Clinical Study Protocol GE067-027

GE Healthcare

Title	A Post-Authorisation Safety Study to Evaluate the Effectiveness of VIZAMYL™ Reader Training in Europe
Protocol version identifier	2.0
Date of PRAC approval of protocol	27 November 2017
EU PAS register number	Study not registered
Active substance	Pharmacotherapeutic group(s): Radionuclide Imaging ATC code: V09AX04
Medicinal product	VIZAMYL™
Product reference	EMEA/H/C/002557
Procedure number	EMEA/H/C/002557/MEA 002
Marketing authorisation holder	GE Healthcare Ltd, Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, United Kingdom
Joint PASS	No
Research question and objectives	Research Question: • How effective is the VIZAMYL™ reader training programme in clinical practice in Europe? Primary Objective: • Assess effectiveness of the VIZAMYL™ reader training programmes (in-person or electronic) in Europe by estimating the diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the visual interpretation of VIZAMYL™ images obtained in clinical practice. Secondary Objective: • Evaluate the impact of demographic and other factors (such as method of training, gap between training and reading, and country) on diagnostic accuracy to try to identify factors that may be associated with image interpretation errors.
Countries of study	European countries where VIZAMYL™ is commercially available and where high use is expected during the study period
Author	Paul Sherwin, MD, PhD GE Healthcare Life Sciences 100 Results Way, Marlborough, MA 01752 USA Tel: +1 774 843 3888 (office) or +1 609 510 3686 (mobile)
MAH contact person	Paul Sherwin, MD, PhD GE Healthcare Life Sciences 100 Results Way, Marlborough, MA 01752 USA Tel: +1 774 843 3888 (office) or +1 609 510 3686 (mobile)

Confidentiality Statement

Investigator's Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature

Date

Print Name

1 TABLE OF CONTENTS

1.1 Overall Table of Contents

Page Number

1.2 List of Tables

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Alzheimer's Disease
AE	Adverse Event
CI	Confidence Interval
CRO	Contract Research Organization
CT	Computed Tomography
CTECS	Clinical Trial Emergency Contact Service
EANM	European Association of Nuclear Medicine
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EFNS	European Federation of the Neurological Societies
EMA	European Medicines Agency
ETP	Electronic Training Programme
EU	European Union
Flutemetamol	INN for drug substance
Flutemetamol (^{18}F) Injection	Generic name for VIZAMYL™. Drug product; the product that is injected containing drug substance and excipients
Flutemetamol (^{18}F)	Active component of the drug product
FN	False Negative
FP	False Positive
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
MRI	Magnetic Resonance Imaging
NPV	Negative Predictive Value
PET	Positron Emission Tomography
PiB	Pittsburgh Compound B
PPV	Positive Predictive Value
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TN	True Negative
TP	True Positive
VIZAMYL™	Trade name for Flutemetamol (^{18}F) Injection

3 RESPONSIBLE PARTIES

Contact information for investigators and other study personnel is provided in the standalone document, “VIZAMYL Study GE067-027 Study Personnel” listed in Annex 1. It is available upon request.

4 ABSTRACT

Title

A Post-Authorisation Safety Study to Evaluate the Effectiveness of VIZAMYL™ Reader Training in Europe. Protocol Version 2.0. 16 February 2018. Main Author: Paul Sherwin, MD, PhD, Senior Medical Director, GE Healthcare Life Sciences.

Rationale and background

VIZAMYL™ (Flutemetamol (^{18}F) Injection) was approved by the United States Food and Drug Administration (FDA) on 25 October 2013 and by the European Medicines Agency (EMA) on 22 August 2014. VIZAMYL™ is a radiopharmaceutical medicinal product indicated for positron emission tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. VIZAMYL™ is for diagnostic use only and should be used in conjunction with clinical evaluation. Owing to its radioactive nature and consequent short shelf-life, VIZAMYL™ is manufactured on demand in response to a valid prescription.

GE Healthcare was asked by the EMA to conduct a study to determine the rate of VIZAMYL™ image interpretation errors in clinical practice and to evaluate the effectiveness of the VIZAMYL™ reader training programme in Europe. This study, designed in response to those requests, will assess effectiveness of the electronic training programme (ETP) in clinical practice by determining the diagnostic accuracy of the visual image interpretations made by clinical readers (i.e., readers who mainly interpret nuclear medicine images in clinical practice rather than in research) in European countries where VIZAMYL™ is commercially available and where high use is expected during the study period. Each reader will interpret images from his/her site, for a total of at least 200 images across all sites. The standard of truth (SOT) will be the majority blinded visual interpretation of 5 expert readers who will independently review the same ≥200 images. The majority interpretation is the image interpretation made separately by at least 3 of the 5 expert readers (expert readers will not be allowed to discuss images with each other and will be blinded to the interpretations of the other expert and clinical readers).

Research question and objectives

Primary Objective:

- Assess effectiveness of the VIZAMYL™ reader training programmes (in-person or electronic) in Europe by estimating the diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), of the visual interpretation of VIZAMYL™ images obtained in clinical practice.

Each recruited clinical reader will review the VIZAMYL™ images obtained in clinical practice at his/her institution, for a net total of at least 200 subjects across all readers. The SOT will be the majority blinded visual image interpretations of the same images by 5 independent expert readers.

Secondary Objective

- Evaluate the impact of demographic and other factors (such as method of training, gap between training and reading, and country) on diagnostic accuracy to try to identify factors that may be associated with image interpretation errors.

Study design

Overview

To evaluate the effectiveness of the VIZAMYL™ reader training programme in Europe, the diagnostic accuracy of the visual interpretation of VIZAMYL™ images in clinical practice will be determined. Clinical readers (1 to 5 per country) will be recruited from European countries where VIZAMYL™ is commercially available and where high use is expected during the study period.

Clinical readers will interpret VIZAMYL™ images obtained in clinical practice (with anatomic images when available and if part of normal practice) at his/her institution; a total of at least 200 images will be collected in the study. Following local practices at the institution, each reader will interpret images as positive (significant levels of amyloid present) or negative (significant levels of amyloid absent); these image classifications are consistent with the VIZAMYL™ reader training programme, the VIZAMYL™ Summary of Product Characteristics, and the European Association of Nuclear Medicine (EANM) guidelines on interpretation of amyloid PET images [Minoshima et al. 2016]. Each image interpretation will be compared to the corresponding majority blinded visual interpretation of 5 expert readers and sub-classified as true positive (TP), true negative (TN), false positive (FP), or false negative (FN). Diagnostic accuracy (the percentage of all images correctly interpreted) will be determined based on all images. Since the maximum possible value of diagnostic accuracy is 1, one minus the diagnostic accuracy will give the overall rate of image interpretation errors.

The standard measures of diagnostic test performance, sensitivity (TP rate for image interpretation), and specificity (TN rate for image interpretation), will also be determined based on all images. Other study endpoints will include PPV and NPV.

All of the above metrics will be determined for subsets of images by country and by reader. Further details may be found below in the body of the protocol.

