities of daily living - basic or complex

Areas of disease involvement are isolated to the brain and include:

- global cortex
- hippocampus
- amygdala
- entorhinal cortex
- posterior temporal lobe
- locus ceruleus

The prevalence of AD increases with age and it's believed that 12.5% of persons in the U.S. greater than 65 years of age are living with the disease; AD affect approximately 2% of Americans aged 65-74 years, 19% aged 75-84 years, and up to 42% aged 85 years and older. There are an estimated 5.1 million people living with AD in the U.S., and AD was listed as the cause of death for over 65,000 Americans in 2004. The exact cause is unknown, but beta peptide (component of amyloid plaques) is thought by some to be involved early in the disease pathology. The risk of disease is believed to be elevated by smoking, depression, diabetes, and the APOE-e4 genotype.

A clinical diagnosis of AD is made through careful review of the patient's history (symptoms, medications, past medical history, family history) combined with established questionnaires (mental status exam) and physical examination. Additional testing may include a multitude of laboratory evaluations, as well as imaging tests (CT, MRI, PET) and sometimes tissue biopsies to rule out other disease processes.

National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) publishes recommendations on the clinical diagnosis of dementia and AD. However, a definitive diagnosis of AD can only be made by pathological evaluation of brain tissue at autopsy.

\* Note, AD is also known as Alzheimer dementia, Senile Dementia of Alzheimer Type (SDAT), primary degenerative dementia of the Alzheimer type (DAT).

## **2.2 Currently Available Treatments for Proposed Indications**

The only currently approved diagnostic radiopharmaceutical for the assessment of beta amyloid plaque in the brain is Amyvid (Florbetapir F-18 - NDA 202008), which is manufactured by Bayer and was approved by FDA on 4/06/2012.

The summary review for Amyvid can be seen at the following web link:  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/202008Orig1s000SumR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202008Orig1s000SumR.pdf)

### **2.3 Availability of Proposed Active Ingredient in the United States**

Vizamyl will be manufactured at multiple sites in the U.S.; there are no issues to address regarding the availability of the proposed active ingredient.

### **2.4 Important Safety Issues with Consideration to Related Drugs**

There are no significant safety issues to consider for related drugs.

### **2.5 Summary of Pre-submission Regulatory Activity Related to Submission**

#### **Regulatory History**

A Pre-IND meeting was held between the sponsor and FDA on 5/19/2008. During the development of Vizamyl, FDA worked with stakeholders including academic investigators, clinicians, industry and the public to develop clear regulatory approaches to evaluating the clinical usefulness and performance characteristics of amyloid imaging agents. On, 10/23/2008 an FDA Advisory Committee meeting was held in Silver Spring, MD.

The major outcomes of this advisory committee meeting were:

- The committee agreed that a "negative" amyloid test could have clinical utility in ruling out a diagnosis of Alzheimer's Disease (AD), but the committee noted a "positive" test would have very limited utility.
- Committee members overwhelmingly agreed that histopathological correlation (autopsy brain evaluations) should serve as the standard of truth in confirmatory clinical trials involving amyloid imaging agents.

Please use the below web link to view the summary minutes of the 2008 Advisory Committee meeting discussion and conclusions:

<http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4382m1-Final.pdf>

A type C meeting to discuss the sponsor's clinical development plan for Vizamyl was held between the Agency and GE Healthcare on 3/26/2009. On 9/07/2010, an end of phase 2 meeting also took place to discuss the clinical development plan, which included discussion of the proposed training program for image interpretation. Additionally, a pre-NDA meeting to discuss NDA submission documentation took place on 4/12/2012.

Also of relevance: an advisory committee meeting was held to discuss approval considerations for Amyvid on 1/20/2011.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

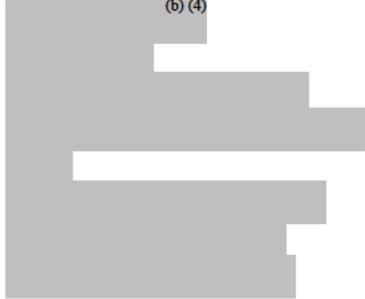
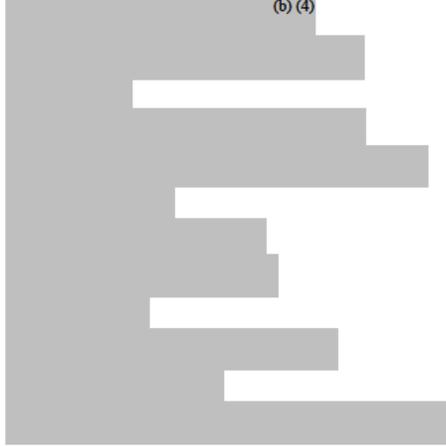
DMIP consulted the office of compliance (DSI) regarding site inspections for this NDA. Table 1 describes the sites selected for inspection, which were based upon the following reasons:

- locations where blinded image reads were conducted for pivotal phase 3 studies
- location where pathological analysis of brain tissue was conducted; these results were used as the truth standard for GE-067-007
- location that managed, analyzed and reported pivotal phase 3 study data

\* Note, there were no concerns raised from the submitted data for individual study centers

**Table 1: Description of studies and study sites selected for DSI inspections**

Site Name & Contact Information	Protocol ID	Number of Subjects	Reason for Inspection
<p><b>The Grove Center</b>  <b>Dr. Chris Buckley</b>            White Lion Road            Amersham, Buckinghamshire            HP7 9LL, UK            Tel: +44 1494 54 4096            Fax: +44 1494 545006</p>	<p>GE-067-  <b>007</b>             GE-067-  <b>015</b></p>	<p>176 subjects underwent visual image interpretation             (The submitted image charter for study 007 states all images were interpreted at this center.)</p>	<p>All images for the blinded, independent, interpretation are stated to have occurred at this center. We sought verification that the image charter protocol was followed.</p>
<p>(b) (4)</p>	<p>GE-067-  <b>007</b></p>	<p>The submission states 69 subjects underwent brain autopsy</p>	<p>This site performed the specimen processing, staining, assaying and analyses of brain tissue specimens that were used as the truth standard. DMIP sought verification that the results were documented correctly and final data was accurately submitted to GE and the Agency.</p>

Site Name & Contact Information	Protocol ID	Number of Subjects	Reason for Inspection
<p>(b) (4)</p> 	<p>GE-067-007</p> <p>GE-067-015</p>	<p>N=180</p> <p>N=181</p>	<p>(b) (4) was responsible for data management, analysis and reporting and record keeping. We sought verification that data was accurately submitted to the Agency.</p>
<p>(b) (4)</p> 	<p>GE-067-021</p>	<p>N= 276 subjects and unique images sets</p>	<p>This site was responsible for reader training and conducting the BIE. We sought verification that the image charter protocol was followed.</p>

Site Name & Contact Information	Protocol ID	Number of Subjects	Reason for Inspection
<p><b>GE Healthcare</b>  <b>Kevin Daryl White, MBA</b>            Senior Director &amp; Americas            Head, Regulatory Affairs            101 Carnegie Center            Princeton, NJ 08540            Tel: (609) 514-6025            Fax : (609) 228-5604            Kevin.D.White@ge.com</p> <p>Or :</p> <p><b>Paula M. Clark</b>            Global Regulatory Lead            101 Carnegie Center            Princeton, NJ 08540            Tel: (609) 514-6883            Fax : (609) 228-6198            Paula.clark@ge.com</p>	<p>GE-067-007, GE-067-015 &amp; GE-067-021</p>		<p>Inspection was requested of the site that collected and managed the NDA data and submitted it to the Agency.</p>

**Reviewers Comments**

Inspections of the above named facilities are still under review.

There are no other current ethics/good clinical practice issues that are expected to impact the overall clinical review and/or recommended regulatory action for Vizamyl.

**3.2 Compliance with Good Clinical Practices**

The application states that for each pivotal phase 3 study, the protocol was “submitted to and approved by, or received a favorable opinion from, an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) according to national or local regulations”. The sponsor states that studies were conducted according to the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline* approved by the International Conference on Harmonisation (ICH), and any applicable national and local laws and regulations.

Study investigators were responsible for performing the study in accordance with the protocol and ICH E6-Good Clinical Practice, for collecting, recording, and reporting the data accurately and properly. The principal investigator at each center was responsible

for the conduct and administration of the study at that center, and for contacts with study center management, the IEC/IRB, and with local non-regulatory bodies.

The application states that written and oral information about the study in a language understandable by the subject was given to all subjects or, if applicable, the subject's legally acceptable representative. The information provided an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was also obtained from each subject, or the subject's legally acceptable representative, before any procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained to study subjects. It was explained to all subjects, or to the legal representatives, that subjects were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

### 3.3 Financial Disclosures

Three investigators who participated in study 007 and one investigator who participated in study 005 reported financial interests, which are seen below.

Dr. (b) (6), who served as a sub-investigator for Protocol (b) (6), reported receiving research grants from GE Healthcare with a value greater than \$25,000. A total of (b) (6) subjects were enrolled at (b) (6) centers and (b) (6) subjects were dosed at Center (b) (6) where Dr. (b) (6) was an investigator, constituting (b) (6) of the (b) (6) subjects enrolled. No one at Dr. (b) (6) site was involved in the (b) (6)

Dr. (b) (6) also served as a sub-investigator for Protocol (b) (6). A total of (b) (6) subjects in study (b) (6) were dosed at Center (b) (6) where Dr. (b) (6) was a sub-investigator

Dr. (b) (6) who served as an investigator for Protocol (b) (6), reported an equity interest in GE common stock greater than \$50,000. (b) (6) was one (b) (6) phase 3 studies; a total of (b) (6) subjects were enrolled at (b) (6) centers and a total of (b) (6) subjects were dosed at Center (b) (6) where Dr. (b) (6) was an investigator.

Dr. (b) (6), who served as one of the (b) (6), has reported that the head of his department, (b) (6), has an arrangement with GE Healthcare's Discovery Department to fund part of their new GMP radiochemistry facility. This arrangement is valued at greater than \$25,000. The sponsor notes that even if Dr. (b) (6) reads had been excluded from study (b) (6), the study would have still met its success criteria.

### Reviewer's Comments

The review team does not believe any of these financial interests have affected the integrity of data obtained at the above mentioned investigators' study sites or the overall estimates of Vizamyl performance characteristics.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

There are no product issues that could impact the clinical safety or efficacy of Vizamyl.

### 4.2 Clinical Microbiology

There are no microbial issues that could impact the clinical safety or efficacy of Vizamyl.

### 4.3 Preclinical Pharmacology/Toxicology

There are no pre-clinical pharmacology or toxicology issues that could impact the clinical safety or efficacy of Vizamyl.

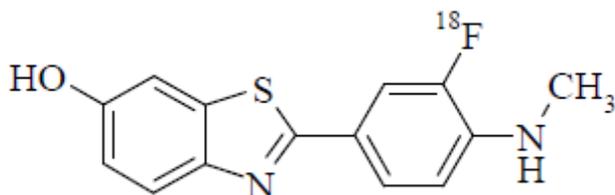
### 4.4 Clinical Pharmacology

The clinical pharmacology review team recommends approval of the application.

#### 4.4.1 Mechanism of Action

Flutemetamol is a small, lipophilic, neutral molecule (Figure 1) with a molecular weight of 274.32 (flutemetamol, non-radiolabelled).

**Figure 1.** Chemical structure of Vizamyl ( $[^{18}\text{F}]$  flutemetamol)



The following (indented) is the mechanism of action statement as it appears in the applicant's current, revised package insert:

Flutemetamol F 18 binds to  $\beta$ -amyloid plaques in the brain and the F-18 isotope produces a positron signal that is detected by a PET scanner. In *in vitro* binding studies using postmortem human brain homogenates containing fibrillar  $\beta$ -amyloid, the dissociation constant ( $K_d$ ) for flutemetamol was 6.7 nM.

Selectivity of [ $^3$ H]flutemetamol binding in post-mortem human brain sections was demonstrated using autoradiography, silver-stained protein, and immunohistochemistry (monoclonal antibody to  $\beta$ -amyloid) correlation studies.

