Clinical Study Protocol GE067-028

GE Healthcare

Title	Post-Authorisation Survey of Nuclear Medicine Physicians and Radiologists in Europe to Evaluate Trends and Patterns in VIZAMYL™ Use in Everyday Clinical Practice in the EU
Protocol version identifier	2.0
Date of PRAC approval of protocol	19 December 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 003
Marketing authorisation holders	GE Healthcare Ltd, Amersham Place, Little Chalfont, Buckinghamshire, HP7 9NA, United Kingdom
Joint PASS	No
Research question and objectives	**Research Question:** • How is VIZAMYL™ used in everyday EU clinical practice? **Primary Objective:** • To retrospectively determine post-authorisation use of VIZAMYL™ in everyday clinical practice in the EU **Secondary Objectives:** • To retrospectively describe VIZAMYL™ use in everyday clinical practice in the EU with regard to: 1. Indication (reason for ordering) 2. Administered dose of radioactivity of VIZAMYL™ 3. Body region imaged 4. Time from dosing to scan initiation 5. Duration of scanning 6. Type(s) of other images used to assist in interpretation of VIZAMYL™ images 7. Percentage of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned 8. Percentage of VIZAMYL™ readers who have completed training in the interpretation of VIZAMYL™ PET images
Countries of study	EU countries where VIZAMYL™ is commercially available, where high use is expected during the study period
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Confidentiality Statement

This protocol is provided for conducting a clinical research study. The information contained in this document is confidential and, except to the extent necessary to obtain informed consent or IEC/IRB approval, cannot be disclosed unless required by governmental regulation. Persons to whom any portion of the contents of this document is disclosed must be informed that the information is confidential and may not be further disclosed by them.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AD	Alzheimer's Disease
CRO	Contract Research Organization
EMA	European Medicines Agency
EU	European Union
Flutemetamol	Drug substance in VIZAMYL™ Injection
Flutemetamol (^{18}F) Injection	Generic name for VIZAMYL™ Injection
[^{18}F]Flutemetamol (^{18}F)	Active component of the drug product VIZAMYL™ Injection
PET	Positron Emission Tomography
PiB	Pittsburgh Compound B
SmPC	Summary of Product Characteristics
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 GE067-028 Study Personnel" listed in Annex 1. It is available upon request.

4 ABSTRACT

Title

Post-Authorisation Survey of Nuclear Medicine Physicians and Radiologists in Europe to Evaluate Trends and Patterns in VIZAMYL™ Use in Everyday Clinical Practice in the EU

Protocol Version: 2.0

Protocol Date: 16 February 2018

Main Author: Paul Sherwin, MD, PhD, Senior Medical Director, GE Healthcare.

Rationale and background

VIZAMYL™ (Flutemetamol (^{18}F) Injection) was approved by the United States Food and Drug Administration 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, VIZAMYL™ is manufactured on demand in response to a valid prescription.

GE Healthcare was asked by the EMA to assess the understanding and compliance of readers with the approved indication. This drug utilisation study will retrospectively assess the actual use of VIZAMYL™ PET scans in the everyday clinical settings and determine the level of off-label use in Europe. The study will retrospectively survey VIZAMYL™ readers in European countries where VIZAMYL™ is commercially available and where high use is expected during the study period to determine trends and patterns of VIZAMYL™ use in everyday clinical practice.

Research question and objectives

Research Question

The research question that this study will answer retrospectively is: "*How is VIZAMYL™ used in everyday EU clinical practice*?"

Primary Objective:

- To retrospectively determine post-authorisation use of VIZAMYL™ in everyday clinical practice in the EU

Secondary Objectives:

- To retrospectively describe VIZAMYL™ use in everyday clinical practice in the EU with regard to:

    1. Indication (reason for ordering)
    2. Administered dose of radioactivity of VIZAMYL™
    3. Body region imaged
    4. Time from dosing to scan initiation
    5. Duration of scanning
    6. Type(s) of other images used to assist in interpretation of VIZAMYL™ images
    7. Percentage of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned
    8. Percentage of VIZAMYL™ readers who have completed training in the interpretation of VIZAMYL™ PET images

Safety Endpoints:

Not applicable.