Population

At least 200 VIZAMYL™ images will be collected prospectively from at least 200 subjects. Subjects will be patients who are being evaluated for AD and other causes of cognitive impairment, who are referred by their physician for a clinically indicated VIZAMYL™ PET brain scan.

The study will be conducted in European countries where VIZAMYL™ is commercially available and where high use is expected during the study period. Imaging sites that fall within the regions of VIZAMYL™ supply may participate within this study. Imaging sites must also meet instrumentation requirements for PET imaging, obtain Independent Ethics Committees

(IEC) approval of the study protocol, have a reasonable probability of conducting amyloid PET imaging (i.e., they must serve the relevant population), agree to obtain written informed consent from potential study subjects, and agree to collect and transmit subjects' study data.

Each potential clinical reader contacted will be asked to complete a screening survey, which asks, among other things, if they are willing to participate in the study, and if they are authorised by their institution to read VIZAMYL™ PET images. Those who meet eligibility criteria and are willing to participate will be included in the study, 1 to 5 clinical readers per country. To avoid overrepresentation of any reader, institution, or country in the study results, the following restrictions will apply:

- No clinical reader may contribute more than 7.5% of the total number of images (e.g., 15 of 200 images)
- No institution may contribute more than 15% of the total number of images (e.g., 30 of 200 images)
- No country may contribute more than 25% of the total number of images (e.g., 50 of 200 images)

The expert readers will consist of 5 experienced nuclear medicine physicians or radiologists, with extensive experience in PET imaging (including VIZAMYL™ imaging), who have completed the VIZAMYL™ training programme. They may have participated in VIZAMYL™ clinical trials. The expert readers will have a minimum of 5 years of experience in nuclear medicine brain imaging and must have reviewed a minimum of 100 amyloid PET images within the previous 5 years from the start of the study.

Variables

Each clinical reader's classification of each VIZAMYL™ image as positive or negative will be recorded. Each image classification will then be sub-classified as a TP, TN, FP, or FN based on a comparison with the majority blinded visual interpretation of 5 expert readers, and the numbers of each sub-classification will be used to calculate diagnostic accuracy, sensitivity, specificity, PPV, and NPV. Clinical and expert readers will also record their certainty in the classification on a scale of 1 to 5 (1 = lowest, 5 = highest).

Data sources

All data will be obtained prospectively from subjects, clinical readers, and expert readers who consent to participate. Data sources will be the images and patient medical records. Image interpretations and other data will be recorded directly onto electronic case report forms (eCRFs); images will be provided to the Sponsor electronically. All measurements are considered standard for assessment of a diagnostic test.

Study size

At least 200 VIZAMYL™ images collected from at least 200 subjects will be interpreted by clinical readers from the institution where the images were obtained (i.e., each reader will interpret only those images collected at his/her institution). The readers' interpretations will be compared to the majority blinded visual interpretations of the same images made subsequently by 5 expert readers to determine diagnostic accuracy, sensitivity, specificity, PPV, and NPV.

Data analysis

Diagnostic accuracy, sensitivity, specificity, PPV, and NPV value will be determined for each reader, and reported as point estimates with exact 95% confidence intervals (CIs).

Milestones

Milestone	**Planned date**
Registration in the EU PAS register	Q1 2018
Start of data collection	Q2 2018
End of data collection	Q1 2020
Final report of study results	Q2 2020
Study progress reports	Annually

5 AMENDMENTS AND UPDATES

GE Healthcare Version Number	Original Status	PRAC Version	Date	Key Reasons for New Version
1.0	Approved	1.0	03 Dec 2014	Original document.
2.0	Approved	1.0	15 Apr 2015	This document was revised to reformat the protocol to the PASS Protocol style.
3.0	Approved	1.0	25 Aug 2015	This document was revised to incorporate the following changes: • Changed and clarified the number of readers per country to avoid overrepresentation of any reader, institution, or country in the study. The discussion of study limitations was updated to reflect these changes. • Moved sensitivity, specificity, PPV, and NPV as secondary objectives to a primary objective, and updated the endpoints and analyses to reflect this change. • Clarified the definition of positive and negative image results to be significant levels of amyloid present and absent, respectively. • It was added that each reader would provide his/her level of certainty for each image classification. This version was submitted to, and approved by, the EMA.
4.0	Approved	2.0	27 Nov 2017	This document was revised to incorporate the following changes: • Changed and clarified the readers, countries, and subjects to be selected for participation in this study to allow for flexibility. • The option of classifying an image as indeterminate was removed. • A reader certainty scale was added. • Study milestones were updated.
5.0	Effective	2.0	16 Feb 2018	Administrative changes to clarify the version on the title page as the PRAC approved version. In addition, study milestones were updated.

6 MILESTONES

Table 1 Study Milestones

Milestone	Planned date
Registration in the EU PAS register	Q1 2018
Start of data collection	Q2 2018
End of data collection	Q1 2020
Final report of study results	Q2 2020
Study progress reports	Annually

7 RATIONALE AND BACKGROUND

Neuropathological diagnostic criteria for Alzheimer's disease (AD) include whether or not there are neuritic plaques in the brain, and if so, their relative frequency [Khachaturian, 1985]; [Mirra et al. 1991]; [NIA-Reagan, 1997]. Plaques can be found in aged cognitively normal subjects, so although plaques are necessary for a diagnosis of AD, they are not sufficient (neurofibrillary tangles must also be present). On the other hand, the *absence* of significant levels of amyloid plaques in the brain is sufficient to rule out AD.

Positron emission tomography (PET) imaging using VIZAMYL™, Flutemetamol (^{18}F) Injection, is a method to detect abnormal neuritic plaque density. Flutemetamol (^{18}F), the active ingredient, is an analogue of Pittsburgh Compound B (PiB; 2-[4-methylamino phenyl]-1, 3-benzothiazol-6-ol) radiolabelled with the positron-emitting isotope ^{18}F. Both flutemetamol and PiB are neutral analogues of Thioflavin T, an accepted histological stain for detecting neuritic plaques. PiB was designed to cross the blood-brain barrier, bind to neuritic plaques with high affinity at low nanomolar concentrations, and clear rapidly from normal brain tissue. The PET imaging properties of PiB derive from the positron-emitting isotope, carbon-11 (^{11}C), which has a radioactive half-life of 20 minutes, too short for commercial distribution. The longer radioactive half-life of fluorine-18 (110 minutes) permits fluorine-labelled PET amyloid imaging agents such as VIZAMYL™ to be distributed commercially, offering more flexibility in scheduling of PET imaging. Visual interpretation of flutemetamol (^{18}F) PET images has high sensitivity and specificity for the *in vivo* detection of abnormal brain neuritic plaque density in the brain.

VIZAMYL™ was approved by the United States FDA 25 October 2013 and by the EMA 22 August 2014. VIZAMYL™ is a radiopharmaceutical medicinal product indicated for PET imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive impairment. VIZAMYL™ is for diagnostic use only and should be used in conjunction with clinical evaluation. Owing to its radioactive nature and consequent short shelf-life, VIZAMYL™ is manufactured on demand in response to a valid prescription.