(b) (4)

#### 4.4.2 Pharmacodynamics

At the administered dose of 20 micrograms, Vizamyl is not known to display clinical pharmacologic activity.

#### 4.4.3 Pharmacokinetics

Vizamyl is administered as a single-time intravenous injection; it is 100% bioavailable to the systemic circulation.

A biodistribution study was conducted in European and Japanese subjects and patients using a single dose of Vizamyl. Following intravenous injection of 185 MBq (5 mCi) of Vizamyl in humans, approximately 25% of the active compound (flutemetamol F 18) remained in the circulation 20 minutes post-injection and approximately 10% at 180 minutes. The F 18 in circulation during the 30-120 minutes imaging window in plasma was principally associated with flutemetamol metabolites. The apparent elimination half-life was 4.5 hours. Elimination of  $^{18}$ F was approximately 37% renal (28-45%; n=6) and 52% hepatobiliary (40-65%; n=6).

The proposed dose and imaging time window for Vizamyl is based on the dose ranging portion of Study ALZ103. The applicant started out with 100 MBq (2.7 mCi) in two healthy volunteers; dosimetry was determined and radiation absorbed doses were estimated using OLINDA software. The 100 MBq dose resulted in 3.2 mSv of absorbed radiation dose. The next cohort of healthy volunteers (n=4) were administered 150 MBq (4.0 mCi) of Vizamyl; radiation dosimetry and brain kinetics were evaluated. The next cohort of healthy volunteers (n=3) and probable Alzheimer Disease patients (n=3) were administered a 185 MBq (5.0 mCi) dose of Vizamyl. Brain imaging was performed from 0-90 min, 150-200 min and 260-300 min post-injection. The recommended imaging time from this cohort was determined to be 80-140 min post-injection. Another cohort of healthy volunteers (n=5) and probable AD (n=5) were administered 5 mCi of tracer to

acquire additional imaging time data. The optimal imaging time carried forward was 90-120 min. A clinical dose of 185 MBq (5 mCi) was chosen based on sufficient radioactivity in brain and the brain target to background ratio. The mass dose was < 20 micrograms.

The proposed 185 MBq (5 mCi) dose of Vizamyl results in an effective dose (*E*) of 5.9 millisieverts (mSv). For comparison, the mean natural-source background radiation in the USA is approximately 3.1 mSv per year, and the occupational exposure limit is 50 mSv per year.

## 5 Sources of Clinical Data

### Tables of Studies/Clinical Trials

**Table 2. Clinical studies submitted in NDA.**

<b>Study Identifier</b>	<b>N, Population, Vizamyl dosing</b>	<b>Design, Reference Standard, Image analysis methods</b>	<b>Endpoint(s)</b>
<b>Phase 1 and 2</b> <i>Exploratory studies</i>			
ALZ103	N = 22 (14 HV; 8 with pAD); 100, 150, or 185 MBq by intravenous (IV) injection	Phase 1, single center (European), open label study evaluating the safety of a single dose of Vizamyl	Safety, biodistribution and radiation dosimetry
GE067-014	N = 22 Japanese subjects (14 HV; 8 with pAD); 100, 150, or 185 MBq by IV injection	Phase 1, single center (Japanese), open label study evaluating the safety of a single dose of Vizamyl	Safety, biodistribution and radiation dosimetry
ALZ201	N = 72 patients and HV; • pAD/aMCI: single dose of	Phase 2 multi-center (8 European centers), open label study examining visual assessment of	Exploratory estimates of Vizamyl performance

	185 MBq (5 mCi) Vizamyl AND single dose of 333 MBq (9 mCi) [ <sup>11</sup> C]PiB <ul style="list-style-type: none"> <li>• pAD two 120 MBq (3.2 mCi) Vizamyl doses</li> <li>• HV: single dose of 185 MBq (5 mCi) Vizamyl, <i>all by IV injection</i></li> </ul>	Vizamyl for differentiating subjects with pAD from HVs and assigning aMCI cases to either a pAD or HV category.	characteristics
<b>Phase 3</b> <i>Supportive studies</i>			
GE 067-005 (ongoing study)	N = 232 subjects ≥ 55 years with MCI; 185 MBq (5 mCi) by IV injection	Phase 3 open label, multicenter (28 U.S. & European), study evaluating inter-reader and intra-reader agreement of blinded image interpretation of Vizamyl PET images.	Safety and reader agreement  Ongoing: prediction of conversion from MCI to pAD
GE 067-008	N = 7 subjects ≥ 55 years with normal pressure hydrocephalus; 185 MBq (5 mCi) by IV injection	Open label, single center, study evaluating associations between PET brain uptake of Vizamyl (contralateral cortex from biopsy site – imaging after biopsy) and levels of fibrillar amyloid β detected in biopsy samples taken from the frontal cortex of NPH patients undergoing shunt placement; the monoclonal antibody NAB 228 was used as a reference standard for brain amyloid; blinded visual interpretations and	Standard uptake value ratios (SUVRs) and exploratory estimates of Vizamyl performance characteristics.

		SUVR assessments of images were performed	
GE 067-009	N = 12 subjects ≥ 55 years with normal pressure hydrocephalus; 185 MBq (5 mCi) by IV injection	Phase 3 open label, single center, study evaluating associations between quantitative estimates of brain uptake of Vizamyl at biopsy sites (imaging prior to biopsy) and levels of fibrillar amyloid β detected in biopsy samples taken from the frontal cortex of NPH patients undergoing shunt placement; the monoclonal antibody 4G8 was used as a reference standard for brain amyloid; blinded visual interpretations and SUVR assessments of images were performed	Standard uptake value ratios (SUVRs) and exploratory estimates of Vizamyl performance characteristics.
GE 067-010	N = 15 subjects ≥ 55 years with normal pressure hydrocephalus; 185 MBq (5 mCi) by IV injection	Open label, single center, study evaluating PET brain uptake of Vizamyl (contralateral cortex from biopsy site – imaging after biopsy) and levels of fibrillar amyloid β detected in biopsy samples taken from the frontal cortex of NPH patients undergoing shunt placement; the monoclonal antibody 4G8 was used as a reference standard for brain amyloid; blinded visual interpretations and SUVR assessments of images were performed	Standard uptake value ratios (SUVRs) and exploratory estimates of Vizamyl performance characteristics.

GE 067-011	N = 18 subjects ≥ 55 years with normal pressure hydrocephalus; 185 MBq (5 mCi) by IV injection	Phase 3 open label, single center, study evaluating PET brain uptake of Vizamyl at biopsy sites (imaging prior to biopsy) and levels of fibrillar amyloid β detected in biopsy samples taken from the frontal cortex of NPH patients undergoing shunt placement; the monoclonal antibody 4G8 was used as a reference standard for brain amyloid; blinded visual interpretations and SUVR assessments of images were performed	Standard uptake value ratios (SUVRs) and exploratory estimates of Vizamyl performance characteristics.
<b>Phase 3</b> <i>Pivotal studies</i>			
GE 067-007	N = 180 scanned subjects, 69 underwent brain autopsy (68 evaluable); subjects were ≥ 55 years with life expectancy ≤ 1 year 185 MBq to 370 MBq (5 – 10 mCi) by intravenous (IV) injection	Phase 3 open label, multi-center, non-controlled prospective study estimating the sensitivity of blinded visual image interpretations (without anatomic correlation) of [18F] flutemetamol PET for detecting brain fibrillar amyloid β; Whole brain autopsy CERAD neuritic plaque count results were used as the gold standard for amyloid detection; Blinded, centralized, independent reads were performed.	1° endpoint: Sensitivity  2° endpoint: Specificity

GE 067-015	N = 181 healthy adult subjects ≤ 40 years of age; 185 MBq (5 mCi) by intravenous (IV) injection	Phase 3 open label study evaluating performance characteristics of Vizamyl PET imaging in healthy young adults; all subjects assumed negative for significant brain amyloid burden; blinded, independent image reviews conducted.	1° - Specificity of blinded, independent Vizamyl scan interpretations  * Sensitivity not calculated due to lack of truth standard
GE 067-021	N = 305 images from 276 subjects	Phase 3 non-enrollment study evaluating the effectiveness of an electronic training program for teaching Vizamyl scan orientation and interpretation; multiple truth standards utilized; blinded, independent image reviews conducted following completion of the electronic training program.	Sensitivity and specificity of blinded, independent Vizamyl scan interpretations

### Review Strategy

For the evaluation of [18F] flutemetamol efficacy (demonstration of clinical usefulness, reliability and accuracy in a defined clinical setting), this clinical review concentrates on the 3 studies described in table two and detailed in tables three through five. We focus on the primary endpoints of sensitivity and specificity of blinded Vizamyl PET image reads (conducted without anatomic correlation) in detecting fibrillar amyloid in the brain; selected secondary analyses (e.g. inter-reader and intra-reader agreement, sensitivity/specificity with anatomic correlation) also played a key role in the review process.

For the review of safety, information was evaluated from the sponsor's 10 clinical studies, including a total of 761 subjects.

## Discussion of Individual Studies/Clinical Trials

### Overview

All applicant sponsored phase 3 studies were multicenter, single arm, open label investigations of blinded Vizamyl PET image results compared to a reference standard of either: whole brain autopsy evaluation (007), assumed clinical status (015), or a combination of autopsy, clinical status and brain biopsy results (study 021).

### Individual Studies

**Table 3. Study GE 067-007 (007)**

<b>Study 007</b>	
Design	Multicenter, open label study to evaluate efficacy and safety of Vizamyl PET imaging for the detection of brain fibrillar amyloid $\beta$ using brain autopsy pathological evaluation as a truth standard.
Protocol date (Original)	8/02/2010
Amendment dates	12/30/2010, 9/15/2011
Statistical plan date	11/10/2011 (signed), 11/02/2011 (created)
Imaging review charter date	5/04/2011
Image review training manual date	5/06/2011
Pathology technical manual date	10/18/2011
Study period	6/22/2010 to 11/23/2011
Study population	Male and female subjects aged 55 years or older with a range of cognitive abilities previously diagnosed with a terminal illness and expected to live one year or less.
Main Inclusion criteria	<ul style="list-style-type: none"> <li>Subjects <math>\geq</math> 55 years of age with terminal illness and a life expectancy of 1 year or</li> </ul>

	<p>less.</p> <ul style="list-style-type: none"> <li>• The subject and/or the subject's legally acceptable representative provided informed consent.</li> <li>• The subject had a caregiver who was reliable and ensured that the subject complied with the protocol, if necessary in the judgment of the Investigator.</li> <li>• The subject's general health was adequate to undergo the study procedures.</li> <li>• For women of childbearing potential, the results of a serum and urine HCG pregnancy test (with the result known on the day of and before Flutemetamol F 18 Injection administration) had to be negative. For women who were either surgically sterile or were postmenopausal enrollment in the study without a pregnancy test at screening was allowed.</li> <li>• The subject was able to tolerate undergoing diagnostic quality anatomic brain imaging (usually CT).</li> </ul>
Main exclusion criteria	<ul style="list-style-type: none"> <li>• The subject had known or suspected structural brain abnormalities, such as infarcts or tumors, which might interfere with the interpretation of PET images.</li> <li>• Contraindication for PET.</li> <li>• Subject was pregnant or lactating.</li> <li>• Subject had a known or suspected hypersensitivity/allergy to Flutemetamol F 18 Injection or to any of the excipients.</li> <li>• Subject was unable to tolerate or cooperate with study procedures.</li> <li>• Subject had participated in any clinical study using an investigational agent within 30 days of signing consent</li> </ul>
Primary endpoint(s)	Sensitivity and of blinded interpretation of Vizamyl PET images (without anatomic correlation) for detecting brain amyloid compared to the brain autopsy SOT

	results.
Vizamyl dosing	Single IV injection of 185 to 370 MBq (5 to 10 mCi)
Secondary endpoint(s)	<ul style="list-style-type: none"> <li>• Specificity and of blinded interpretation of Vizamyl PET images (without anatomic correlation) compared to the brain autopsy SOT results.</li> <li>• Sensitivity and Specificity of blinded interpretation of Vizamyl PET images with anatomic correlation compared to the brain autopsy SOT results.</li> <li>• Global and region-specific estimates of Vizamyl uptake using a standard uptake value ratio (SUVR) determined by quantitative analysis of Vizamyl PET images.</li> </ul>
Safety analyses	Adverse events were recorded from administration of Flutemetamol F 18 Injection until 24 hours after study drug administration. Investigators were instructed to report SAEs that occurred within 30 days after study drug administration and for which a causal relationship could not be ruled out.
Reference Standard	<p>Whole brain autopsy CERAD based neuritic plaque count scores (normalized) were used as the gold standard for amyloid detection. Eight regions (2 blocks for each region) were assessed by blinded pathologists using Bielschowsky silver stained slides. Findings were scored and averaged based on the number of plaques observed in each region, using 6 slides per region (3 slides for each block) and five 100X fields of view per slide.</p> <p>Scoring: 0 – none (0 plaques), 1 – sparse (1-5 plaques) , 2 – moderate (6-19 plaques), or 3 - frequent (≥ 20 plaques).</p>