Study design

VIZAMYL™ was approved in the EU in August 2014 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. According to the approved Summary of Product Characteristics (SmPC) for VIZAMYL™: 1) the recommended dose is 185 MBq of radioactivity administered intravenously; 2) the scan duration should typically be 20 minutes in length and started 90 minutes after injection; and 3) persons interpreting the scans should be trained beforehand in the interpretation of PET images with VIZAMYL™.

This retrospective post-authorisation study will survey VIZAMYL™ readers (nuclear medicine physicians and radiologists) to determine the post-authorisation use of VIZAMYL™ in everyday clinical practice in the EU over approximately a 2.5-year period.

The survey will be conducted in 3 rounds at approximately 12-month intervals in each of the target countries (European countries where VIZAMYL™ is commercially available and where high use is expected during the study period). Before the beginning of each round, a list of names of physicians (nuclear medicine physicians and radiologists) will be created by GE Healthcare for each target country based on records of VIZAMYL™ orders for the country. Physicians are encouraged to participate more than once, and physicians who do not participate in earlier rounds can participate in later rounds. In each round of the survey, potential

participating physicians will be selected sequentially from each target country's list and contacted through telephone or email. During the initial contact, each candidate will be assessed for eligibility and willingness to participate in the study by using a screening questionnaire. The initial contact and screening of potential participating physicians will continue for at least 6 months. It is assumed that the number of physicians sampled in each target country will be proportional to the use of VIZAMYL™ in each target country.

The Sponsor (or designee) will provide instructions for accessing the web-based survey. The survey will collect demographic data and ask about their awareness of the correct indication for VIZAMYL™ and their recollection of previous experience in using VIZAMYL™ will be collected. These procedures will be repeated for subsequent rounds of the survey. The survey will be available in local languages as well as in English.

Population

To be eligible to participate in the survey, physicians must meet the following criteria:

1. Must be a practicing nuclear medicine physician or radiologist in at least one of the target countries (European countries where VIZAMYL™ is commercially available and where high use is expected during the study period)

2. Must have reviewed at least 3 VIZAMYL™ scans in the preceding quarter

3. Must consent to completing the survey

Variables

Primary Endpoint:

- Summary across survey respondents of reported percentage of patients referred for a VIZAMYL™ scan for the indication listed in the SmPC.

This will be determined separately for each survey round (3 rounds, conducted at 12-month intervals).

Secondary Endpoints:

Each of the following secondary endpoints will be determined separately for each survey round.

1. Summary across survey respondents of reported percentages of patients referred for a VIZAMYL™ scan for another indication.

2. Summary across survey respondents of reported percentages of patients with each type of cognitive status.

3. Summary across survey respondents of reported percentages of patients receiving VIZAMYL™ doses in each range (<165 MBq, 165 to 205 MBq, >205 MBq).

4. Summary across survey respondents of reported percentages of patients scanned in each body region following VIZAMYL™ administration (head, neck, thorax, abdomen/pelvis, upper extremity, lower extremity).

5. Summary across survey respondents of reported percentages of patients in whom VIZAMYL™ scanning is initiated <80, 80 to 100, and >100 minutes after dosing.

6. Summary across survey respondents of reported percentages of patients scanned for <15 and ≥15 minutes. The threshold of 15 minutes instead of 20 minutes reflects the fact that the scanning time needed is a function of both administered radioactivity and scanner sensitivity, and allows for variation in clinical practice.

7. Summary across survey respondents of reported percentages of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned.

8. Percentage of survey respondents reporting that the safety profile of VIZAMYL™ is consistent with that reported in the SmPC.