The efficacy of VIZAMYL™ was established in 2 pivotal clinical studies, GE067-007 and GE067-026. Both studies used histopathological analysis of brain tissue as the standard of truth (SOT) to confirm VIZAMYL™ PET scan findings.

Study GE067-007 used 5 blinded independent readers to interpret VIZAMYL™ scans. These readers had been trained to interpret VIZAMYL™ images using an in-person training programme. Four of the readers showed high sensitivity and specificity, while the last reader showed high sensitivity but lower specificity [Curtis et al. 2015]. Analysis of reader performance resulted in recommendations for changes in the training programme, which were incorporated into an electronic training programme (ETP) which GE Healthcare developed to avoid the need for time-intensive, in-person training. The effectiveness of the ETP was evaluated in a clinical study (GE067-021) by estimating post-training sensitivity and specificity for each of 5 readers previously naïve to VIZAMYL™ image interpretation; each reader showed high sensitivity and specificity, indicating that the ETP was effective [Buckley et al. 2017].

Subsequently, GE Healthcare was asked by the EMA to analyse additional brains that had been collected but not yet analysed in Study GE067-007. This study, GE067-026, analysed data from 106 subjects for whom histopathological analyses of brain tissue were available. Five new readers were used to read the 106 images, and these readers were trained with the ETP, in contrast to Study GE067-007. This study also showed high sensitivity and specificity for all readers [Salloway et al. 2017].

Few, if any, diagnostic tests are perfect, and thus, sensitivity and specificity are rarely both 100%. This means that false-positive (FP) and false-negative (FN) results are possible. Because these inaccurate results may be acted on by physicians, FP and FN test results are potential safety issues. Image interpretation errors were thus included in the VIZAMYL™ Risk Management Plan, and the VIZAMYL™ Summary of Product Characteristics contains language recommending that all readers of VIZAMYL™ images first undergo training in the interpretation of VIZAMYL™ images.

In addition, GE Healthcare was asked by the EMA to conduct a study to determine the rate of VIZAMYL™ image interpretation errors in clinical practice and to evaluate the effectiveness of the reader training programme in Europe.

This study, designed in response to those requests, will assess effectiveness of the training programme (in-person or electronic) in clinical practice by determining the diagnostic accuracy of the visual image interpretations made by clinical readers (i.e., readers who mainly interpret nuclear medicine images in clinical practice rather than in research) in European countries where VIZAMYL™ is commercially available and where high use is expected during the study period. Each reader will interpret images from his/her site, for a total of at least 200 images across all sites. The SOT will be the majority blinded visual interpretation of 5 expert readers who will independently review the same ≥200 images. The majority interpretation is the image interpretation made separately by at least 3 of the 5 expert readers (expert readers will not be allowed to discuss images with each other and will be blinded to the interpretations of the other expert and clinical readers).

Description of the Training Programme

The training programme that is being made available to European physicians to support clinical practice is essentially identical to the one used in Studies GE067-021 and GE067-026. It contains the following modules, which include a final test. The trainee must correctly assess a minimum of 14 cases (93%) out of 15 to successfully complete the training.

- Brain anatomy in magnetic resonance imaging (MRI) and PET
- Image orientation & displaying images
- Reviewing images
- Pre-test cases (10) with guided reviews
- Test cases (15) with reviews in the event of incorrect assessment and second test cases (15) in the event of not passing the test on the first 15 cases

8 RESEARCH QUESTIONS AND OBJECTIVES

The research question to be answered by this study is: *How effective is the VIZAMYL™ reader training programme in clinical practice in Europe?* To answer this question, the study has the following primary and secondary objectives.

Primary:

The primary study objective is to assess the effectiveness of the VIZAMYL™ reader training programmes (in-person or electronic) in Europe by estimating the diagnostic accuracy, sensitivity, specificity, PPV, and NPV, of the visual interpretation of VIZAMYL™ images obtained in the course of clinical practice. Diagnostic accuracy is the overall true-interpretation rate for all subjects. One minus the diagnostic accuracy gives the overall image interpretation error rate.

At least 200 VIZAMYL™ images obtained in clinical practice will be reviewed by clinical readers recruited from European countries where VIZAMYL™ is commercially available and where high use is expected during the study period. The SOT will be the majority blinded visual image interpretations of the same images by 5 independent expert readers.

Secondary:

The secondary study objective is:

Evaluate the impact of demographic and other factors (such as method of training, gap between training and reading, and country) on diagnostic accuracy to try to identify factors that may be associated with image interpretation errors.

Sensitivity is the true-positive (TP) image interpretation rate in subjects with brain amyloid. *Specificity* is the true-negative (TN) image interpretation rate in subjects without brain amyloid. *Positive predictive value (PPV)* is the TP image interpretation rate for subjects with positive VIZAMYL™ scans. *Negative predictive value* (NPV) is the TN image interpretation rate for subjects with negative VIZAMYL™ scans.

9 RESEARCH METHODS

9.1 Study Design

9.1.1 Overall Study Design and Plan

This is a Phase 4, post-authorisation safety study with the primary objective of assessing effectiveness of the VIZAMYL™ reader training programmes (in-person or electronic) in Europe by estimating the diagnostic accuracy of the visual interpretation of VIZAMYL™ images by clinical readers recruited from European countries where VIZAMYL™ is commercially available and where high use is expected during the study period (each reader will interpret images collected at his/her institution, for a total of at least 200 images). The diagnostic accuracy of image interpretation will be determined across all images as well as for subsets of images by country and by reader. Sensitivity, specificity, PPV, and NPV will also be determined and will be reported as point estimates along with exact 95% CIs. The SOT for classifying each image as correct (true positive or true negative) or incorrect (false positive or false negative) will be the majority blinded visual interpretations of 5 independent expert readers.

Imaging sites will be selected according to the criteria detailed below in Section 9.2.2. Each imaging site will be assigned a 3-digit identifying number. The VIZAMYL™ images at each participating site will be obtained in clinical practice from consecutively consenting subjects.

All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Section 9.2.3. Signed and dated informed consent must be obtained from all subjects or the subject's legally acceptable representative, if applicable, in accordance with local regulations, prior to collection of any study-specific data. Each subject will be assigned a 7-digit identifying number; the first 3 digits will be the identifying number for the site at which the subject's VIZAMYL™ scan was obtained (as described in the preceding paragraph), and the remaining 4 digits will be assigned consecutively at each site. Demographic data (see Table 5) will be recorded for each subject.

The images will be de-identified (i.e., subject identifying information will be removed) so that inspection of an image will not reveal the identity of the subject from whom the image was obtained.

If anatomic images are used in the interpretation of the VIZAMYL™ images, they will also be de-identified and transmitted to the core image lab, and will be interpreted with the VIZAMYL™ images by the expert readers.

The clinical reader eligibility criteria are discussed below in Section 9.2.4. Demographic data (see Table 5) will be recorded for each clinical reader. Each clinical reader will be assigned an identifying letter that starts with C (for Clinical): *CA, CB, CC,* etc.