	<p>The five scores for each slide were averaged for a mean slide score and the six mean slide scores were averaged to give a mean region score. Any region score above 1.5 resulted in an overall subject standard of truth assessment as positive for significant amyloid.</p>
<p>Pre-specified efficacy thresholds</p>	<p>Sensitivity greater than 70% for at least 3 of 5 readers based on lower bound of two-sided 95% confidence limit.</p>
<p>Image interpretation methods</p>	<p>Five blinded readers (neurologists, nuclear medicine physicians, medical physicists) were trained at the sponsor’s centralized image review center to interpret Vizamyl PET images as negative or positive for clinically significant Vizamyl uptake in the brain. Images were presented to readers in a random order and readers were blinded to clinical information, personal information and subject identification. Readers interpreted images without anatomic correlation using a regional brain analysis approach, which included these five regions:</p> <ol style="list-style-type: none"> <li>1. Frontal and Anterior Cinguli</li> <li>2. Posterior cinguli and precuneus</li> <li>3. Insula</li> <li>4. Lateral Temporal lobe</li> <li>5. Striatum</li> </ol> <p>Normal or abnormal patterns of Vizamyl grey matter uptake were recorded for these regions on the CRF. If any one region was read as abnormal, the subject’s overall image interpretation was abnormal.</p> <p>In order to assess intra-reader agreement, 10% of images were re-read in a blinded fashion.</p>

Image Review Training and Interpretation Location	Grove Center, UK
Image acquisition methods	Vizamyl PET images were acquired over a 10 minute duration beginning approximately 90 minutes post injection of study drug.
Disease severity of patients at baseline	Of the 68 subjects who died during the study and were included in the post-mortem analysis set, reported <u>baseline</u> medical histories related to dementia included: 30 (44%) patients with Alzheimer's Disease, 7 (25%) with other cognitive disorders, and 21 (31%) patients with no history of cognitive impairment.

### Reviewer's Comments

Study 007 was a prospective, open-label study designed to evaluate the diagnostic performance (sensitivity as primary analysis, specificity as secondary analysis) of Vizamyl PET imaging for detecting amyloid in the brains of patients who were diagnosed with terminal illnesses and had a life expectancy of less than 1 year. The protocol did not specify a baseline level of cognitive function required for enrollment; all subjects with a terminal illness and one year or less life expectancy were eligible for the study. Subjects were screened and underwent the Vizamyl injection and imaging within 35 days of each other, then followed until either: 1) the subject died, or 2) completion of the study.

Image interpretations were conducted by five independent, blinded readers at the sponsor's image review center England (The Grove Centre, Amersham, Buckinghamshire). Prior to image interpretations, readers were provided a copy of the image review charter and the reader training manual. Readers were then trained in person at the IRC by an external trainer who was a nuclear medicine physician with teaching experience. Reader training consisted a "common training session for all readers" which included a "power point presentation, hands-on workstation training and printed material". Readers were given six sample datasets of Vizamyl PET images (selected from previous Vizamyl studies) representing a range of study drug uptake and image quality (some with brain atrophy included). After completing the sample image reviews, readers proceeded to a mock read consisting of eight datasets of images different than the sample images. The mock read images consisted of four datasets without anatomic correlation and four datasets with anatomic correlation obtained from previous Vizamyl studies. The sponsor states the mock read images were "classified unanimously by the phase 2 readers as having normal or abnormal uptake pattern" of Vizamyl.

### Image Read Methods

Readers were trained in-person at the sponsor's centralized image review center to interpret Vizamyl PET images as negative or positive for clinically significant Vizamyl uptake in the brain. Prior to the blinded read, an external trainer (nuclear medicine physician with teaching experience) conducted a common training session for all readers together which included a PowerPoint presentation, hands-on workstation training and printed material. This training was based on the manual "GE-067-007 Image Review Training Manual 2", which was also given to all readers. Readers learned to interpret Vizamyl images without anatomic correlation based on review of five key regions which should not have Vizamyl uptake in normal individuals. If one region was deemed positive for significant Vizamyl uptake, then that patient's images were interpreted as positive. Readers were required to train on six image sets (images from previous Vizamyl studies), then pass a mock read consisting of eight different image sets (from previous Vizamyl studies); four of these image sets were PET only images and four sets consisted of PET images with "CT anatomical reference available".

The reference standard was whole brain autopsy evaluations using a *region based* assessment of amyloid plaque density. Scoring of amyloid plaque in 8 different regions was based on modification of the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) criteria, which is the accepted method for analyzing brain tissue to determine if patients meet criteria for a definitive diagnosis of AD. The modifications consisted of averaging the plaque count scores for each slide (up to five counts per slide, six slides per region), then determining regional means and an overall mean for each subject. Any regional mean greater than 1.5 was considered abnormal and equated to an overall abnormal amyloid assessment for that subject. The reviewer believes the truth standard for study 007 is appropriate and acceptable.

### Summary Comments

Study 007 was appropriately designed to estimate the sensitivity of blinded Vizamyl PET image interpretations as compared to the truth standard of brain autopsy evaluations based on CERAD criteria in a population of patients with a range of cognitive ability and terminal illness with  $\leq$  one year of life expectancy.

Although the reviewer finds the design of 007 to be well controlled to meet its objectives, it should be noted that the enrolled patients (terminal illness with short life expectancy) do not likely represent the population in which Vizamyl will be used upon introduction into the U.S marketplace. Thus, study 007 alone would not likely be sufficient to support the *reliability* and *accuracy* of Vizamyl in "adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other cognitive complaints". Study 007 was well designed provide a confident estimate of Vizamyl PET performance in detecting brain amyloid plaques in terminally ill patients at an advanced stage of cognitive decline, in which a substantial percentage were (logically) expected to have significant amyloid burden. How the level of amyloid

burden in this population of patients correlates with amyloid levels in the intended population of use remains in question, though the reviewer notes the sponsor followed the Agency and professional community's recommendations (2008 Advisory Committee Meeting) on study design and truth standard evaluation. Additionally, the reviewer acknowledges it would not be feasible to conduct a study in patients at an earlier stage of disease/cognitive decline (intended clinical use) with the preferred truth standard of autopsy evaluation. Thus, study 007 likely represents the *best case scenario* for estimating the sensitivity and specificity of Vizamyl PET images for detecting beta amyloid plaques in the brain.

**Table 4. Study GE 067-015 (015)**

<b>Study 015</b>	
Design	Multicenter, open label study conducted to estimate the specificity of blinded Vizamyl PET image evaluations for excluding brain amyloid plaques in a population of healthy young adults aged 18 to 40 years.
Protocol date (Original)	11/01/2010
Amendment dates	6/16/2011, 6/30/2011
Statistical plan date	6/16/2011 and amended 8/16/2011
Imaging review manual	8/14/2009 (also used for study 005)
Image review training manual	10/09/2009 (also used for study 005)
Study dates	12/02/2010 to 3/18/2011
Study Population	Healthy male and female adults ages 18 to 40 years assumed to be negative for brain amyloid pathology or other significant medical history. N = up to 300 initially planned for enrollment.
Main Inclusion criteria	<ul style="list-style-type: none"> <li>• Subjects &gt;18 and &lt; 40 years old with no evidence of cognitive impairment by medical history and willing to give informed consent.</li> <li>• Mini-Mental Status Examination score of <math>\geq 28</math>, and considered cognitively</li> </ul>

	<p>normal by investigator.</p> <ul style="list-style-type: none"> <li>• The subject had a normal MRI scan as part of the screening visit.</li> <li>• At least 6 years of education or a work history sufficient to exclude mental retardation.</li> <li>• The subject's general health was adequate to comply with study procedures as determined during screening.</li> <li>• For women of childbearing potential, the results of a serum and urine human chorionic gonadotropin pregnancy test needed to be negative prior to study drug administration.</li> </ul>
<p>Main exclusion criteria</p>	<ul style="list-style-type: none"> <li>• Any subjects who received medical ionizing radiation exposure within 12 months or participated in any other clinical study within 30 days of study entry.</li> <li>• Known allergies to Flutemetamol F 18 Injection or to any of the drug constituents.</li> <li>• The subject was pregnant or breast-feeding.</li> <li>• History of alcohol and/or drug abuse within 2 years.</li> <li>• Contraindication for MRI.</li> <li>• History of head injury with loss of consciousness.</li> <li>• Any clinically significant medical, psychiatric or neurological condition or any clinically significant abnormality on physical, neurological or laboratory examination that might be associated with brain pathology as determined by study investigator.</li> <li>• Family history of AD.</li> <li>• Subject was undergoing monitoring of occupational ionizing radiation exposure.</li> <li>• History of HIV infection or hepatitis.</li> </ul>

Vizamyl dosing	Single IV injection of 185 MBq (5 mCi).
Primary endpoint(s)	Specificity of blinded, independent assessment (negative/positive) of Vizamyl PET images for the presence of brain amyloid as compared to clinical status, which was assumed to be negative for all enrolled subjects.
Secondary endpoint(s)	<ol style="list-style-type: none"> <li>1. Inter-reader agreement</li> <li>2. Intra-reader agreement was assessed through a randomized re-read of 10% of images by each reader.</li> </ol> <p>Additionally, composite SUVR defined as an average of frontal, anterior cingulate, parietal, lateral-temporal and posterior cingulate/precuneous Vizamyl uptake was evaluated.</p>
Safety endpoint(s)	Adverse events (AEs) were recorded throughout the study and at a 24 hour AE safety follow-up telephone call. Subjects were asked to report AEs that occurred within 30 days of study drug administration.
Reference Standard	Baseline clinical status (all enrolled subjects assumed negative for presence of brain amyloid)
Pre-specified efficacy thresholds	The study was successful if at least 3 of 5 blinded readers demonstrated specificity of 80%, as determined by a lower bound of the 95% confidence interval exceeding 80%.
Image interpretation methods	Five blinded readers (neurologists, nuclear medicine physicians, medical physicists) were trained in-person at the sponsor's centralized image review centers to interpret Vizamyl PET images as negative or positive for clinically significant Vizamyl

	<p>uptake in the brain.</p> <p>Vizamyl PET images were interpreted by independent, blinded readers. Images were presented to readers in a random order to readers who were blinded to clinical information, personal information and subject identification. Readers interpreted images without anatomic correlation using a regional brain analysis approach, which included these five regions:</p> <ol style="list-style-type: none"> <li>1. Frontal and Anterior Cinguli</li> <li>2. Posterior cinguli and precuneus</li> <li>3. Insula</li> <li>4. Lateral Temporal lobe</li> <li>5. Striatum</li> </ol> <p>Normal or abnormal patterns of Vizamyl grey matter uptake were recorded for these regions on the CRF. If any one region was read as abnormal, the subject's overall image interpretation was abnormal. Readers had the liberty of choosing between different color scales, including the grey scale.</p> <p>* In attempt to address the issue of reader bias towards normal scan interpretations, all scans from this study (n=181) were blindly and randomly mixed with all Vizamyl scans (n=232) study GE-067-005 (mild cognitive impairment subjects) which was expected to contain approximately 110 abnormal Vizamyl images. Thus the image read for study 015 (413 images) was expected to contain approximately one in four abnormal scans.</p>
<p>Image Review Training and Interpretation Location</p>	<p>The sponsor's image review centers in Oslo, Norway and Princeton, NJ functioned as the core laboratories for the training and blinded image evaluation.</p>

	These centers are a part of GE Healthcare.
Image acquisition methods	Vizamyl PET images were acquired over a 10 minute duration beginning approximately 90 minutes post injection of study drug.
Disease severity of patients at baseline	All subjects were in basic good health at baseline.