9. Summary across survey respondents of reported percentages of cases in which other types of images were used to assist in interpretation of VIZAMYL™ images.

10. Proportion of survey respondents who report having taken training in the interpretation of VIZAMYL™ PET images.

11. Proportion of survey respondents who report having taken training who report Electronic, In-person, and Other as the type of training taken.

12. Proportion of survey respondents who report not having taken training who report planning to take training.

13. Proportion of survey respondents who report not having taken training and who report planning to take training, who report Electronic, In-person, Other, or Undecided for the type of planned training.

14. Proportion of survey respondents who report using quantitative image analysis to assist in image interpretation.

15. Summary across survey respondents of reported percentages of paediatric referrals for a VIZAMYL™ scan.

16. Summary of reported indications for paediatric use, if any paediatric use is reported.

Other Variables:

The following information will be collected from each survey participant for each round of the survey:

1. Age in years
2. Gender
3. Experience (average number of scans per month) in interpreting VIZAMYL™ (flutemetamol), Amyvid™ (florbetapir), and Neuraceq™ (florbetaben) images
4. Medical specialty (nuclear medicine, radiology, medical physics, other)
5. Years of experience in neuroimaging
6. Main practice setting (hospital, standalone imaging centre, other)
7. Main type of patient care at practice setting from which patients are referred (primary, secondary, or tertiary)
8. Practice location (urban, suburban, rural)
9. Country

Data sources

Data will be collected solely from the web-based survey forms.

Study size

It is assumed that the number of survey participants will be proportional to VIZAMYL™ use in each target country. At least 100 survey respondents per survey round are planned.

Data analysis

Primary Analysis:

The primary analysis will be the summarization across survey respondents of the estimated percentages of patients referred for each indication. This will be done separately for each of the 3 survey rounds (conducted at 12-month intervals). Any response other than "*To image β amyloid neuritic plaque density in the brain*" will be considered off-label.

Secondary Analyses:

Determination of each of the following for each of the 3 rounds of the survey:

1. Summary across survey respondents of reported percentages of patients with each type of cognitive status (cognitive impairment (dementia, mild cognitive impairment, unknown

type), normal cognitive function, and unknown). Only use in patients with normal cognitive function will be considered to be off-label.

2. Summary across survey respondents of reported percentages of patients referred for a VIZAMYL™ scan for another indication. Any response other than "*To image β amyloid neuritic plaque density in the brain*" will be considered off-label.

3. Summary across survey respondents of reported percentages of patients receiving VIZAMYL™ doses in each range (<165 MBq, 165 to 205 MBq, >205 MBq). Any response other than "*165 to 205 MBq*" will be considered off-label.

4. Summary across survey respondents of reported percentages of patients scanned in each body region following VIZAMYL™ administration (head, neck, thorax, abdomen/pelvis, upper extremity, lower extremity). Any response other than "*head*" will be considered off-label.

5. Summary across survey respondents of reported percentages of patients in whom VIZAMYL™ scanning is initiated <80, 80 to 100, and >100 minutes after dosing. Any response other than "*80 to 100*" will be considered off-label.

6. Summary across survey respondents of reported percentages of patients scanned for <15 and ≥15 minutes. A response of <15 minutes will be considered off-label.

7. Summary across survey respondents of reported percentages of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned. Scanning of patients with a contraindication will be considered off-label.

8. Proportion of survey respondents reporting a VIZAMYL™ safety profile consistent with the SmPC. Any explanations of a "no" answer will be reviewed for possible evidence of off-label use.

9. Summary across survey respondents of reported percentages of VIZAMYL™ scans interpreted 1) without consulting other types of images and 2) with other types of images. No responses will be considered off-label.

10. Proportion of survey respondents who report having taken training in the interpretation of VIZAMYL™ PET images. No responses will be considered off-label.

11. Proportion of survey respondents who report having taken training who report Electronic, In-person, and Other as the type of training taken. No responses will be considered off-label.