During the image interpretations, the clinical readers will not be blinded to the subjects' clinical information, but will be blinded to the interpretations of the expert readers (which will not be available yet). Each clinical reader will interpret the VIZAMYL™ images as they are

collected at his/her site. VIZAMYL™ images will be interpreted as positive (significant levels of amyloid present) or negative (significant levels of amyloid absent) according to local practices at the institution; these classifications are consistent with the VIZAMYL™ reader training programme, the VIZAMYL™ Summary of Product Characteristics, and the EANM guidelines on interpretation of amyloid PET images [Minoshima et al. 2016]. If anatomic images (MRI and/or computed tomography [CT]) are available for a subject, the normal institutional clinical practice regarding use of these images in PET interpretation will be followed. After interpreting the image, the clinical reader will enter his/her interpretation and other data into an eCRF. The site will remove identifying information (except for subject number) from the image and transmit the image electronically to the GE Healthcare image core lab.

The image core lab will assign a randomization code to the image and will remove the subject number.

The ≥200 images collected in this study will be interpreted separately by each of 5 expert readers, who will classify each image as positive or negative for brain amyloid. The expert readers will consist of 5 experienced nuclear medicine physicians or radiologists, with extensive experience in PET imaging (including amyloid imaging), who have completed a VIZAMYL™ training programme. The selection criteria for these 5 expert readers are detailed below in Section 9.2.6. The expert readers will be blinded to the subjects' clinical information and to the interpretations of the other expert readers and clinical readers, and will not be permitted to discuss images or interpretations with anyone. The expert read will result in at least 200 x 5 = 1000 expert blinded visual interpretations, which will be analysed by subject to determine the majority blinded visual interpretation, as follows. Each image will have 5 expert interpretations, each of which will be positive or negative. The image interpretation (positive or negative) made by the majority of the 5 expert readers will be taken as the majority interpretation. For example, if 3, 4, or 5 of the expert readers interpreted a specific subject's image as positive, then the majority interpretation for that image will be positive. The result of this analysis will be at least 200 majority interpretations (1 per image). The level of reader certainty will also be recorded on a scale of 1 to 5 (1 = lowest, 5 = highest).

Using subject number, each of the ≥200 clinical image interpretations will be matched to the corresponding expert reader majority interpretation for the subject and the image interpretation will be classified as a TP, TN, FP or FN using the expert reader majority interpretation as the SOT. For example, if an image interpretation is "positive" and the expert reader majority interpretation is "positive", the image interpretation would be classified a true positive (TP). If the expert reader majority interpretation were "negative", however, then the image interpretation would be classified as a FP. The numbers of TP, TN, FP, and FN images among the ≥200 original images will be used to calculate diagnostic accuracy:

$$\text{Diagnostic accuracy} = (nTP + nTN) / (nTP + nTN + nFP + nFN)$$

Where nTP is the number of true-positive scans, nTN is the number of true-negative scans, nFP is the number of false-positive scans, and nFN is the number of false-negative scans.

Sensitivity, specificity, PPV, and NPV will also be calculated:

$$\text{Sensitivity} = nTP / (nTP + nFN)$$

$$\text{Specificity} = nTN / (nTN + nFP)$$

$$PPV = nTP / (nTP + nFP)$$

$$NPV = nTN / (nTN + nFN)$$

Treatment-emergent adverse events (AEs) with onset or worsening between the start of VIZAMYL™ injection and subject discharge from the imaging suite will be recorded on an AE eCRF, along with the centre's assessment of relationship to VIZAMYL™, severity, seriousness, timing, need for treatment, and outcome.

Study procedures are summarised in the Study Schedule of Events (Table 2 and Table 3).

Table 2 Study Schedule of Events for Image Collection

Procedures	Subject Enrolment	Imaging Visit	Post-Imaging	Responsible
Selection of imaging sites				Sponsor
Informed consent obtained from subject	X			Centre
Subject inclusion/exclusion criteria assessed	X			Centre
Subject demographic information recorded	X			Centre
VIZAMYL™ administration and PET imaging; AE monitoring from start of injection until discharge from imaging centre		X		Centre
Completion of electronic case report form			X	
De-identification of subject's images			X	Centre
Transmittal of subject's images to Sponsor image core lab			X	Centre
Preparation of images for expert readers			X	Sponsor

Table 3 Study Schedule of Events for Image Evaluation by Expert Readers

Procedures	Expert Selection	Expert Image Evaluation	Responsible
Identification of expert reader candidates	X		Sponsor
Informed consent obtained from expert reader candidates	X		Sponsor
Expert reader candidate inclusion/exclusion criteria assessed	X		Sponsor
Selection of 5 expert readers	X		Sponsor
Expert reader demographic information recorded	X		Sponsor
Independent review of images		X	Readers

The criteria for blinding are shown below in Table 4.

Table 4 Blinding of Persons Involved in the Study

Personnel	Blinded To:
Subjects	Expert readers' image interpretations
Imaging Centre Site Personnel	Expert readers' image interpretations
Clinical Readers	Other clinical readers' image interpretations Expert readers' image interpretations
Expert Readers	Clinical readers' image interpretations Other expert readers' image interpretations Subject clinical information

No direct benefits to subjects enrolled in this study are expected. Each subject will be referred for a VIZAMYL™ scan according to clinical need determined by his/her physician. The potential risks to subjects are described in the VIZAMYL™ Summary of Product Characteristics, and include adverse drug reactions and image interpretation errors.

9.2 Setting

This study will allow patients and clinical readers from any healthcare setting (i.e., primary, secondary, and tertiary care) to participate. However, it is anticipated that referrals for VIZAMYL™ imaging will be made predominantly by specialists (e.g., neurologists and psychiatrists) rather than by primary care physicians and that a substantial proportion will be made by dementia specialists who may be based in tertiary care centres. It is anticipated that the main use of amyloid PET imaging will be to assist in the diagnosis of cases of dementia that are difficult because of atypical symptoms and/or early onset), as suggested by the European Federation of the Neurological Societies (EFNS) task force's publication on the use of neuroimaging in the diagnosis of dementia [Filippi et al. 2012]. The type of medical practice for the referring physicians and for the readers will be collected as part of the demographic data.

9.2.1 Selection and Replacement of Countries

The study will be conducted in European countries where VIZAMYL™ is commercially available and where high use is expected during the study period.

9.2.2 Selection and Replacement of Imaging Sites

Because of the short radioactive half-life (~110 minutes) of the fluorine 18 isotope in [^{18}F]flutemetamol (the active component of VIZAMYL™), the ability to supply VIZAMYL™ is limited to within a finite radius around each manufacturing site, and therefore only imaging sites that fall within the regions of VIZAMYL™ supply may participate.

Imaging sites must also meet the instrumentation requirements for PET imaging, obtain Independent Ethics Committee (IEC) approval of the study protocol, have a reasonable probability of conducting amyloid PET imaging (i.e., they must serve the relevant population), agree to obtain written informed consent from potential study subjects, and agree to collect and transmit subjects' study data.