### **Reviewer's Comments**

Study 015 was designed to estimate the specificity (primary efficacy analysis) of blinded Vizamyl PET image evaluations for detecting brain amyloid in a population of younger, "healthy" subjects who were all assumed to be negative for brain amyloid. Thus, there was no truth standard employed in this study, simply the reference standard of baseline clinical status. Secondary efficacy analyses included inter-reader agreement and intra-reader agreement.

### **Image Read Methods**

Readers were trained in-person at the sponsor's centralized image review centers to interpret Vizamyl PET images as negative or positive for clinically significant Vizamyl uptake in the brain. Prior to the blinded read, an external trainer (nuclear medicine physician with teaching experience) conducted a common training session for all readers together which included a PowerPoint presentation, hands-on workstation training and printed material. This training was based on the manual "GE-067-005 Image Review Training Manual", which was also given to all readers. Readers learned to interpret Vizamyl images without anatomic correlation based on review of five key regions which should not have Vizamyl uptake in normal individuals. If one region was deemed positive for significant Vizamyl uptake, then that patient's images were interpreted as positive. Readers were required to train on 10 sample training image datasets (images from previous phase 1 and 2 Vizamyl studies), then pass a mock read consisting of five different image sets (from previous Vizamyl studies); none of these image sets were from the phase 3 study or included in the actual BIE.

One inherent source of bias in study 015 was that image readers saw a large number of normal Vizamyl images. Thus, during the image review process, readers may have developed a bias to interpret images as normal. The sponsor attempted to minimize this source of bias by mixing in all previously acquired images (n=232) from study 005 (mild cognitive impairment subjects), 110 of these "mixed-in" images are believed to be positive for clinically significant brain amyloid accumulation. The reviewer notes that final efficacy results for study 005 (image reads compared to the reference standard of

clinical diagnosis of probable AD) were not know at the time of this NDA review, as study 005 is ongoing and the sponsor was still blinded to these results. Thus, it is not known how many “mixed-in images” were actually positive for significant brain amyloid accumulation. This source of bias could lead to an over-estimation of specificity and reader agreement.

The reviewer also notes the study population for 015 does not represent the intended population of Vizamyl clinical use and there is a lack of a disease spectrum in the study population. We would expect this to also lead to an over-estimation of performance characteristics. Additionally, it is possible that the appearance of younger subjects’ brains on PET images may have given clues to readers that subjects were younger. This could have resulted in readers interpreting more images as normal, which would also lead to over-estimating specificity and reader agreement.

#### Summary Comments

The reviewer notes that study 015 contains the inherent weakness of lacking a truth standard given enrolled subjects were less than 40 years old and healthy at baseline, thus pathological brain tissue analysis for amyloid could not be pursued. There is also the issue of an unknown level of reader bias towards interpreting images as normal, which will likely result in an over-estimation of specificity and reader agreement rates.

Given the lack of a truth standard, the reviewer believes the most valuable data gained from study 015 may be the estimates of inter-reader and intra-reader agreement, as it is helpful to know agreement rates in a group of subjects who are expected to have no significant brain amyloid accumulation and should have normal Vizamyl PET image interpretations. The reviewer notes that high rates of agreement would be expected for study 015 given the above mentioned bias issues. If low agreement rates are seen for this study, the reader would have significant concerns regarding the ability of different clinicians to consistently interpret Vizamyl PET images correctly

Even when considering the potential bias issues for study 015, the reader believes that combined with performance (sensitivity/specificity and reader agreement) estimates from study 007 that utilized a gold standard of autopsy evaluation, sufficient data exists to allow a thorough evaluation of Vizamyl for the intended indication.

**Table 5. Study GE 067-021 (021)**

<b>Study 021</b>	
Design	Study to evaluate the effectiveness of an electronic reader training program to teach image interpretation and orientation using pre-existing Vizamyl PET images.

Protocol date (Original)	7/11/2012
Statistical plan date	7/11/2012
Study dates	7/09/2012 – 8/23/2012
Image Selection	Images were selected from previously conducted Vizamyl clinical studies.
Nuclear medicine technologist (NMT) inclusion/exclusion criteria	<ul style="list-style-type: none"> <li>• NMT was practicing in the U.S. and certified by either the American Registry of Radiologic Technologists or the Nuclear Medicine Technology Certification Board.</li> <li>• The NMT candidate was experienced in acquisition, processing, and orientation for reading of nuclear images of the brain.</li> <li>• The NMT had passed the tests which accompany the image orientation electronic training module.</li> </ul>
Blinded reader inclusion/exclusion criteria	<ul style="list-style-type: none"> <li>• U.S. board certified nuclear medicine doctor or board certified radiologist with nuclear medicine training.</li> <li>• Reader passed training tests and completed the reader qualification attestation.</li> <li>• Experience in reading clinical nuclear medicine images.</li> <li>• Agreed to scope, timeframe and commitment of BIE program.</li> </ul>
Vizamyl dosing	Single IV injection of 185 MBq (5 mCi) for primary efficacy population.
Primary endpoint(s)	Sensitivity and specificity of blinded visual image interpretations of Vizamyl PET images from subjects with any standard of truth (brain autopsy, brain biopsy, assumed clinical status)
Secondary endpoint(s)	<ul style="list-style-type: none"> <li>• Sensitivity and specificity of blinded</li> </ul>

	<p>visual image interpretations without anatomic image correlation for autopsy group (study 007 images).</p> <ul style="list-style-type: none"> <li>• Sensitivity and specificity of blinded visual image interpretations with anatomic image correlation.</li> <li>• Positive predictive value and negative predictive value of blinded Vizamyl PET reads with and without anatomic image correlation.</li> <li>• Inter and Intra-reader agreement without anatomic image correlation.</li> </ul>
Safety endpoint(s)	No new safety data was obtained.
Reference Standard	Reference standards included autopsy (study 007) brain evaluation, brain biopsy (studies 009, 010, &011) and assumed baseline clinical status (study 015).
Pre-specified efficacy thresholds	Study success was achieved if the same 3 out of 5 readers achieved greater than 70% sensitivity and specificity in their blinded image interpretations for the primary endpoint analysis.
Image interpretation methods	<p>Five blinded independent readers (3 nuclear medicine physicians and 2 radiologists) were trained using the sponsor's DVD program.</p> <p>Images were presented to readers in a random order to readers who were blinded to clinical information, personal information and subject identification. Readers interpreted images without anatomic correlation using a regional brain analysis approach, which included these five regions:</p> <ol style="list-style-type: none"> <li>1. Frontal and Anterior Cinguli</li> <li>2. Posterior cinguli and precuneus</li> <li>3. Insula</li> <li>4. Lateral Temporal lobe</li> </ol>

	<p>5. Striatum</p> <p>Normal or abnormal patterns of Vizamyl grey matter uptake were recorded for these regions on the CRF. If any one region was read as abnormal, the subject's overall image interpretation was abnormal. Readers had the liberty of choosing between different color scales, including the grey scale.</p>
Image acquisition methods	The study utilized previously acquired Vizamyl PET images from the sponsor's clinical development program.
Disease severity of study subjects at baseline.	No new subjects were enrolled in this study.

**Reviewer's Comments**

Study 021 enrolled no new subjects and utilized Vizamyl PET images from the sponsor's previously conducted clinical studies in order to validate the effectiveness (sensitivity and specificity) of an electronic DVD training program developed by the sponsor to teach both proper image orientation and blinded interpretation of Vizamyl images.

The primary efficacy endpoint included images from studies with a variety of reference standards including autopsy evaluation (007), brain biopsy (009,010,011) and baseline clinical status (015). The reviewer notes this inclusion of multiple reference standards in the primary efficacy analysis raises some concern regarding reliability of performance characteristic estimates in this study.

Image Read Methods

The sponsor's image interpretation training DVD teaches readers to evaluate Vizamyl scans using a color scale and region-based analysis, without the use of anatomic (CT or MRI) correlation. Details of the recommended image interpretation methods (*from the DVD training program*) are summarized below.

Image Orientation

Axial and coronal images are oriented so that brain structures are seen symmetrically, with equal heights of structures bilaterally. Sagittal images are oriented so that the patient's head and neck are neither flexed nor extended; the anterior and posterior aspects of the corpus callosum should be parallel to the AC-PC line.

### Image Display

- All image planes (axial, sagittal and coronal planes) are linked by crosshairs.
- The reader selects a color scale (e.g., rainbow, spectrum, or Sokoloff scale) that should (1) provide distinct colors to clearly discriminate intensity levels above and below the intensity level of the pons, (2) provide a distinct color for regions with little or no amyloid binding such as the cerebellar cortex, and (3) provide a range of at least five distinct colors above 50 to 60% of the peak intensity.
- The reader adjusts the color scale to set the pons at approximately 90% maximum intensity. The cerebellar cortex should represent approximately 20-30% of peak intensity on both negative and positive Vizamyl scans.
- The reader briefly looks through axial brain slices from bottom to top and looks for signs of brain atrophy.
- Next, readers should systematically review the following brain regions for Vizamyl uptake:
  - Frontal lobes (axial, with optional sagittal plane display)
  - Posterior cingulate and precuneus (sagittal, with optional coronal plane display)
  - Lateral temporal lobes (axial, with optional coronal plane display)
  - Inferolateral parietal lobes (coronal, with optional axial plane display)
  - Striatum (axial, with optional sagittal plane display)

### Image Interpretation

Image interpretation is based upon the distribution of radioactive signal within the brain; clinical information is not a component of the image assessment. Images are designated as positive or negative by comparing the radioactivity in cortical grey matter with activity in adjacent white matter, or based on the intensity in the five regions mentioned above. The signal uptake in the cerebellum does not contribute to scan interpretation (for example, a positive scan may show retained cerebellar grey-white contrast even when the cortical grey-white contrast is lost).

- **Negative scans** show more Vizamyl uptake in white matter than in the grey matter, creating clear grey-white contrast. Specifically, a negative scan would have the following characteristics:
  - frontal, lateral temporal, inferolateral parietal lobes: gradual gradient from bright intensity of the white matter to lower intensity at the periphery of the brain; distinct sulci with concave surfaces (white matter sulcal pattern)

*and*

- posterior cingulate and precuneus: grey matter uptake below 50-60% of peak intensity; gap of lower intensity separates two hemispheres on coronal view

*and*

- striatum: approximately 50% of peak intensity in the region between the higher intensities of the thalamus and frontal white matter (striatal “gap”)

- **Positive scans** show at least one cortical region with reduction or loss of the normally distinct grey-white matter contrast. These scans have one or more regions with increased cortical grey matter signal (above 50-60% peak intensity) and/or reduced (or absent) grey-white matter contrast (white matter sulcal pattern is less distinct). A positive scan may have one or more regions in which grey matter radioactivity is as intense or exceeds the intensity in adjacent white matter.

Specifically, a positive scan would have the following characteristics:

- frontal, lateral temporal, or inferolateral parietal lobes: high intensity seen to the periphery of the brain, with sharp reduction of intensity at the brain margin; sulci not distinct due to fill-in by high intensity grey matter, resulting in a convex surface at the edge of the brain

*or*

- posterior cingulate and precuneus: grey matter uptake above 50-60% of peak intensity; high grey matter intensity that closes the gap between the two hemispheres on coronal view

*or*

- striatum: intensity above 50-60% of peak intensity; gap between thalamus and frontal white matter not distinct

If any one of the five brain regions systematically reviewed for Vizamyl uptake is positive, then the overall scan is considered positive. Otherwise, the scan is considered negative.