12. Proportion of survey respondents who report not having taken training who report planning to take training. No responses will be considered off-label.

13. Proportion of survey respondents who report not having taken training and who report planning to take training, who report Electronic, In-person, Other, or Undecided for the type of planned training. No responses will be considered off-label.

14. Summary across survey respondents of reported percentages of paediatric referrals for a VIZAMYL™ scan. All such referrals will be considered to be off-label.

15. Summary of reported indications for paediatric use. All such indications in paediatric patients will be considered to be off-label.

Milestones[a]

Milestone	**Planned date**
Registration in the EU PAS register	Q1 2018
Survey Round 1	
Survey available	Q2 2018
Start of data collection	Q2 2018
End of data collection	Q4 2018
Survey Round 2	
Survey available[b]	Q2 2019
Start of data collection	Q2 2019
End of data collection	Q4 2019
Survey Round 3	
Survey available[b]	Q2 2020
Start of data collection	Q2 2020
End of data collection	Q4 2020
Final report of study results	Q1 2021
Study progress reports	Annually

[a]Milestones will be re-evaluated once the study is underway, based on actual rate of physician participation.
[b]These milestones allow for survey improvement based on experience, and may be unnecessary.

5 AMENDMENTS AND UPDATES

GE Healthcare Version Number	Original Status	PRAC Version	Date	Key Reasons for New Version
1.0	Approved	1.0	20 Nov 2014	Original document.
2.0	Approved	1.0	13 May 2015	This document was revised to reformat the protocol to the PASS Protocol style.
3.0	Approved	1.0	15 Oct 2015	This document was revised to incorporate the following changes: • The study sample size was updated to be based on the expected primary endpoint results. • Analyses were added to assess physician screening and identify differences between physicians willing and not willing to participate in the study. This version was submitted to, and approved by, the EMA.
4.0	Approved	2.0	19 Dec 2017	This document was revised to incorporate the following changes: • Changed and clarified the readers and countries to be selected for participation in this study to allow for flexibility. • Survey question number references have been removed from protocol and data to be collected via the screening and survey questionnaires has been updated. The screening and survey questionnaires have been revised to align with the changes to the data being collected. • Manual data listing review and source data verification were removed from the list of data monitoring tasks. • Study timelines and 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.

6 MILESTONES

Table 1 Study Milestones

Milestone[a]	**Planned date**
Registration in the EU PAS register	Q1 2018
Survey Round 1	
Survey available	Q2 2018
Start of data collection	Q2 2018
End of data collection	Q4 2018
Survey Round 2	
Survey available[b]	Q2 2019
Start of data collection	Q2 2019
End of data collection	Q4 2019
Survey Round 3	
Survey available[b]	Q2 2020
Start of data collection	Q2 2020
End of data collection	Q4 2020
Final report of study results	Q1 2021
Study progress reports	Annually

[a]Milestones will be re-evaluated once the study is underway, based on actual rate of physician participation.
[b]These milestones allow for survey improvement based on experience, and may be unnecessary.

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 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, which is 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 Food and Drug Administration on 25 October 2013 and by the European Medicines Agency (EMA) on 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.

GE Healthcare was asked by the EMA to assess the understanding and compliance of readers with the approved indication. This retrospective drug utilisation study will assess the actual use of VIZAMYL™ PET scans in the everyday clinical settings and to determine the level of off-label use in Europe. The study will survey VIZAMYL™ readers in European countries where VIZAMYL™ is commercially available and where high use is expected during the study period to determine trends and patterns of VIZAMYL™ use in everyday clinical practice.

8 RESEARCH QUESTIONS AND OBJECTIVES

The research question to be answered retrospectively by this study is: *"How is VIZAMYL™ used in everyday EU clinical practice?"* To answer this question, the study has the following primary and secondary objectives.