9.2.3 Selection and Replacement of Subjects

Consenting subjects who receive VIZAMYL™ as part of routine clinical practice will be eligible; patients scheduled for a VIZAMYL™ scan as part of a clinical study will be excluded from this study. Subjects must provide written informed consent before any study-specific data are collected. A subject will be considered enrolled in the study if he/she has provided written informed consent and any study-specific data have been collected about the subject. Subjects meeting the following criteria may be enrolled:

1. The subject is an adult (aged 18 years or older) of any race or gender and has been referred for a VIZAMYL™ PET brain scan as part of the assessment of his/her cognitive impairment.

2. The VIZAMYL™ scan was ordered as part of the clinical care of the subject and is not exclusively for a clinical trial.

3. The subject, or his/her legally authorised representative, is willing and able to sign consent for use of their de-identified VIZAMYL™ PET images and associated anatomic images (brain CT and/or MRI) used in the interpretation of the VIZAMYL™ images as well as de-identified demographic information.

Subjects must be excluded from this study if the following criterion is met:

1. The subject (or representative) is not willing to consent to their de-identified images and other data being used in this study.

No withdrawal criteria for this study have been formalised. In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. Subjects who withdraw from the study will be asked if their de-identified data may be used; if consent to use their de-identified data is withdrawn, every effort will be made to exclude their data from analysis. Incomplete data sets from withdrawn subjects may be excluded from analysis even if permission has been granted for use if critical data are missing. Subjects whose data are excluded from analysis may be replaced.

No termination criteria for this study have been formalised. The Sponsor reserves the right to terminate the study at any time.

9.2.4 Inclusion and Exclusion of VIZAMYL™ Images

To be included in efficacy analyses, a subject's VIZAMYL™ PET scan must be interpretable and it must be transferred to the Sponsor.

Interpretability of the image will be determined by the nuclear medicine personnel obtaining the PET scan at each imaging centre. For example, if the subject moves during the scan, the scan may be severely blurred and therefore uninterpretable. Images that are not interpretable will be excluded from efficacy analyses and the subject data will be included in safety analyses only. Additional images may be collected to ensure a minimum of interpretable 200 images.

Images that cannot be transferred to the Sponsor for technical reasons will not be included in analyses and subject data will be included in safety analyses only. Additional images may be collected if necessary to ensure a minimum of 200 images total for the efficacy analyses.

9.2.5 Selection and Replacement of Clinical Readers

Potential clinical readers will be identified in each of the European countries where VIZAMYL™ is commercially available and where high use is expected during the study period. They cannot be one of the readers selected to be an expert reader, and cannot have participated in any of the VIZAMYL™ clinical trials sponsored by GE Healthcare. They must consent to have demographic information collected about them.

Each potential clinical reader contacted will be asked to complete a screening survey, which asks, among other things, if they are willing to participate in the study, and if they are authorised by their institution to read VIZAMYL™ PET images. Those who meet eligibility criteria and are willing to participate will be included in the study, 1 to 5 clinical readers per country.

To avoid overrepresentation of any reader, institution, or country in the study results, the following restrictions will apply:

- No clinical reader may contribute more than 7.5% of the total number of images (e.g., 15 of 200 images)
- No institution may contribute more than 15% of the total number of images (e.g., 30 of 200 images)
- No country may contribute more than 25% of the total number of images (e.g., 50 of 200 images)

Additional clinical readers may be added as necessary to replace clinical readers who withdraw. In the event that a clinical reader withdraws, the reason for withdrawal will be recorded, and permission to use his/her data will be sought; if declined, he/she will be replaced and his/her data will not be used.

9.2.6 Selection and Replacement of Expert Readers

The expert readers will consist of 5 experienced nuclear medicine physicians or radiologists, with extensive experience in PET imaging (including VIZAMYL™ imaging), who have completed the VIZAMYL™ training programme. They may have participated in VIZAMYL™ clinical trials. The expert readers will have a minimum of 5 years of experience in nuclear medicine brain imaging and must have reviewed a minimum of 100 amyloid PET images within the previous 5 years from the start of the study.

In the event that an expert reader withdraws, the reason for withdrawal will be recorded. If the expert reader withdraws before reading all of the images, or withdraws permission to use his/her demographic information, he/she will be replaced. The replacement reader will be

asked to read all images and his/her results will be used. The incomplete results from the expert reader who withdrew will not be used.

9.3 Variables

9.3.1 Demographic Data

The demographic data listed in Table 5 will be collected about subjects and readers. In addition, every effort will be made to collect these data from readers who decline to participate as well.

Table 5 Demographic Data to Be Collected

Group	Demographic Factors
Subjects	• Age • Gender • Race • Reason for scan • Country • Imaging centre • Type of medical practice of referring physician (primary, secondary, tertiary) • VIZAMYL™ dose in MBq or mCi • Type of anatomic images available, if any (MRI and/or CT)
Clinical readers	• Age • Gender • Race • Country • Institution • VIZAMYL™ reading training status • VIZAMYL™ reading training method (electronic, in-person, or both) • Date(s) of VIZAMYL™ reading training (this will be used to determine the time from last training to the date of image interpretation) • Training with other amyloid PET imaging agents • Medical specialty • Years of experience reading PET images • Number of brain PET scans read in clinical practice • Type of medical practice (primary, secondary, tertiary) • Prior experience (clinical or research) with any amyloid PET imaging agent (including VIZAMYL™)

9.3.2 Exposures

Subjects will receive VIZAMYL™ intravenously prior to PET imaging, according to clinical practice.

Clinical readers may or may not have completed any training in reading VIZAMYL™ images, and some may have completed 1 or more VIZAMYL™ reader training programmes. They also may or may not have prior experience in reading VIZAMYL™ images.

Expert readers will have been trained in reading VIZAMYL™ images and will have experience in reading amyloid PET images.

9.3.3 Outcome Measures

The primary outcome measure will be diagnostic accuracy (point estimates and exact 95% CIs) determined across all images (at least 200 images), as indicators of the collective proficiency of the clinical readers at interpreting VIZAMYL™ PET images. Diagnostic accuracy will give an indication of the overall image interpretation error rate (1 minus diagnostic accuracy). Additional outcome measures will be sensitivity, specificity, PPV, and NPV.

9.3.4 Risk Factors

Demographic variables about the clinical readers will be analysed to try to determine reader-associated variables associated with image interpretation errors.

9.3.5 Co-Morbidities

Except for structural abnormalities of the brain (which can be detected on MRI and/or CT and possibly adjusted for during PET image interpretation), there are no known co-morbidities that would affect PET image interpretation.

The AE profile in patients with renal impairment and/or hepatic impairment is currently unknown. In accordance with the current risk management plan for VIZAMYL™, a history of renal impairment and/or hepatic impairment will be captured in the eCRF. For documentation of AEs in these patients see Section 11.1.4.

9.3.6 Co-Medications

There are no known drug interactions that would affect image interpretation and so data on co-medications will not be collected.

9.3.7 Potential Confounders and Effect Modifiers

Potential factors that may affect image interpretation are brain atrophy, enlarged ventricles, and intracranial masses (which may distort brain anatomy). These can be detected on MRI and/or CT scans (which should be available for most if not all subjects as they are a standard component of patient workup for cognitive impairment) and taken into account during PET image interpretation.