### Summary Comments

Study 021 was designed to test the sensitivity and specificity of blinded, visual interpretation of Vizamyl PET images following reader training with the sponsor’s DVD program. The reviewer believes this to be an important study providing useful data on the ability of readers to consistently interpret Vizamyl images using a standardized approach to image review. However, the study contains the inherent bias of using multiple reference standards (autopsy, biopsy & clinical status) in the primary efficacy

analysis population. Thus, the reviewer believes the secondary analysis conducted for the autopsy population (n=68), which is seen in table 16, may provide more useful information for understanding the effectiveness of the DVD training program. Comparison of the performance estimates for the autopsy population for study 021 compared to study 007 will provide insight into the performance of Vizamyl readers following in-person training vs. standardized electronic training.

## 6 Review of Efficacy

### Efficacy Summary

Upon review of the total submitted data in support of Vizamyl effectiveness for estimating brain  $\beta$  amyloid neuritic plaque density, the reviewer finds the performance characteristics acceptable for the intended population.

Please note, the reviewer highlights the adjunctive nature of this diagnostic test and that Vizamyl PET imaging alone is not intended to diagnose AD or other disease states associated with cognitive decline. The reviewer notes that Vizamyl scans should be interpreted by readers without knowledge of the patient's clinical information (e.g. diagnostic test results), but that final image interpretations should be used by patient providers in the context of the patient's entire clinical picture and all available information.

### Indication

Sponsor's original proposed indication:

(b) (4)



Current, revised indication statement:

The below indication statement represents the most current version as revised by the FDA review team. The most significant changes were:

- Changing (b) (4) to negative/positive
- Changing (b) (4) to “estimate  $\beta$  amyloid neuritic plaque density”

The above label changes were implemented to make the Vizamyl label more consistent with the submitted data.

Vizamyl is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate  $\beta$  amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) or other causes of cognitive decline. A negative Vizamyl scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient’s cognitive impairment is due to AD. A positive Vizamyl scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Vizamyl is an adjunct to other diagnostic evaluations. (1)

Limitations of Use:

- A positive Vizamyl scan does not establish a diagnosis of AD or other cognitive disorder (1).
- Safety and effectiveness of Vizamyl have not been established for:
  - Predicting the development of dementia or other neurological condition;
  - Monitoring responses to therapies (1).

**Dose**

The majority of subjects in the phase 3 pivotal studies received IV Vizamyl at a dose of 185 MBq (5 mCi). However, 175 of 180 subjects in study 007 receive single doses of Vizamyl between 182 MBq to 403 (5mCi – 11mCi), with a median dose of 359 MBq (~10 mCi).

**Reviewer’s Comments**

Vizamyl dosing used in the sponsor’s phase 3 pivotal studies is consistent with the proposed label dosage.

### 6.1.1 Methods

This efficacy review focuses on the primary endpoints of sensitivity and specificity obtained from studies 007 (sensitivity), 015 (specificity) and 021 (sensitivity and specificity) for estimating the performance characteristics of Vizamyl PET imaging in detecting  $\beta$  amyloid burden in the brain. These studies provide the main supportive data for the clinical usefulness, reliability and accuracy of Vizamyl for detection of  $\beta$  amyloid neuritic plaques in the brains of adult patients with cognitive impairment.

The reviewer notes the sponsor is not seeking a diagnostic indication for Vizamyl, but rather “functional, physiological, or biochemical assessment” type indication, which is described in the FDA Guidance for Industry titled: Developing Medical Imaging Drug and Biological Products, Part 2: Clinical Indications.

### 6.1.2 Demographics

**Table 6. Demographic data for studies 007, 015 and 021.**

Study	007 <sup>a</sup>	015	021 <sup>b</sup> (N=135)
<b>Mean Age</b> <b>Min, Max,</b>	81 (60,95)	30 (18,40)	65 (20,95)
<b>Gender</b> <b>Male</b> <b>Female</b>	33 (49) 35 (51)	78 (43) 103 (57)	70 (52) 65 (48)
<b>Race</b> <b>White</b> <b>Black</b> <b>Asian</b> <b>Other</b>	64 (94) 2 (3) 0 2 (3)	156 (86) 19 (10) 3 (2) 3 (2)	127 (94) 4 (3) 1 (1) 3 (2)

- a. Includes only subjects from the post-mortem brain autopsy group, from which all efficacy analyses were performed.  
 b. Includes subjects from brain autopsy study (GE067-007), brain biopsy studies (GE067-009, GE067-010, GE067-011), and young healthy volunteer study of specificity (GE067-015); this group represents the primary efficacy analysis.

#### Reviewer Comments

The reviewer notes that the intended population for clinical use will include mostly people above the age of 60; this population of subjects was included in the pivotal phase 3 investigations. The reviewer also highlights that few minorities were included in the pivotal studies submitted in support of Vizamyl.

### 6.1.3 Subject Disposition

**Table 7. Subject disposition data for studies 007, 015 and 021.**

<b>Study</b>	<b>007</b>	<b>015</b>	<b>021</b>
<b>Enrolled</b>	203	218	276
<b>Dosed</b>	180	181	N/A
<b>Efficacy</b>	68	181	276
<b>SOT Evaluated</b>	68	181	276
<b>Primary Efficacy Evaluated</b>	68 <sup>a</sup>	181	135 <sup>b</sup>

- a. Includes only subjects from the post-mortem brain autopsy group, from which all efficacy analyses were performed.  
b. Includes subjects from brain autopsy study (GE067-007), brain biopsy studies (GE067-009, GE067-010, GE067-011), and young healthy volunteer study of specificity (GE067-015); primary efficacy analysis was performed in this group.

#### **Reviewer Comments**

The reviewer notes that the above differences in dosed patients and efficacy and/or SOT evaluated subjects does not relate to missing data, but to other factors such as availability of autopsy evaluation (study 007) and specific sub-populations being selected for the primary efficacy analysis (021).

### 6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints used to evaluate the performance of Vizamyl PET imaging for detecting clinically significant beta amyloid in the brain were sensitivity and specificity for studies 007, 015 and 021. The reviewer notes that specificity was considered by the sponsor as a secondary endpoint in study 007 and that sensitivity estimates were not possible in study 015 due to lack of a truth standard.

Vizamyl final image interpretations were categorized as:

True positive (TP), Visual read identified PET image as showing “abnormal Vizamyl uptake” from the baseline PET scan and SOT categorization as abnormal, or

True negative (TN): Visual read identified PET image as showing “normal Vizamyl uptake” from the baseline PET scan and SOT categorization as normal, or

False positive (FP): Visual read identified PET image as showing “abnormal Vizamyl uptake” from the baseline PET scan and SOT categorization as normal, or

False negative (FN): Visual read identified PET image as showing “normal Vizamyl uptake” from the baseline PET scan and SOT categorization as abnormal.

These data were used to calculate estimates of sensitivity and specificity for each study.

Sensitivity was defined as:  $\frac{nTP}{nTP + nFN}$ .

Specificity was defined as:  $\frac{nTN}{nTN + nFP}$ .

### Study GE 067-007 (autopsy study)

**Table 8. Estimates of sensitivity and specificity of Vizamyl PET imaging in a population of terminally ill patients with a range of cognitive function (N=68).** Image reads were performed without anatomic correlation following in person reader training; brain autopsy evaluation served as the standard of truth.

Reader	Sensitivity (confidence interval)	Specificity * (confidence interval)
1	81 (67,92)	88 (69,98)
2	88 (74,96)	92 (74,99)
3	93 (81,99)	44 (24,65)
4	93 (81,99)	80 (59,93)
5	88 (75,96)	92 (74,99)

\* Specificity was designated as a secondary endpoint by the sponsor; the reviewer includes it here due to the equal importance of specificity for understanding Vizamyl performance.

### Reviewer Comments

The sponsor exceeded the pre-defined success threshold of 70% sensitivity for four out of five blinded readers; therefore study 007 successfully met its objectives.

To fully understand the performance of Vizamyl brain imaging, the reviewer finds it helpful to also consider the specificity estimates (secondary endpoints) in study 007. As seen above, three of five readers were below the 70% threshold (lower bound of 95%CI) for specificity, albeit one reader just missed the mark at 69% (88% point estimate) for the lower bound of his/her confidence interval. This finding is related to false positive image interpretations and the positive predictive value of Vizamyl PET scanning. Importantly, the sponsor's proposed labeling reflects this issue with the text referencing positive Vizamyl scans and the adjunctive nature of Vizamyl PET imaging.

In conclusion, the sponsor met their success criteria for sensitivity and study 007 provides reasonable confidence in the ability of blinded interpretations of Vizamyl PET images to detect clinically significant beta amyloid plaque in the brain.

**GE 067-015 (healthy young subjects)**

**Table 9. Estimates of Specificity of Vizamyl PET imaging in a population of young healthy subjects (N=181).** Image reads were performed without anatomic correlation following in person reader training; all subjects were assumed negative for brain amyloid accumulation.

Reader	Specificity (confidence interval)
1	100 (98,100)
2	68 (61,75)
3	99 (97,100)
4	99 (97,100)
5	99 (96,100)

**Reviewer Comments**

The sponsor met their success threshold of 80% specificity (lower bound of confidence interval) for at least three of five blinded readers, with four readers exceeding 96% for the lower bound of the 95% confidence interval. These estimates provide reasonable assurance that Vizamyl scans should be negative in people who have no beta amyloid accumulation in their brain. Comparing these results to the specificity estimates for study 007 allows one to see that in older, sicker patients, there is a greater chance for false positive Vizamyl scan interpretations. As briefly mentioned above, this important observation underscores the importance of the entire clinical workup, rather than reliance on Vizamyl (adjunctive test) alone for clinical decision making.

Specificity estimates for reader 2 were clearly lower than all the other readers and the lower bound of the confidence interval (61%) did not exceed the success threshold of 80%. The sponsor explained this reader as a “systematic outlier”.

Given the unknown level of inherent bias towards interpreting images as normal in study 015, it’s somewhat expected, and reassuring, to see estimates of specificity close to 100% for four out of five readers. The reviewer believes “lower” specificity estimates would raise significant concern regarding the reliability of positive (related to specificity) Vizamyl scan interpretations.

**Study GE067-021 (validation of electronic reader training program)**

**Table 10. Estimates of sensitivity and specificity of Vizamyl PET imaging (without anatomic correlation) with use of the electronic training program (N=135).**

Population includes a mix of truth standards including those with histopathological confirmation by biopsy (studies 009, 010 and 011), by autopsy (007), or assumed based on clinical status (study 015). N = 135 for all readers.

<b>Reader</b>	<b>Sensitivity (confidence interval)</b>	<b>Specificity (confidence interval)</b>
1	94 (84,99)	79 (68,77)
2	92 (81,98)	81 (71,89)
3	90 (79,97)	93 (81,97)
4	94 (84,99)	77 (67,86)
5	84	96

	(71,93)	(90,99)
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**Reviewer Comments**

The above primary efficacy analysis results for study 021 (utilizing a mix of truth standards) reveal sensitivity and specificity estimates that exceeded the sponsor’s pre-defined success threshold of 70% for the lower bound of the 95% confidence interval. Although study success was achieved for the primary efficacy analysis, the reviewer believes the autopsy alone analysis population (table 16) provides more clinically meaningful data from this study and allows one to compare the electronic training method to the in person training method in study 007.

**6.1.5 Analysis of Secondary Endpoints(s)**

**Study GE067-007**

**Table 11. Estimates of sensitivity and specificity of Vizamyl PET imaging (with anatomic correlation) in a population of terminally ill patients with a range of cognitive function (N=68).** Image reads were performed following in person reader training; brain autopsy evaluation served as the standard of truth.

<b>Reader</b>	<b>Sensitivity (confidence interval)</b>	<b>Specificity (confidence interval)</b>
1	91 (78,97)	92 (74,99)
2	95 (84,99)	88 (69,98)
3	98 (88,100)	56 (35,76)
4	91 (78,97)	88 (69,98)
5	91 (77,97)	92 (74,99)

**Reviewer Comments**

Sensitivity estimates tended to be slightly higher for the autopsy population in study 007 when anatomic correlation was used for image evaluation, but specificity results were again lower than 70% (lower bound of confidence interval) for three of five readers.