Primary Objective:

- To retrospectively determine post-authorisation use of VIZAMYL™ in everyday clinical practice in the EU

Secondary Objectives:

- To retrospectively describe VIZAMYL™ use in everyday clinical practice in the EU with regard to:

    1. Indication (reason for ordering)
    2. Administered dose of radioactivity of VIZAMYL™
    3. Body region imaged
    4. Time from dosing to scan initiation
    5. Duration of scanning
    6. Type(s) of other images used to assist in interpretation of VIZAMYL™ images
    7. Percentage of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned
    8. Percentage of VIZAMYL™ readers who have completed training in the interpretation of VIZAMYL™ PET images

9 RESEARCH METHODS

9.1 Study Design

VIZAMYL™ was approved in the EU in August 2014 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. According to the approved Summary of Product Characteristics (SmPC) for VIZAMYL™: 1) the recommended dose is 185 MBq of radioactivity administered intravenously; 2) the scan duration should typically be 20 minutes in length and started 90 minutes after injection; and 3) persons interpreting the scans should be trained beforehand in the interpretation of PET images with VIZAMYL™.

This retrospective post-authorisation study will survey VIZAMYL™ readers (nuclear medicine physicians and radiologists) to determine the post-authorisation use of VIZAMYL™ in everyday clinical practice in the EU over approximately a 2.5-year period.

The survey will be conducted in 3 rounds at 12-month intervals in each of the target countries (European countries where VIZAMYL™ is commercially available and where high use is expected during the study period). Before the beginning of each round, a list of names of physicians (nuclear medicine physicians and radiologists) will be created by GE Healthcare for each target country based on records of VIZAMYL™ orders for the country. Physicians are encouraged to participate more than once, and physicians who do not participate in earlier rounds can participate in later rounds. In each round of the survey, potential participating physicians will be selected sequentially from each target country's list and contacted through telephone or email. During the initial contact, each candidate will be assessed for eligibility and willingness to participate in the study by using a screening questionnaire (see standalone document [GE067-028 Screening Questionnaire]). The initial contact and screening of potential participating physicians will continue for at least 6 months. It is assumed that the number of physicians sampled in each target country will be proportional to the use of VIZAMYL™ in each target country.

The Sponsor (or designee) will provide instructions for accessing the web-based survey. The survey will collect demographic data and ask about their awareness of the correct indication for VIZAMYL™ and their recollection of previous experience in using VIZAMYL™ will be collected. These procedures will be repeated for subsequent rounds of the survey. The survey will be available in local languages as well as in English.

The sample size will not be based on statistical considerations as the study does not formally test a hypothesis; however, it is believed that a large enough survey sample will be available to assess post-authorisation utilisation trends and a reasonable sampling relative to the anticipated annual product volume in the EU. The standalone document [GE067-028 Survey Questionnaire] contains the detailed questions for the survey.

9.2 Setting

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 Screening, Selection and Replacement of Survey Participants

Before the beginning of each survey round, a list of names of physicians (nuclear medicine physicians and radiologists) will be created by GE Healthcare for each target country based on records of VIZAMYL™ orders for the country.

Potential participating physicians will be selected sequentially from each target country's list. Candidates will be contacted through telephone or email. During the initial contact, each will be assessed for eligibility and willingness to participate in the study by using a screening questionnaire (see standalone document [GE067-028 Screening Questionnaire]).

To be eligible to participate in the survey, physicians must meet the following criteria:

1. Must be a practicing nuclear medicine physician or radiologist in at least one of the target countries (European countries where VIZAMYL™ is commercially available and where high use is expected during the study period)

2. Must have reviewed at least 3 VIZAMYL™ scans in the preceding quarter

3. Must consent to completing the survey

Survey participants who do not complete the survey may be replaced if possible.

9.3 Variables

9.3.1 Primary Endpoint

- Summary across survey respondents of reported percentage of patients referred for a VIZAMYL™ scan for the indication listed in the SmPC.