9.4 Data Sources

9.4.1 Strategies and Data Sources

All data will be obtained prospectively from subjects, clinical readers, and expert readers who consent to participate. Data sources will be the images and patient medical records. Image interpretations and other data will be recorded directly onto eCRFs; images will be provided electronically. All measurements are considered standard for assessment of a diagnostic test.

Consenting eligible clinical readers (1 to 5 per country) will be selected and demographic information about them will be collected. They will each read VIZAMYL™ PET images obtained in clinical practice from consecutively enrolled subjects to generate the primary data that will be used to determine diagnostic accuracy.

Participating subjects will be administered VIZAMYL™ intravenously and will subsequently undergo PET brain imaging. Demographic information about the subject will be obtained from the imaging site where the subject is scanned. All VIZAMYL™ PET images (at least 200 images) and any associated anatomic images (brain CT and/or MRI) in this study will be acquired as part of clinical practice in Europe.

9.4.2 Expert Committees

Five consenting expert readers will each be asked to separately and independently read the images obtained in clinical practice from the subjects, and their majority image interpretations will be used as the SOT for determining diagnostic accuracy, sensitivity, specificity, PPV, and NPV. The interpretation of the images by the expert readers may be split up into multiple small reads for convenience as well as to accrue data steadily throughout the study.

9.5 Study Size

Number of Subjects

This study has no formal hypothesis and no statistical tests will be performed. The endpoints of accuracy, sensitivity, and specificity will be summarised descriptively with point estimates and 95% CIs. Although no formal hypothesis will be tested, the sample size is determined to achieve the desired precision in estimating the primary endpoint of the percentage of subjects whose images are correctly classified as positive or negative (accuracy). Assuming that VIZAMYL™ images from 90% of subjects are read correctly by readers who have taken the VIZAMYL™ training programme, 200 subjects will achieve a 95% CI width of less than 10%.

The endpoints of sensitivity and specificity will also be summarised descriptively. This study aims to characterise reader performance in clinical practice so the number of positive and negative images will not be controlled. However, it is expected that most patients who are referred for a VIZAMYL™ scan will have dementia, and most cases of dementia are AD. Since brain amyloid is present in AD, it is expected that the majority of patients in this study will have brain amyloid. It is assumed that the majority blinded interpretation of the expert readers will be SOT-positive for approximately 65% of scans, giving a total of approximately 130 scans for sensitivity, with the remaining 70 scans being SOT-negative and therefore usable for calculating specificity. Assuming a sensitivity of 90% and a specificity of 90%, these sample sizes should give reasonably precise 95% CIs for estimating sensitivity and specificity in this scenario (95% CI width of approximately 15% or less).

Accuracy, sensitivity, and specificity will also be calculated by country where all study images from sites within a given country will be pooled for analysis. No country may contribute more than 25% of the total number of images. Because the number of subjects per country is smaller than the overall number of subjects, the level of precision and the width of the CI will be

impacted. Again, since the aim of the study is to characterise reader performance in clinical practice, the exact number of images obtained per country and per site is unknown. Table 6 provides examples of 95% CI widths for accuracy assuming a few different sample sizes per country to illustrate the change in precision.

Table 6 95% Confidence Interval Width for Different Sample Sizes Assuming 90% Diagnostic Accuracy

Sample Size	Actual 95% CI Width	Lower Confidence Limit	Upper Confidence Limit
30	24.4%	73.5%	97.9%
40	20.9%	76.3%	97.2%
50	18.5%	78.2%	96.7%
60	16.7%	79.5%	96.2%

When calculating sensitivity and specificity per country, precision will again be impacted because the sample size per country will be further divided into SOT-positive and SOT-negative scans. For example, if a country enrols 40 subjects and 65% of the scans are SOT-positive (n = 26) then the width of the 95% CI for sensitivity would be 26.4% (lower confidence limit = 71.8%) and the width for specificity would be 37% (lower confidence limit = 62.4%).

Accuracy by reader will also be presented in a tabular form, though it may be expected that some institutions will have very few scans per reader.

Number of Clinical Readers

The number of clinical readers (1 to 5 per country) was chosen to allow each European country where VIZAMYL™ is commercially available and where high use is expected during the study period to be represented.

Number of Expert Readers

The number of expert readers (5) was chosen based on precedent set in prior clinical studies of VIZAMYL™.

9.6 Data Management

9.6.1 Data Collection

Non-imaging data will be collected directly from sites, clinical readers, and expert readers using eCRFs. Images will be transferred from imaging sites to the Sponsor using electronic transfer protocols.

9.6.2 Data Monitoring

Data will be monitored for completeness and logic using electronic edit checks, manual data listing review, and source data verification.

9.6.3 Data Retrieval from Sites

This is described above in Section 9.6.1.

9.6.4 Data Preparation

When necessary, the Sponsor or a designee will remove identifying information from the ≥200 VIZAMYL™ PET images, which thereafter will be designated only by subject number.

The images received by the GE Healthcare core lab will have been transferred by a system which de-identifies the images. This will be confirmed in a quality control step when images are received.

9.6.5 Data Management and Statistical Hardware

An electronic data capture (EDC) system will be used to collect data. A single data management contract research organization (CRO) will oversee the data collection at all sites. The data management CRO will be responsible for developing the database, training site personnel to enter data, data cleaning, and query resolution. The handling of data, including data quality control, will comply with all applicable regulatory guidelines. Appropriate access controls will be built into the database to ensure image blinding is maintained. The data management process will be outlined in more detail in the Data Management Plan.

9.7 Data Analysis

The data will be analysed by the sponsor-designated CRO. Any data analysis carried out independently by the investigator should be submitted to the Sponsor before publication or presentation.

Data from participating centres in this protocol will be combined so that an adequate number of subject images will be available for analysis. The data will be summarised with respect to demographic characteristics and efficacy observations and measurements.

General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software, Version 9.3 or higher. Descriptive statistics for continuous data in summary tables will include the number of subjects in the analysis (n), mean, standard deviation, median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. All data entered into the database will be provided in separate data listings showing individual subject values. The planning and reporting of statistical analysis will be carried out as described in the Sponsor and CRO's standard operating procedures (SOPs) governing clinical studies. Details of the analysis will be provided in the Statistical Analysis Plan.

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects enrolled and imaged in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

Subjects who do not meet the definition of the evaluable population will be excluded from the analyses. This will be determined prior to database freeze and image unblinding.

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

Populations for Analysis

The safety population will consist of all subjects who were enrolled in the study and received a dose of VIZAMYL™.

The efficacy subject population will consist of all subjects who have an interpretable image that has an available expert majority image interpretation.

The efficacy clinical reader population will consist of each clinical reader who has interpreted the images included from his/her institution and has had their image interpretations classified as TP, TN, FP, or FN through comparison with the SOT (the expert reader majority interpretation).

Subject Demographics/Other Baseline Characteristics

A table will be provided with the following information:

- Number of subjects enrolled.
- Number of subjects in the safety population.
- Number of subjects with VIZAMYL™ images included in the efficacy analysis.

Demographic information (Table 5 above) will be summarised using descriptive statistics.