**Table 12. Study 007 Inter-reader agreement results.**

Reader Pair	N	Agreement n (%)
Reader 1 vs. Reader 2	175	159 (91)
Reader 1 vs. Reader 3	176	140 (80)
Reader 1 vs. Reader 4	175	164 (94)
Reader 1 vs. Reader 5	176	169 (96)
Reader 2 vs. Reader 3	175	148 (85)
Reader 2 vs. Reader 4	175	158 (90)
Reader 2 vs. Reader 5	175	163 (93)
Reader 3 vs. Reader 4	175	141 (81)
Reader 3 vs. Reader 5	176	145 (82)
Reader 4 vs. Reader 5	175	168 (96)
Readers 1, 2, 3, 4, 5	175	131 (75)

**Table 13. Study 007 Intra-reader agreement results.**

Reader Pair	N	Agreement n (%)
Reader 1	17	16 (94)
Reader 2	17	17 (100)
Reader 3	17	15 (88)
Reader 4	17	17 (100)
Reader 5	17	17 (100)

**Reviewer Comments**

The inter-reader and intra-reader agreement rates for study 007 are seen above and provide confidence in the ability of different readers to interpret Vizamyl scans fairly consistently, as inter-reader agreement rates were in the 90-96% range when excluding reader 3 and in the 80-96% range with reader 3 comparisons included. Within reader reproducibility was also found to be acceptable and ranged from 88% (reader 3) to 100%.

**Study GE067-015**

Tables fourteen and fifteen provide the inter-reader and intra-reader agreement (re-reads) numbers for study 015 in which all subjects were assumed negative for amyloid accumulation.

**Table 14. Study 015 Inter-reader agreement in a population of healthy subjects.**

Reader Pair	N	Agreement n (%)
Reader 1 vs. Reader 2	181	123 ( 68)
Reader 1 vs. Reader 3	181	180 ( 99)
Reader 1 vs. Reader 4	181	180 ( 99)
Reader 1 vs. Reader 5	181	179 ( 99)
Reader 2 vs. Reader 3	181	124 ( 69)
Reader 2 vs. Reader 4	181	124 ( 69)
Reader 2 vs. Reader 5	181	125 ( 69)
Reader 3 vs. Reader 4	181	181 (100)
Reader 3 vs. Reader 5	181	180 ( 99)
Reader 4 vs. Reader 5	180	180 ( 99)
Readers 1, 2, 3, 4, 5	180	123 (68)

**Table 15. Study 015 Intra-reader agreement in a population of healthy subjects.**

Reader Pair	N	Agreement n (%)
Reader 1	13	13 (100)
Reader 2	16	12 (75)
Reader 3	21	21 (100)
Reader 4	13	13 (100)
Reader 5	13	13 (100)

**Reviewer Comments**

When excluding reader 2, inter-reader agreement was found to be 99-100% and within reader reproducibility was 100%. The sponsor described reader 2 as a “systematic outlier”. These data on reader agreement in healthy subjects are acceptable to the reviewer, and when considered along with agreement rates from study 007, provide confidence that Vizamyl scans can be interpreted consistently among readers in both patients with and without clinically significant brain amyloid accumulation.

The reviewer again notes the inherent potential for bias in study 015 due to the high number of normal Vizamyl images seen by readers, which likely has led to some over-estimation of the agreement rates seen above.

**Study GE067-021**

**Table 16. Sensitivity and specificity of Vizamyl PET imaging by reader following completion of DVD training program in the autopsy truth standard population only (N=68).** Images were interpreted without anatomic correlation.

Reader	Sensitivity (confidence interval)	Specificity (confidence interval)
1	93	72

	(81,99)	(51,88)
2	93 (81,99)	84 (64,86)
3	91 (78,97)	88 (69,98)
4	93 (81,99)	60 (39,79)
5	86 (72,95)	92 (74,99)

**Studies 007 and 021 compared for autopsy population only.**

**Table 17. Vizamyl scan performance (median and range) by reader training method in autopsy standard of truth population (N = 68). Images were interpreted without anatomic correlation.**

Test Performance		In-Person Training (Study 007)	Electronic Media Training (Study 021)
Sensitivity (%)	Median	<b>88</b>	<b>91</b>
	Range among the 5 readers	(81 – 93)	(86 – 98)
Specificity (%)	Median	<b>88</b>	<b>76</b>
	Range among the 5 readers	(44 – 92)	(60 – 88)

**Reviewer Comments**

The reviewer notes that comparing the performance results for Vizamyl following use of the DVD reader training program vs. in-person training (study 007) reveals no important differences between the two training methods.

### 6.1.6 Other Endpoints

**Table 18. Vizamyl scan interpretations by reader training method among autopsied patients (N = 68 for both studies).**

		In-Person Training (Study 007)					Electronic Media Training (Study 021)				
		Reader					Reader				
		1	2	3	4	5	6	7	8	9	10
All scans with autopsy (n = 68)	Correct	62	62	56	61	61	58	61	61	55	60
	False Negative	4	2	1	4	4	3	3	4	3	6
	False Positive	2	3	11	3	2	7	4	3	10	2

#### Reviewer Comments

The reviewer notes similar numbers of correct, false negative and false positive Vizamyl scan interpretations among the different readers for study 007 (in-person training) and study 021 (DVD reader training).

### 6.1.7 Subpopulations

The submitted data did not reveal important differences in Vizamyl efficacy for subpopulations of the pivotal studies.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dose and imaging time window for Vizamyl is based on the dose ranging portion of Study ALZ103. For details, please see section 4.4.3.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

This is not believed to be applicable to administration of Vizamyl.

### 6.1.10 Additional Data

**Table 19. Time from Vizamyl PET scan to patient death in study 007.**

Time from Vizamyl PET scan to death	Average time: 3.5 months
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(post mortem analysis set; N=68)	Minimum: 0 months Maximum: 13 months
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### Reviewer Comments

The reviewer notes that for study 007, the average time from Vizamyl PET scanning to patient death was only 3.5 months, with the longest interval being 13 months. This is important to consider as the time when brain specimens were fixed/preserved for autopsy analysis was immediately after death. Upon considering these numbers, the reviewer has confidence that the pathology of patients' brains, related to amyloid deposition, at the time of Vizamyl PET imaging was similar to the pathology of their brains during the autopsy (standard of truth) evaluations.

### Summary of Vizamyl doses administered in study 007.

The reviewer notes that for study 007, the average dose of Vizamyl was greater than that administered in studies 015 and 021. For the autopsy population (primary efficacy), doses ranged from 185 MBq (5mCi) to 388.5 MBq (~10 mCi), with a median dose of 359 MBq (~10 mCi).

## 7 Review of Safety

The safety database for Vizamyl consists of 761 subjects evaluated in 10 separate clinical studies. There have been no deaths attributable to Vizamyl; one hypersensitivity type reaction SAE was deemed related to Vizamyl injection by study investigators. Analyses of data from clinical laboratory evaluations, vital sign monitoring and ECG assessments have revealed no important concerns regarding Vizamyl administration.

The medical officer believes the safety database for Vizamyl is of acceptable size and scope, and there are no significant safety concerns for the clinical use of Vizamyl as related to the proposed indication.

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

**Table 20. All studies included in safety database.**

Study	Phase	N	Baseline status
ALZ103	1	22	pAD (8) and HV (14)
ALZ201	2	72	pAD (27), aMCI (20) and

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			HV (25)
GE-067-005	3	232	aMCI (232)
GE-067-007	3	180	Terminal illness (180)
GE-067-008	3	7	NPH
GE-067-009	3	12	NPH
GE-067-010	1	15	NPH
GE-067-011	3	18	NPH
GE-067-014	1	22	pAD (8) and HV (4)
GE-067-015	3	181	HV

aMCI = amnesic MCI; HV = healthy volunteer; MCI = mild cognitive impairment;  
 NPH = normal pressure hydrocephalus; pAD = probable Alzheimer's disease.

**Table 21. Patient Demographics for overall safety database.**

Characteristic	Statistic	Safety Analysis Set <sup>a</sup>
Age, y <sup>b</sup>	N	761
	Mean (Standard deviation)	62 (21.24)
	Median	69
	Min, Max	18, 98
	95% Confidence Interval	(60.6, 63.6)
Gender, n (%)	Female	394 (52)
	Male	367 (48)
Race, n (%)	American Indian or Alaska Native	1 (<0.5)
	Asian	27 (4)
	Black	33 (4)
	Native Hawaiian or other Pacific Islander	1 (<0.5)
	White	693 (91)
	Other	6 (1)
Ethnicity, n (%)	Not Hispanic or Latino	557 (73)
	Hispanic or Latino	160 (21)
	Missing	44 (6)
Height, cm	N	726
	Mean (Standard deviation)	167.3 (10.31)
	Median	167.5
	Min, Max	137.2, 197.3
	95% Confidence Interval	(166.6, 168.1)
Weight, kg	N	742
	Mean (Standard deviation)	73.1 (17.38)
	Median	71.8
	Min, Max	26.8, 156.0
	95% Confidence Interval	(71.9, 74.4)
Body mass index, kg/m <sup>2</sup>	N	724
	Mean (Standard deviation)	26.1 (5.30)
	Median	25.3
	Min, Max	11.9, 58.0
	95% Confidence Interval	(25.7, 26.4)

cm = centimeters; kg = kilograms; kg/m<sup>2</sup> = kilograms per square meter of body surface area; Max = maximum value observed; Min = minimum value observed; n = number of subjects in subcategory; N = number of subjects overall (denominator); y = years.

<sup>a</sup> Includes subjects from ALZ103, ALZ201, GE067-005, GE067-007, GE067-008, GE067-009, GE067-010, GE067-011, GE067-014, and GE067-015.

<sup>b</sup> Age calculated as [Date of inclusion – Date of birth] / 365.25 rounded down to the nearest integer.

REF: ISS Table [1.2]

### 7.1.2 Categorization of Adverse Events

Classification of the adverse event data was based on the Medical Dictionary for Regulatory Activities (MedDRA) classification system, Version 13.1.

### **7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence**

Safety data for Vizamyl were pooled across the 10 clinical studies due to the small number of subjects enrolled in the majority of studies.

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

All subjects enrolled in the clinical studies were adults over the age of 18 years who received a single\* IV Vizamyl dose, with a range from 93.4 MBq to 403 MBq (~2.5 – 11 mCi) and a median dose of **183.5 (5 mCi)**. The majority of subjects in the phase 3 pivotal studies received IV Vizamyl at a dose of 185 MBq (5 mCi). However, 175 of 180 subjects in study 007 receive single doses of Vizamyl between 182 MBq to 403 (5mCi – 11mCi), with a median dose of 359 MBq (~10 mCi).

\* In the proof-of-concept Phase 2 study ALZ201, 7 subjects each received 2 administrations of Vizamyl; however, only the safety data collected during the first administration of Vizamyl were used in the sponsor's integrated summary of safety, because of the small number of subjects, which is less than 1% of the overall program.

### **Reviewer's Comments**

The medical officer believes dosing and administration of Vizamyl in the sponsor's clinical development program was appropriate to allow an adequate safety evaluation of the drug for its proposed indication. Analysis of data from study ALZ201 does not reveal any concerning safety signals from subjects who received 2 administrations of Vizamyl.

### **7.2.2 Explorations for Dose Response**

Exploratory studies using multiple radioactive and mass doses were conducted in a small number of subjects to obtain data on Vizamyl biodistribution, clearance, and radiation dosimetry estimates. These data were utilized to determine the optimum dose and imaging time for Vizamyl. No significant differences in safety outcomes were identified for different doses of Vizamyl. See section 4.4.3 for further details.

### **7.2.3 Special Animal and/or In Vitro Testing**

Not applicable for this NDA.