This will be determined separately for each survey round (3 rounds, conducted at 12-month intervals).

9.3.2 Secondary Endpoints

Each of the following secondary endpoints will be determined separately for each survey round.

1. Summary across survey respondents of reported percentages of patients referred for a VIZAMYL™ scan for another indication.

2. Summary across survey respondents of reported percentages of patients with each type of cognitive status.

3. Summary across survey respondents of reported percentages of patients receiving VIZAMYL™ doses in each range (<165 MBq, 165 to 205 MBq, >205 MBq).

4. Summary across survey respondents of reported percentages of patients scanned in each body region following VIZAMYL™ administration (head, neck, thorax, abdomen/pelvis, upper extremity, lower extremity).

5. Summary across survey respondents of reported percentages of patients in whom VIZAMYL™ scanning is initiated <80, 80 to 100, and >100 minutes after dosing.

6. Summary across survey respondents of reported percentages of patients scanned for <15 and ≥15 minutes. The threshold of 15 minutes instead of 20 minutes reflects the fact that the scanning time needed is a function of both administered radioactivity and scanner sensitivity, and allows for variation in clinical practice.

7. Summary across survey respondents of reported percentages of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned.

8. Percentage of survey respondents reporting that the safety profile of VIZAMYL™ is consistent with that reported in the SmPC.

9. Summary across survey respondents of reported percentages of cases in which other types of images were used to assist in interpretation of VIZAMYL™ images.

10. Proportion of survey respondents who report having taken training in the interpretation of VIZAMYL™ PET images.

11. Proportion of survey respondents who report having taken training who report Electronic, In-person, and Other as the type of training taken.

12. Proportion of survey respondents who report not having taken training who report planning to take training.

13. Proportion of survey respondents who report not having taken training and who report planning to take training, who report Electronic, In-person, Other, or Undecided for the type of planned training.

14. Proportion of survey respondents who report using quantitative image analysis to assist in image interpretation.

15. Summary across survey respondents of reported percentages of paediatric referrals for a VIZAMYL™ scan.

16. Summary of reported indications for paediatric use, if any paediatric use is reported.

9.3.3 Other Variables

The following information will be collected from each survey participant for each round of the survey:

1. Age in years
2. Gender
3. Experience (average number of scans per month) in interpreting VIZAMYL™ (flutemetamol), Amyvid™ (florbetapir), and Neuraceq™ (florbetaben) images
4. Medical specialty (nuclear medicine, radiology, medical physics, other)
5. Years of experience in neuroimaging
6. Main practice setting (hospital, standalone imaging centre, other)
7. Main type of patient care at practice setting from which patients are referred (primary, secondary, or tertiary)
8. Practice location (urban, suburban, rural)
9. Country

9.3.4 Exposures

No patients will be enrolled in this study.

Physicians participating in the survey must have had some experience in interpreting VIZAMYL™ images but may or may not have completed any training in such interpretation.

9.4 Data Sources

9.4.1 Strategies and Data Sources

All survey data will be obtained from the web-based survey forms. Eligible physicians who agree to participate will be selected and demographic information about them will be collected. They will answer a series of survey questions about their recollection of personal experience using VIZAMYL™ in everyday clinical practice.

9.5 Study Size

This study has no formal hypothesis and no statistical tests will be performed. The sample size is based on the expected results for the primary endpoint. The study primary endpoint is the summary across survey respondents of the reported percentage of patients referred for a VIZAMYL™ scan for the indication listed in the SmPC. The study will determine this statistic and report the point estimate along with the limits of the exact two-sided 95% confidence interval. The sample size is based on the anticipated rate of physician compliance with the approved indication measured in each round of the survey. It is assumed that compliance with the approved indication in the SmPC will be approximately 95%. The sample size needed to estimate this proportion is reported in Table 2 below for various widths of the exact two-sided 95% confidence interval. Based on these sample size estimates, it is planned to enrol at least 100 physicians in each round of the survey. This will give a confidence interval width of approximately 10%. Enrolment will be monitored during the study and make every effort to attain the planned level of precision. However, the feasibility of the sample size is in part dependent on actual product usage and physician participation rates. Enrolling fewer than 94 participants will result in a wider confidence interval as illustrated in Table 2.