Study Treatments

All subjects will have received VIZAMYL™ as part of routine clinical practice. The dose and volume administered will be summarised across all subjects.

Clinical Reader Demographics/Other Baseline Characteristics

A table will be provided with the following information:

- Number of clinical readers participating.
- Number of clinical readers' image interpretations included in the efficacy analysis.

Demographic information (Table 5 above) will be summarised using descriptive statistics. Demographic information will be reported for readers who are randomly chosen to participate as well as the complete pool of potential readers who agreed to participate in addition to readers who decided not to participate where data are available.

Primary Analysis

The primary analysis will be the determination of diagnostic accuracy, sensitivity, specificity, PPV, and NPV across readers based on all evaluable images (at least 200 images) (point estimates and exact 95% CIs).

Secondary Analyses

The numbers and percentages of images for which 5 expert readers agree, 4 expert readers agree, and 3 expert readers agree will be summarised. In addition, results will be analysed by the following variables:

- Country
- Time from training to image interpretation (<6 months, ≥6 months)
- Specialty of the reader
- Training method(s) used by the clinical reader (in-person, electronic, or both)
- Number of scans read by the clinical reader in practice prior to the study (<50, ≥50)
- Reader classification certainty (1 to 5)

The by-variable summaries will include estimates of diagnostic accuracy, sensitivity, specificity, PPV, and NPV along with 95% CIs for data pooled within each category. They will also show the number of clinical readers in each category and the number and percentage of clinical readers in each category with diagnostic accuracy <70%, >70% to ≤80%, >80% to ≤90%, and >90%.

The certainty of image classification will be summarised.

Safety Analyses

The number and percentage of subjects with 1 or more treatment-emergent AEs will be summarised. Additionally, treatment-emergent AEs will be coded and summarised by system organ class and preferred term. Treatment-emergent AE summaries will be provided by relationship to study drug and severity. Treatment-emergent serious AEs (SAEs) will also be summarised.

Interim Analysis

No formal interim analyses of the data are planned for this study. Interim progress reports of enrolment and safety will be provided annually.

Analyses of Study Limitations

Please see Section 9.9 below.

9.8 Quality Control

9.8.1 Mechanisms and Procedures to Ensure Data Quality and Integrity

For eCRFs, data will be entered by trained site personnel with reasons given for any missing data. Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided. Any data recorded directly in the eCRF, for which no other written or electronic record will be maintained in the subject's medical record, will be considered source data and should be signed by the investigator(s). Data collected from sites via eCRFs will be subject to source verification and edit checks for completeness, consistency, and logic.

Audit and Inspection

According to International Conference on Harmonization (ICH) E6-Good Clinical Practice (GCP), the Sponsor or regulatory authorities may audit the investigational site. The Sponsor's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

Confidentiality Regarding Study Subjects

The investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In eCRFs and other documents or image material (including materials from all examinations, e.g., CT, PET, and MRI examinations) submitted to the Sponsor/CRO, subjects will not be identified by their names, but by an identification code (e.g., study subject number).

Personal medical information may be scrutinised for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorised persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

9.8.2 Source Data Verification

Source data verification will be conducted by the CRO. The monitor(s), auditor(s), authorised personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorised members of the IECs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements. Image evaluation data from the clinical readers and expert readers will be entered directly into the eCRF and so no source verification is required.

9.8.3 Validation of Endpoints

The endpoint (diagnostic accuracy, sensitivity, specificity, PPV, and NPV) are well accepted for assessing diagnostic test performance. The endpoints of inter-reader agreement and intra-reader reproducibility will not be possible because each reader will interpret only the images collected at his/her institution, and it is assumed that each reader will interpret each image only once.

9.8.4 Storage of Records including Archiving of Statistical Programming

All study documentation will be archived in accordance with ICH E6- GCP and the Sponsor/CRO's quality standards and SOPs.

9.8.5 Certification and Qualifications of Supporting Laboratory or Research Groups

Not applicable to this study.

9.9 Limitations of the Research Methods

The main limitations of this study are:

1. Not all countries and sites can be represented because of restrictions due to approval and manufacturing locations.

2. Readers who participate may not be fully representative of the population of readers in clinical practice (e.g., untrained readers may be unwilling to participate, and there may not be a balanced split among clinical readers for subgroups such as training type, specialty, etc. since we are not controlling these factors).

The potential for bias from the first limitation cannot be assessed in this study. The potential for bias from the second limitation will be assessed by reporting demographic data (see Table 5) for readers who are randomly chosen to participate as well as the complete pool of potential readers who agreed to participate in addition to readers who decided not to participate, where data are available.

9.10 Other Aspects

Before starting this study, the protocol (authorised by the Sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC for evaluation. The protocol will also be signed by the principal investigator before submission to the IEC. The study will not start before the IEC gives written approval or a favourable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No changes from the final approved (authorised) protocol will be initiated without the IEC's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Sponsor will authorise and the principal investigator(s) will sign the

protocol amendment prior to submission to the IEC. Protocol amendments should be submitted to the IEC without delay.

9.10.1 Overall Responsibilities of Investigators

The investigators are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centres participating in this study that cannot comply with these standards will be documented.

9.10.2 Subject Informed Consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated informed consent form before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the investigator will sign, date and time the informed consent form after the subject has signed, dated, and recorded the time. The investigators will keep the original consent forms and copies will be given to the subjects.

9.10.3 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the Sponsor under any circumstances.

10 PROTECTION OF HUMAN SUBJECTS

The study protocol will be reviewed by an IEC at each imaging site. Each participating subject and clinical reader must provide informed consent prior to participation.

Subject and clinical reader confidentiality will be maintained in accordance with local requirement. Personal information will always be treated as confidential.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 Safety Assessments

The imaging agent VIZAMYL™ is approved and non-investigational in this study. It will be ordered and used in the course of everyday clinical practice. For the purposes of this study it is not considered to be an intervention. The collection of safety data is therefore aimed at post-approval supplementation of the safety profile described in the VIZAMYL™ Summary of Product Characteristics.

The investigator(s) and the Sponsor will review the data on treatment-emergent events (AEs and SAEs).

11.1.1 Treatment-Emergent Adverse Events

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life-threatening. Personnel who are trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available for 30 minutes after dosing. Treatment of SAEs should be primarily supportive of vital functions.

AE Definition: An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to that product. Only symptoms/signs that begin or worsen in severity and/or frequency after study drug administration/use will be recorded as AEs in the eCRF.

The subjects will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with non-leading questioning (e.g., “How do you feel?”). The subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

Both the investigator(s) and Sponsor will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the study drug caused the event.

Expectedness of an AE/reaction will be assessed against the approved VIZAMYL™ Summary of Product Characteristics.

Adverse Reaction: An AE that is caused by the study drug.

Suspected Adverse Event: A reasonable possibility exists for causality between the study drug and the AE.

11.1.2 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event.*

*Other important medical events are those that may not result in death, be life threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical intervention to prevent one of the outcomes listed above.

11.1.3 Other Significant Adverse Events

Clinical laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that lead to an intervention (including premature discontinuation of study drug, dose reduction or significant additional concomitant therapy), other than those reported as SAEs, will be reported and evaluated as other significant AEs.