### 7.2.4 Routine Clinical Testing

The routine clinical testing of study subjects was adequate to address the safety of the drug; no important safety signals were identified.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Please see section (4.4) of this review, as well as the clinical pharmacology reviewer's document for details on the metabolism and clearance of Vizamyl.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pharmacological effects from intravenous administration of Vizamyl are not observed in humans following the proposed dose of 20 micrograms. Clinical experience with the other related drug, Amyvid, has not revealed any important safety signals.

## 7.3 Major Safety Results

**Table 22. Summary of safety results for subjects in Vizamyl clinical development program.**

N = 761 subjects	Overall n (%)	Possibly Vizamyl related * n (%)
Subjects with at least one treatment emergent adverse event (TEAE)	76 (10)	44 (6)
Subjects with at least one TEAE leading to study drug discontinuation	0	0
Subjects with at least one TEAE leading to study drug discontinuation	3 (0.4)	2 (0.3)
Subjects with at least one serious non-fatal TEAE	3 (0.4)	1 (0.1)
Subjects with at least one TEAE leading to death	2 (<0.5)	0

\*Relation to Vizamyl administration was determined by study investigator

### 7.3.1 Deaths

There were no deaths attributed to Vizamyl in any of the studies submitted in the sponsor's NDA. Two subjects died in study 007 within the 24 hour adverse event monitoring period and were reported as serious adverse events; the fatal events were prostate cancer and senile dementia. These deaths, which are discussed below, were not thought to be related to Vizamyl administration as judged by the study investigators.

**Subject 109-0006**, an 80 year-old white man, had active medical conditions including AD, pulmonary embolism (multiple), and a life expectancy of less than 24 hours due to endstage prostatic cancer at enrollment on (b) (6). No concomitant medications were used. On examination, the subject was cachectic, with little spontaneous movement, and responsive only to deep pain. A CT of the brain showed severe atrophic changes consistent with a clinical diagnosis of dementia of the Alzheimer's type. At 13:41 hours, the subject received an intravenous administration of 358.9 MBq (9.7 mCi) of study drug. Prior to injection, the subject was tachycardic, hypotensive, and hyperventilating but afebrile. Status remained constant through to completion of study procedures, with no clinical changes evident before and after flutemetamol PET imaging, and he was discharged in the same condition at approximately (b) (6) hours. At approximately (b) (6) the facility was notified that the subject had died; death had been imminent and expected. The investigator ascribed death as being due to prostate cancer (preferred term = prostate cancer) and unrelated to study drug.

**Subject 122-0022**, an 86-year-old white man, had active medical conditions including dementia (probably Alzheimer's type), psychosis, agitation, cellulitis, constipation, and pruritus when he enrolled in the study. Past medical conditions included a recent fall in the residential nursing home. Concomitant drugs included fentanyl, risperidone, cephalexin (Keflex), lorazepam (Ativan), polyethylene glycol, oxycodone hydrochloride, and diphenhydramine (Benadryl). At the screening examination on (b) (6), an index CT brain scan was performed. At the baseline examination on (b) (6), the ECG was abnormal but not clinically meaningful (heart rate was 115 beats/min). Reflexes were normal but the subject was lethargic and unable to follow commands. At 14:21 hours, 325.6 MBq (8.8 mCi) of study drug was administered intravenously followed by a 10 mL saline flush. Image acquisition started at 15:57 hours. At end-of-scanning ECG, physical examination, and neurological examination showed no changes from baseline. The following day (b) (6) the investigator received notification that the subject had died in his sleep at (b) (6) hours. Due to the fall some days earlier, the subject came under the jurisdiction of the Medical Examiner and an autopsy was performed. The index CT scan had shown no cerebral bleeding or cranial fracture. The preliminary pathology report confirmed no cerebral bleeding, and the cause of death was ascribed to Alzheimer's dementia (preferred term = senile dementia). The investigator assessed the event of death as unrelated to study drug. The subject completed the study.

### Reviewer's Comments

Upon review of these two patient reports, the medical officer agrees these two deaths were likely related to the patients' underlying medical diagnoses, not administration of Vizamyl.

### 7.3.2 Nonfatal Serious Adverse Events

Three subjects experienced nonfatal serious adverse events; only one of these SAEs was believed to be related to Vizamyl administration and involved a hypersensitivity type reaction in a 62 year old female subject, which is described below.

The following is taken from the NDA:

The single reported case of *anaphylactic reaction* was reported for Subject 005/013-0021, a female subject in the Phase 3 study of the conversion from aMCI to pAD (GE067-005), who was 62 years old at the time and in good physical condition. After meeting all entry criteria, she received 181 MBq of Flutemetamol F 18 Injection intravenously on 29 September 2010 at 3:23 PM. Within 1 minute after administration, she developed a "strange feeling" and facial flushing, followed by dyspnea, chest pressure, and a brief hypertensive response (from 144/75 mm Hg at baseline to 182/101 mm Hg at 3:26 PM, 3 minutes after onset). She was treated with 1 mg epinephrine intramuscularly. Within 5 minutes, the blood pressure had normalized to 125/81 mm Hg. The reaction resolved within 53 minutes (4:30 PM). Other blood pressure values were: 145/81 mm Hg at 3:30 PM, 153/80 mm Hg at 3:34 PM, and 149/74 mm Hg at 3:48 PM. The timing of the epinephrine injection is unclear, as the blood pressure reportedly normalized to 125/81 mm Hg within 5 minutes after epinephrine was given. The investigator considered this to be an anaphylactic reaction and reported it as such. However, based on the sponsor's review of this SAE, it was actually an anaphylactoid reaction (discussed below).

The investigator assessed the relationship between the reaction and the study drug as related. The subject underwent scanning and subsequent safety assessments successfully (physical and neurological examinations and assessments of vital signs, ECG, and clinical laboratory parameters were reportedly unchanged from screening, at which time they had been normal). The subject had a history of 1 prior hypertensive episode, which was followed by nausea, in 1993. That episode started 15 minutes after induction of anesthesia with Fentanyl, Sukolin, and Thiopental.

### Reviewer's Comments

The reviewer agrees with the site investigator's assessment that this hypersensitivity reaction may have been, at least in part, due to Vizamyl administration. The reviewer notes the exact timing of the epinephrine injection as related to the onset of hypertension is unclear. However, epinephrine would be expected to cause or worsen hypertension and would not usually be given to treat hypertension. The epinephrine

was given in this case to treat the other hypersensitivity-type symptoms described above.

The other two nonfatal SAEs which occurred, but were not thought to be attributed to Vizamyl are discussed below.

Anaemia: Subject 104-0004, was a 72-year-old white woman with a medical history of Parkinson's disease, iron deficiency anemia, low hemoglobin, low erythrocyte count, rectal prolapse, rectal prolapse surgery, hiatal hernia, anterior and posterior colporrhaphy, vaginal hysterectomy, hearing impairment (high tone deafness), and urinary incontinence. She was taking ropinirole, madopar, entacapone, trospium and paracetamol concomitantly and through study completion. On [REDACTED]<sup>(b) (6)</sup>, at 13:33, the subject received an administration of 355.9 MBq of study drug, and PET imaging was completed according to protocol. Blood samples could not be obtained that day. The following day, the research nurse performed the 24-hour phone call for follow up and no AE was reported, although the subject had pain attributed to her rectal prolapse. Later in the evening the same day the subject was hospitalized for feeling unwell and she was found to be anemic. The patient received blood transfusions and her symptoms resolved on [REDACTED]<sup>(b) (6)</sup>. The investigator assessed the event (preferred term = anemia) as severe but unrelated to study drug. The subject continued in the study.

Change in mental status: Subject 123-0001, was an 84 year-old white male nursing home resident with a medical history of AD, altered mental status, hypothyroidism, cardiomegaly, shortness of breath, hypertension, diabetes, hematuria, benign prostate hypertrophy, esophageal ulcer, and gastroesophageal reflux disease. The subject had a gastro-intestinal tube *in situ*, and could not communicate verbally. Concomitant medications and medications taken through study completion included: rivastigmine patch, levothyroxine, metoprolol tartrate, lisinopril, amlodipine, lansoprazole, multivitamin with iron (Multi-Delyn), metoclopramide, insulin glargine (Lantos), ipratropium-albuterol, acetaminophen, insulin aspart [rDNA origin] (Novolog), ceftriaxone, and metronidazole. A screening CT showed evidence of cerebral atrophy and a small area of decreased attenuation adjacent to the left lateral ventricle. Baseline physical and neurological examination on [REDACTED]<sup>(b) (6)</sup> was within normal limits. At 14:00, the subject was administered 355.2 MBq (9.6 mCi) of study drug. No AEs were reported at the 24-hour follow-up. Two days after study drug administration, the subject was hospitalized due to increased lethargy and confusion of 1 day duration. On admission, physical examination was unremarkable; he was alert and awake but not oriented. Serum chemistry showed glucose 130, sodium 138, potassium 4.8, chloride 106, bicarbonate 22, blood urea nitrogen 20, creatinine 0.89, troponin 0.02; hematology showed hemoglobin 12, hematocrit 35.9, platelet count 440,000, and white cell count 9.9 (units for laboratory values were not provided). Urinalysis was not consistent with a urinary tract infection. His ECG showed sinus rhythm with premature atrial complexes and moderate voltage criteria for left-ventricular hypertrophy. The chest x-ray showed clear lung fields with an enlarged heart; CT of the head showed no acute intracranial

process, bilateral lacunar infarcts, stable dilated ventricles, and the possibility of communicating hydrocephalus. Due to leukocytosis, urine and blood cultures were initiated and treatment with ceftriaxone started. Neurological consultation assigned a diagnosis of mental status changes likely due to toxic encephalopathy secondary to an infection. The subject remained afebrile and the leukocytosis improved. Blood and urine cultures were negative, so ceftriaxone was stopped. The subject then experienced diarrhea, and stool was positive for *Clostridium difficile* for which metronidazole (Flagyl) therapy was started. Nine days after hospital admission, when diarrhea resolved, the subject was discharged to nursing home care. Principal diagnoses at discharge were altered mental status, likely progression of Alzheimer's dementia, and toxic encephalopathy. The investigator assessed the event of change in mental status (preferred term = mental status changes) as not related to study drug. The subject continued in the study. Originally the investigator had considered the event as possibly related to Flutemetamol F 18 Injection; however, follow-up information from hospital records provided sufficient medical evidence that the event was caused by a combination of disease progression and concurrent infection so that the investigator changed the assessment of the relationship between study drug and the event to unrelated.

#### **Reviewer's Comments**

The medical officer agrees that the above detailed serious adverse events were not likely related to Vizamyl administration, but likely due to the patients' underlying complicated disease processes.

### **7.3.3 Dropouts and/or Discontinuations**

The sponsor reports there were no adverse events leading to patients dropping out or being discontinued from the studies. There were three subjects who experienced adverse events leading to discontinuation of study drug; two of these events were considered possibly related to Vizamyl, both were moderate in nature and resolved in 12 minutes.

### **7.3.4 Significant Adverse Events**

Overall, 151 adverse events (AEs) were reported for 76 (10%) subjects, with 44 (6%) subjects having AEs considered by the investigator to be at least possibly related to Vizamyl administration. Of the 44 subjects who experienced an AE possibly related to Vizamyl, the most common were flushing (16 subjects, 2%), blood pressure increased (10 subjects, 1%), headache (10 subjects, 1%), dizziness (8 subjects, 1%) and nausea (8 subjects, 1%).

Table 24 summarizes the most common AEs overall, by body organ system and severity. Overall, 61 subjects experienced a mild AE, 10 subjects experienced a moderate AE, and 5 subjects experienced a severe AE. The most common AEs by

body system were nervous system disorders (22 subjects, 3%), followed by vascular disorders (21 subjects, 3%), general disorders and administration site conditions (19 subjects, 2%), and gastrointestinal (15 subjects, 1%).