Table 2 Numeric Results for Two-Sided Confidence Intervals for One Proportion Confidence Interval Formula: Exact (Clopper-Pearson)

Target CI Width	Sample Size (N)	Lower Limit of CI	Upper Limit of CI
0.10	94	0.884	0.984
0.15	47	0.844	0.992
0.20	29	0.799	0.997
0.25	20	0.751	0.999

9.6 Data Management

9.6.1 Data Collection

Survey data will be collected directly from participants using web-based forms.

9.6.2 Data Monitoring

Data will be monitored for completeness and logic using electronic edit checks.

9.6.3 Data Management and Statistical Hardware

An electronic data capture system will be used to collect data. A single data management contract research organization (CRO) will oversee the data collection at all sites. The handling of data, including data quality control, will comply with all applicable regulatory guidelines. 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.

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 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.

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 analysis population will consist of all survey participants in each survey round who complete at least 1 survey question.

Physician Screening Analyses

To try to identify differences between screened physicians who agree to participate ("willing" group) and screened physicians who do not agree to participate ("unwilling" group), the following characteristics of screened physicians will be reported for each of the 3 survey rounds:

- Number of physicians screened
- Number and percentage of screened physicians who agree to participate ("willing" group)
- Number and percentage of screened physician who do not agree to participate ("unwilling" group)
- Numbers and percentages of physicians in the willing and unwilling groups whose primary area of clinical practice is nuclear medicine, radiology, and both.
- Numbers and percentages of physicians in the willing and unwilling groups who practice in each of the target countries.

- Average number of VIZAMYL™ scans interpreted by physicians in the willing and unwilling groups.
- Numbers and percentages of physicians in the willing and unwilling groups who are male and female
- Average age of physicians in the willing and unwilling groups

Additional analyses of these data may be conducted as appropriate to better understand the results.

Participant Demographics/Other Baseline Characteristics

For each of the 3 survey rounds, a table will be provided with the following information:

- Number of survey participants.
- Number of survey participants in the analysis population.

Survey Participant Demographics/Other Baseline Characteristics

The following demographic and/or information will be summarised using descriptive statistics:

1. Age in years
2. Gender
3. Experience (average number of scans per month) in interpreting VIZAMYL™ (flutemetamol), Amyvid™ (florbetapir), and Neuraceq™ (florbetaben) images
4. Medical specialty (nuclear medicine, radiology, medical physics, other)
5. Years of experience in neuroimaging
6. Main practice setting (hospital, standalone imaging centre, other)
7. Main type of patient care at practice setting from which patients are referred (primary, secondary, or tertiary)
8. Practice location (urban, suburban, rural)
9. Country

Primary Analysis:

The primary analysis will be the summarization across survey respondents of the estimated percentages of patients referred for each indication. This will be done separately for each of the 3 survey rounds (conducted at 12-month intervals). Any response other than "*To image β amyloid neuritic plaque density in the brain*" will be considered off-label.

Secondary Analyses:

Determination of each of the following for each of the 3 rounds of the survey:

1. Summary across survey respondents of reported percentages of patients with each type of cognitive status (cognitive impairment (dementia, mild cognitive impairment, unknown type), normal cognitive function, and unknown). Only use in patients with normal cognitive function will be considered to be off-label.

2. Summary across survey respondents of reported percentages of patients referred for a VIZAMYL™ scan for different uses. Any response other than "*To image β amyloid neuritic plaque density in the brain*" will be considered off-label.

3. Summary across survey respondents of reported percentages of patients receiving VIZAMYL™ doses in each range (<165 MBq, 165 to 205 MBq, >205 MBq). Any response other than "*165 to 205 MBq*" will be considered off-label.