11.1.4 Adverse Event and Serious Adverse Event Reporting

All AEs should be recorded using acceptable diagnoses, if possible. If an AE has already been reported it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine kinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild:	Tolerable.
Moderate:	Interferes with normal activity.
Severe:	Incapacitating (causes inability to perform usual activity or work).

The investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the study drug or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the Sponsor according to a well-recognised dictionary of medical codes.

AEs will be recorded in the eCRF if they occurred as follows:

- From start of injection until discharge from imaging centre, whether or not considered related to the study drug, and
- After discharge from imaging centre, and for which a causal relationship to the study drug is a reasonable possibility.

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

Additional information required in cases of hypersensitivity reactions or AEs in patients with renal and/or hepatic impairment.

In accordance with the Risk Management Plan for VIZAMYL™, hypersensitivity-type adverse reactions (both serious and non-serious) and AEs in patients with renal impairment and/or hepatic impairment (both serious and non-serious) need to be carefully documented. Investigators are requested to fill out the questionnaire (see Annex 1) together with the AE/SAE form.

Study centres are instructed to report all AEs to GE Healthcare Global Pharmacovigilance within 3 days by sending an email to gpv.drugsafety@ge.com.

Individual case safety reports of valid serious and non-serious adverse drug reactions will be classified as solicited reports. The Sponsor will report adverse drug reactions (i.e., AEs for which a causal relationship is at least a reasonable possibility) to health authorities in accordance with Regulation (EC) No. 726/2004 and Sponsor SOPs.

Reports of causally unrelated AEs will be summarised as part of any interim safety analysis and in the final study report, where applicable.

Adverse reactions to medicines other than VIZAMYL™ will be handled according to GE Healthcare Global Pharmacovigilance SOPs.

Events which affect the known risk-benefit balance of VIZAMYL™ and/or impact on public health will be notified to competent authorities and the Agency, in accordance with GE Healthcare Global Pharmacovigilance SOPs.

The centre should also notify the Medical Director of the SAE at one of the contact numbers below. For any protocol or safety-related questions please contact the Medical Director:

Paul Sherwin, MD, PhD
GE Healthcare Life Sciences
100 Results Way
Marlborough, MA 01752 USA
Telephone: +1 774 843 3888 (office) or +1 609 510 3686 (mobile)
E-mail: paulsherwin@ge.com

Subjects will be provided with a Clinical Trial Participant card at the time of study drug administration. This card will list contact details for the investigator and for GE Healthcare medical emergency cover services (Clinical Trial Emergency Contact Service [CTECS]). The CTECS provides 24-hour, 7-day-a-week emergency cover service for advice on trial–related medical questions or problems should a medical emergency arise and the investigator is not available.

11.1.5 Urgent Safety Measures

In accordance with the principles of GCP as laid out in ICH E6, the investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which an investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IEC approval/favourable opinion.

The investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazards to their health or safety. However, the investigator must inform the Sponsor within 24 hours of having taken such measures.

The Sponsor in turn shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant IEC of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the Medical Director using the contact information provided in Section 11.1.4 within 24 hours of having to take such a measure(s). Such reports can be initiated by telephone but must be officially documented by the investigator (by email) and must include details of what measures were taken and the circumstances giving rise to those measures. If there is an associated AE, this should be reported as described in Section 11.1.4.

11.1.6 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to study drug exposure of pregnant women and/or foetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all subjects following exposure to study drug.

Female trial subjects: The trial subject must be advised by the investigator to inform him/her immediately if she suspects she may be pregnant within 30 days after receiving VIZAMYL™.

Male trial subjects: The trial subject must be advised by the investigator to inform him/her immediately if they suspect their partner became pregnant within 30 days after the subject was administered with study drug.

When a trial subject reports a pregnancy (post-study drug administration) to the investigator, a pregnancy test should be arranged for the trial subject (or their partner) by the investigator within 7 days of the pregnancy being reported.

The investigator must inform the Sponsor within 24 hours of receiving positive pregnancy test results using either a copy of the relevant eCRF page (demography or AE) or via email. The investigator should include an estimated date of conception when communicating with the Sponsor.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual progress reports will be submitted to the EMA. The Sponsor may submit the results of the study for publication in a peer-reviewed journal. Abstracts and/or oral presentations of the results at medical professional meetings may also be planned.

13 REFERENCES

[Buckley et al. 2017]
Buckley CJ, Sherwin PF, Smith AP, et al. Validation of an electronic image reader training programme for interpretation of [^{18}F]flutemetamol β-amyloid PET brain images. Nucl Med Commun. 2017 Mar;38(3):234-241. doi: 10.1097/MNM.0000000000000633.

[Curtis et al. 2015]
Curtis C, Gamez JE, Singh U, et al. Phase 3 trial of flutemetamol labeled with radioactive fluorine 18 imaging and neuritic plaque density. JAMA Neurol. 2015 Mar;72(3):287-94. doi: 10.1001/jamaneurol.2014.4144.

[Filippi et al. 2012]
Filippi M, Agosta F, Barkhof F, et al. EFNS task force: the use of neuroimaging in the diagnosis of dementia. Eur J Neurol. 2012;19:1487-1511.

[Khachaturian, 1985]
Khachaturian ZS. Diagnosis of Alzheimer's Disease. Arch Neurol. 1985;42:1097-1105.

[Minoshima et al. 2016]
Minoshima S, Drzezga AE, Barthel H, et al. SNMMI Procedure Standard/EANM Practice Guideline for Amyloid PET Imaging of the Brain 1.0. J Nucl Med. 2016 Aug;57(8):1316-22. doi: 10.2967/jnumed.116.174615.

[Mirra et al. 1991]
Mirra SS, Heyman A, McKeel D. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991;41:479-486.

[NIA-Reagan, 1997]
NIA-Reagan 1997. National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. Neurobiol Aging. 1997;18:(4 suppl):S1–S2.

[Salloway et al. 2017]
Salloway S, Gamez JE, Singh U, et al. Performance of [^{18}F]flutemetamol amyloid imaging against the neuritic plaque component of CERAD and the current (2012) NIA-AA recommendations for the neuropathologic diagnosis of Alzheimer's disease. Alzheimers Dement (Amst). 2017 Jul 1;9:25-34. doi: 10.1016/j.dadm.2017.06.001. eCollection 2017.

Annex 1 List of Stand-Alone Documents

See the [List of Stand-Alone Documents] for other documents associated with this study.

Annex 2 ENCePP Checklist for Study Protocols

See the [ENCePP Checklist for Study Protocols] that has been completed for this study.

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: Mohammed Alam Date of signature: 16-Feb-2018 01:08:37 GMT+0000	Justification: Approved Role: Head of Biometrics
Signed By: Francois Tranquart Date of signature: 16-Feb-2018 10:37:44 GMT+0000	Justification: Approved Role: Head of Clinical Development

This is a representation of an electronic record that was signed electronically in accordance with GxP guidelines and controls. The information above is a valid manifestation of the electronic signature(s) and is legally binding