**Table 23: Adverse events possibly related to Vizamyl administration by organ system and severity.**

Adverse events by system organ class	Total Subjects N (%)	Mild N (%)	Moderate N (%)	Severe/ Incapacitating N (%)
Number of subjects with at least one TEAE	76 (10)	61 (8)	10 (1)	5 (1)
Nervous system	22 (3)	15 (2)	5 (1)	2 (<0.5)
Vascular disorders	21 (3)	17 (2)	4 (0.5)	0
General disorders & administration site AEs	19 (2)	17 (2)	2 (<0.5)	0
Gastrointestinal	15 (1)	11 (1)	4 (1)	0
Investigations	14 (1)	11 (1)	3 (<0.5)	0
Cardiac Disorders	5 (1)	4 (0.5)	1 (< 0.5)	0
Musculoskeletal & connective tissue disorders	8(1)	6 (1)	1 (< 0.5)	1 (< 0.5)
Skin and subcutaneous tissue disorders	6 (1)	6 (1)	0	0
Psychiatric	5 (1)	3 (<0.5)	2 (<0.5)	0
Respiratory, thoracic, mediastinal disorders	6 (1)	5 (1)	1 (<0.5)	0
Reproductive & breast disorders	1 (< 0.5)	1 (< 0.5)	0	0
Immune system disorders	1 (< 0.5)	0	0	1 (< 0.5)
Eye disorders	3 (< 0.5)	3 (< 0.5)	0	0

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### **Reviewers Comments**

In the reviewer's opinion, the adverse event data above does not reveal important safety concerns related to Vizamyl administration that would prevent approval of the drug for its intended population of use.

#### Normal Pressure Hydrocephalus Subjects

The percentages of subjects with TEAEs and Vizamyl related TEAEs were apparently higher among NPH subjects (N=52 subjects) than in the overall population (21% and 12% versus 10% and 6%, respectively). However, caution should be exercised in interpreting these data because of the relatively small number of NPH subjects. The reviewer highlights that no NPH subject died, had a TEAE that was serious, had a TEAE that led to study discontinuation, or had a TEAE that was severe in intensity.

### **7.3.5 Submission Specific Primary Safety Concerns**

There are none to address.

## **7.4 Supportive Safety Results**

### **7.4.1 Common Adverse Events**

Of the 44 subjects who experienced an AE possibly related to Vizamyl, the most common were flushing (16 subjects, 2%), blood pressure increased (10 subjects, 1%), headache (10 subjects, 1%), dizziness (8 subjects, 1%) and nausea (8 subjects, 1%).

### **7.4.2 Laboratory Findings**

Review of observational data collected for serum chemistries, hematology parameters, coagulation parameters reveals no important findings regarding changes from baseline to post Vizamyl administration for these laboratory measurements.

### **7.4.3 Vital Signs**

As can be seen in table 25, review of vital sign data collected for the safety database reveals no concerning safety signals related to baseline and post Vizamyl vital sign assessments.

**Table 24. Summary of vital sign assessments at baseline and post Vizamyl administration (N=761).**

Parameter (Units)	Statistic	Baseline	End of Scan	Change from Baseline to End of Scan
Systolic Blood Pressure (mm Hg)	n	761	759	759
	Mean (SD)	131.0 (18.70)	134.0 (20.43)	3.1 (13.88)
Diastolic Blood Pressure (mm Hg)	n	761	759	759
	Mean (SD)	74.0 (10.14)	76.3 (10.68)	2.2 (8.68)
Heart Rate (bpm)	n	761	758	758
	Mean (SD)	70.1 (12.84)	67.6 (12.52)	-2.5 (9.22)
Respiratory Rate (breaths /min)	n	761	745	745
	Mean (SD)	17.1 (3.03)	16.9 (3.13)	-0.1 (2.79)
Temperature (degrees C)	n	756	740	739
	Mean (SD)	36.5 (0.55)	36.4 (0.52)	-0.05 (0.50)

bpm= beats per minute

**Reviewers Comments**

The medical officer sees no concerning signals from the vital sign data.

**7.4.4 Electrocardiograms (ECGs)**

The mass amount of flutemetamol in a 5 millicurie dose of Vizamyl is less than 20 microgram. A clinically significant effect of [<sup>18</sup>F]Flutemetamol on QT/QTc prolongation is not expected.

No TEAEs related to QT prolongation and no episodes of Torsades de Pointes were reported. No case of clinically meaningful QTc prolongation was observed. Table 26 below provides a summary of the ECG observations.

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**Table 25. Summary and changes from baseline in ECG parameters (N=761).**

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Parameter (Units)	Statistic	Baseline	End of Scan	Change from Baseline to End of Scan
Heart Rate (bpm)	n	757	751	751
	Mean (SD)	68.9 (13.19)	66.6 (13.32)	-2.3 (9.00)
PR Interval (ms)	n	704	702	685
	Mean (SD)	165.7 (32.17)	167.6 (40.00)	1.6 (28.35)
QRS Interval (ms)	n	757	751	751
	Mean (SD)	92.7 (20.34)	92.8 (17.92)	0.1 (13.11)
QT Interval (ms)	n	757	751	751
	Mean (SD)	398.4 (41.93)	406.3 (39.86)	8.1 (28.32)
QTc-Bazett (ms)	n	749	744	743
	Mean (SD)	424.2 (46.57)	425.5 (45.97)	1.3 (31.22)
QTc-Fridericia (ms)	n	749	744	743
	Mean (SD)	414.9 (35.51)	418.4 (34.35)	3.6 (26.03)
RR Interval (ms)	n	749	744	743
	Mean (SD)	897.2 (169.94)	926.9 (173.94)	30.0 (114.19)

bpm = beats per minute; ms = milliseconds; SD= standard deviation.

### Reviewers Comments

The medical officer sees no concerning signals from the ECG data submitted in the NDA, including the summary info in table 26 above.

### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

### 7.4.6 Immunogenicity

No studies performed and none were needed.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

No analyses were performed secondary to Vizamyl being administered primarily as a single 5 millicurie intravenous injection, containing 20 micrograms drug product.

### 7.5.2 Time Dependency for Adverse Events

There are no important safety findings to report related to time dependency for adverse events.

### 7.5.3 Drug-Demographic Interactions

There were no formal evaluations to investigate drug-demographic differences. Observational data from the clinical development program does not reveal any concerning safety signals for Vizamyl related to age, gender, race or ethnicity.

### 7.5.4 Drug-Disease Interactions

It is not expected that Vizamyl would cause any drug-disease interaction.

### 7.5.5 Drug-Drug Interactions

No formal drug interaction studies were performed. In study GE067-007, some patients continued taking commonly prescribed Alzheimer's Disease drugs including donepezil, memantine, galantamine, et al. The composite SUVR scores for cortical regions were compared for patients (n=10) taking AD medications with patients (n=58) not taking AD drugs.

**Table 26. Composite SUVR (Cerebellar Cortex) by Select Concomitant Medication Use (Post-mortem Autopsy Analysis Set, N = 68).**

Select Concomitant Medication Use <sup>a</sup> , Statistic	Composite SUVR
Yes, n	10
Mean (Standard Deviation)	2.1509 (0.42852)
Median	2.329
Minimum, Maximum	1.343, 2.825
95% Confidence Interval	1.844, 2.457
No, n	58
Mean (Standard Deviation)	1.8657 (0.52238)
Median	1.842
Minimum, Maximum	1.014, 3.137
95% Confidence Interval	1.728, 2.003

a Subjects were classified based on the following concomitant medication usage: RIVASTIGMINE, DONEPEZIL, MEMANTINE, GALANTAMINE. These are medications commonly prescribed to patients with Alzheimer's disease.

b Composite SUVR is defined as an average of frontal, anterior cingulate gyri, parietal, lateral-temporal and posterior cingulate gyri /precuneus uptake following administration of Flutemetamol F 18 Injection

### Reviewer's Comments

Use of AD medications was not associated with significant differences in SUVR in study 007. Based on the mechanism of action, there are no present concerns regarding drug-drug interactions affecting the clinical safety or effectiveness of Vizamyl.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

No clinical concerns were raised by the submitted data. Give Vizamyl is given as a single injection, evaluation for human carcinogenicity is not needed.

### **7.6.2 Human Reproduction and Pregnancy Data**

Pregnancy and breast-feeding were exclusion criteria in all Vizamyl clinical trials, thus Flutemetamol F18 Injection has not been studied in pregnant women. No embryonic or fetal toxicity studies to assess radioactive exposure from Vizamyl have been conducted.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Alzheimer's disease manifests in adults and elderly patients. No studies have been performed in the pediatric population because Vizamyl is not intended for use in these patients. A pediatric waiver has been granted to the applicant.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Vizamyl and its components have no pharmacologic effects and the drug is not thought to have any potential for drug abuse or dependence. There is the potential that patients may receive a higher dose than necessary for diagnostic imaging. This would increase a patient's cumulative radiation exposure and its associated risks.

## **7.7 Additional Submissions / Safety Issues**

There are none to address.

## **8 Post-market Experience**

Not applicable. Vizamyl has not been marketed in any country.

## 9 Appendices

### 9.1 References

1. A literature search was performed on [REDACTED] (b) (4) 12/28/2012 and used as a reference for the background on AD provided in this review. The following topics were searched and reviewed:

- Alzheimer's disease
- Dementia evaluation

2. Burns A, Iliffe S. Alzheimer's disease. BMJ. 2009 Feb 5; 338: b158.

### 9.2 Labeling Recommendations

The review team is working in concert with other review disciplines and the sponsor to revise the submitted label so that it is consistent with the submitted NDA data.

### 9.3 Advisory Committee Meeting

An advisory committee was not convened for this NDA.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHILLIP B DAVIS  
06/28/2013

LIBERO L MARZELLA  
06/28/2013

Dr. Davis has performed a complete clinical review of the NDA including a thorough analysis of the safety and efficacy data.



## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<b>Pivotal Study #2: GE067-021</b> Indication: Evaluate the effectiveness of an electronic training program for orienting and interpreting F18-Flutemetamol PET images				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Single administration diagnostic agent
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	New molecular entity, safety of the product appears to have been adequately evaluated
25.	Have narrative summaries been submitted for all deaths and adverse dropouts and serious adverse events if requested by the Division?			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

\* **Note** - the following clinical comments and requests were sent to the sponsor 12/01/12:

### Comments to Sponsor

We acknowledge the receipt of your new drug application for Vizamyl (NDA 203137) submitted and received October 26, 2012. We have begun our initial review and have the following comments and information requests.

1. It appears the “Clinical Sites for Inspection” document may contain inaccuracies with regards to the number of subjects screened and the number of protocol deviations, when compared to the protocol deviation listings document for studies GE 067-015 and GE 067-007. For example, on page 3 of 3 in the “Clinical Sites for Inspection” document (1.1.2) for study GE067-015, 42 subjects are stated to have been screened with 0 protocol deviations. However, in the “Protocol Deviation Listing” document (5.3.5.1.17) for study GE067-015, it appears there were 12 protocol deviations at this site. We note there are other examples of this type scenario in these documents for the pivotal studies. Please cross examine these documents for studies GE067-007, GE067-015 & GE067-021 and provide an accurate report of the number of subjects screened and enrolled, as well as the number of protocol deviations for each site in these pivotal studies.

2. Please confirm that the [REDACTED] (b)(4) was responsible for reader training and conducting the BIE for clinical study GE067-021. If this is not the case, please clarify where the BIE was performed for study GE067-021; include complete contact information with name, address, phone, and fax number.

3. Please confirm that the Grove Center was responsible for reader training and conducting the BIE for clinical study GE067-007. If this is not the case, please clarify where the BIE was performed for study GE067-007; include complete contact information with name, address, phone, and fax number.

4. Please clarify where the blinded image interpretations were performed for study GE067-015; include complete contact information with name, address, phone, and fax number.

5. Based on our initial review of document 16.1.1 (Protocol and Amendments) for study GE067-007, it appears that one histopathologist provided the truth standard read (Bielschowsky stain) for each brain tissue sample. Please confirm or correct our understanding of the number of readers for each subject’s truth standard histopathology read. Please also clarify how many brain tissue samples were read by each histopathologist participating in the truth standard interpretations.

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Phillip B. Davis, MD

12/03/12

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Reviewing Medical Officer

Date

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Clinical Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PHILLIP B DAVIS  
12/03/2012