4. Summary across survey respondents of reported percentages of patients scanned in each body region following VIZAMYL™ administration (head, neck, thorax, abdomen/pelvis, upper extremity, lower extremity). Any response other than "*head*" will be considered off-label.

5. Summary across survey respondents of reported percentages of patients in whom VIZAMYL™ scanning is initiated <80, 80 to 100, and >100 minutes after dosing. Any response other than "*80 to 100*" will be considered off-label.

6. Summary across survey respondents of reported percentages of patients scanned for <15 and ≥15 minutes. A response of <15 minutes will be considered off-label.

7. Summary across survey respondents of reported percentages of patients with a contraindication to VIZAMYL™ use (hypersensitivity to VIZAMYL™ or any ingredient) who were scanned and not scanned. Scanning of patients with a contraindication will be considered off-label.

8. Proportion of survey respondents reporting a VIZAMYL™ safety profile consistent with the SmPC. Any explanations of a "no" answer will be reviewed for possible evidence of off-label use.

9. Summary across survey respondents of reported percentages of VIZAMYL™ scans interpreted 1) without consulting other types of images and 2) with other types of images. No responses will be considered off-label.

10. Proportion of survey respondents who report having taken training in the interpretation of VIZAMYL™ PET images. No responses will be considered off-label.

11. Proportion of survey respondents who report having taken training who report Electronic, In-person, and Other as the type of training taken. No responses will be considered off-label.

12. Proportion of survey respondents who report not having taken training who report planning to take training. No responses will be considered off-label.

13. Proportion of survey respondents who report not having taken training and who report planning to take training, who report Electronic, In-person, Other, or Undecided for the type of planned training. No responses will be considered off-label.

14. Summary across survey respondents of reported percentages of paediatric referrals for a VIZAMYL™ scan. All such referrals will be considered to be off-label.

15. Summary of reported indications for paediatric use. All such indications in paediatric patients will be considered to be off-label.

Interim Analyses

Data from each survey round will be reviewed to look for potential safety issues that may warrant corrective actions. Interim progress reports will be provided annually.

9.8 Quality Control

9.8.1 Mechanisms and Procedures to Ensure Data Quality and Integrity

Confidentiality Regarding Survey Participants

The Sponsor and CRO will protect the privacy of the survey participants' information. No information that could personally identify any survey participant will be made available in data analyses, tables, or reports.

9.9 Limitations of the Research Methods

The main limitations of this study are:

1. Survey participation is dependent on:

    a. VIZAMYL™ use, which is dependent on sales, which are not within the control of the Sponsor

    b. Physician willingness to participate. Physicians who agree to participate ("willing" group) may not be representative of the entire physician population that will use VIZAMYL™. Section 9.7 (Data Analyses) describes analyses aimed at identifying differences between the "willing" group and the "unwilling" group.

2. Survey questions ask about prior use of VIZAMYL™ and thus the accuracy of survey question responses is dependent on the accuracy of participant memory.

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) for evaluation. The study will not start before 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 a formal written amendment, except when the change involves only logistics or administration. Protocol amendments will be submitted to the regulatory bodies/local health authorities.

10 PROTECTION OF HUMAN SUBJECTS

No patients will be enrolled and no medicinal product will be administered as part of this study. This is a survey of physician practices regarding VIZAMYL™ use. Physician privacy with regard to survey participation and responses will be protected.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Because this is a retrospective survey of physician uses of VIZAMYL™, no direct data on adverse events will be collected. However, the survey will ask if in the respondent's experience the safety profile for VIZAMYL™ has been consistent with that reported in the SmPC.

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

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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.

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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.

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 01:58:06 GMT+0000	Justification: Approved Role: Head of Biometrics
Signed By: Francois Tranquart Date of signature: 16-Feb-2018 10:38:07 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