PASS Information

Title	Evaluation of Effectiveness of Amyvid® Reader Training (I6E-AV-AVBE)
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Active substance	florbetapir (^{18}F) V09AX05 Diagnostic Radiopharmaceuticals
Medicinal product(s):	Amyvid 800 MBq/mL solution for injection Amyvid 1900 MBq/mL solution for injection
Product reference:	EU/1/12/805/001-004
Procedure number:	EMEA/H/C/002422
Marketing authorisation holder(s)	Eli Lilly Nederland B.V. Grootslag 1-5 NL-3991 RA Houten The Netherlands
Joint PASS	No
Research question and objectives	Amyvid is a member of a new class of diagnostic radiopharmaceuticals for positron emission tomography (PET) imaging. Because physicians are likely to be unfamiliar with Amyvid scan interpretation, reader training programmes have been developed, tested, and will be provided as a component of the risk management system for the product. While such programmes have been successful in training readers within the setting of clinical trials, it is important to assess the effectiveness of these reader training methods when used by physicians as part of routine clinical practice. Overall objective: Assess the effectiveness of the different Amyvid training methods agreed in the European clinical setting to ensure that accuracy in routine practice is in line with expected accuracy from the clinical trials.
Countries of study	United Kingdom, Spain, Italy
Author	**<name/contact info redacted for privacy purposes>**

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V. Grootslag 1-5 NL-3991 RA Houten The Netherlands

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2. List of Abbreviations

Term	Definition
AD	Alzheimer's disease
ADR	Adverse Drug Reaction
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CRF	Case Report Form
ERB	Ethical Review Board
EU	European Union
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
PET	Positron Emission Tomography
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

3. Responsible Parties

Company Global Medical Director (Study Design, Participant Recruitment, Data Analysis, Reporting):

<name/contact info redacted for privacy purposes >

Company Qualified Person for Pharmacovigilance:

<name/contact info redacted for privacy purposes >

4. Abstract

Title: Evaluation of Effectiveness of Amyvid® Reader Training (16E-AV-AVBE).

Version: 1.0 **Date: 29 January 2016**

Rationale and background: Amyvid® (florbetapir ^{18}F) is a member of a class of diagnostic radiopharmaceuticals 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. Because some physicians may be unfamiliar with Amyvid scan interpretation, reader training programmes have been developed and tested, and will be provided as a component of the risk management system for the product. The Amyvid Summary of Product Characteristics (SmPC) Section 4.2 states that "Amyvid images should only be interpreted by readers trained in the interpretation of PET images with florbetapir (^{18}F)." In accordance with the approved Risk Management Plan (RMP) for Amyvid, the company will make available the training materials in both in-person and online (web-based) programmes. Although there are 2 different training methodologies (in-person and online), the training materials are identical and will include an educational presentation, demonstration, and practice scan review using a standard nuclear medicine viewer, and a reader trainee evaluation procedure. The intended audience for the reader training programme is physicians trained in nuclear medicine or physicians trained in radiology with additional training or commensurate experience in nuclear medicine. While such programmes have been successful in training readers within the setting of clinical trials, it is important to assess the effectiveness of these reader training methods when used by physicians as part of routine clinical practice in the European Union (EU). The study milestones are outlined in Table 4.1.

Research question and objectives: This study will assess the effectiveness of Amyvid reader training methods when used by physicians as part of routine clinical practice.

The overall objective of the study is to assess the effectiveness of the different training methods agreed in the European clinical setting. This will be accomplished via examination of 2 primary objectives: (1) to assess the frequency of reading errors in routine clinical practice after training implementation, and (2) to assess reader understanding of, and compliance with, the indication with respect to scan interpretation after training implementation. The first primary objective will be achieved by calculating reader accuracy (ie, sensitivity, specificity, error rate, and false negative/false positive rates) using a consensus expert panel as the standard of truth for image interpretation. There is no formal *a priori* hypothesis being tested in the study. Accuracy results from this study will be compared with accuracy results from completed trials to assess the level of consistency. The second primary objective will be achieved by scoring readers on their ability to correctly identify statements in hypothetical PET scan reports as consistent or not consistent with the approved SmPC.

Study design: Clinical practice readers ("readers") who have completed Amyvid training and have used Amyvid in clinical practice will be identified from the company's training records and asked to participate in the study. The study will be conducted in 2 phases and each reader will be

asked to participate in both phases. Readers who agree to participate will read separately and remotely, via an internet-based platform.

In Phase 1 of the study, readers will each be shown an identical set of 40 Amyvid PET scans and asked to provide their scan interpretation. The 40 scans will be representative of scans expected to be seen in routine EU clinical practice. Cases will be selected such that at least 8 (20%) of the scans will be considered in the opinion of the sponsor's medical director to be more difficult due to image noise, atrophy with a thinned cortical ribbon, or image blur. Readers will record their visual interpretation of scans and all interpretations will be recorded on a case report form (CRF). A blinded read performed by a consensus panel of Amyvid expert readers will be used as the comparator versus the reader.

In Phase 2 of the study, readers will review hypothetical radiology/nuclear medicine clinical reports for Amyvid PET scans that are consistent and not consistent with the SmPC: for reports that are not consistent with the SmPC, they will be asked to identify which areas of the reports are not consistent.

The study will be conducted in 2 periods. The first period will commence 1 year after Amyvid commercial availability in the third EU country, but in no event later than 18 months after the first commercial availability in any EU country, and an interim report will be generated. The second period will commence 12 months after the close of the first period and a final report containing results from both 1-year periods will be generated. Results will be presented by year and in aggregate across both years.

Population: This study will include readers who meet the following criteria:

- have completed an Amyvid reader training programme provided by the company
- have agreed to be contacted by the company (in accordance with EU privacy laws)
- have interpreted Amyvid scan(s) in their own clinical practice setting

Qualified physicians from countries where Amyvid is commercially available will be invited to participate in the study. Randomisation will be employed in countries where at least 25 eligible readers are identified. Readers who agree to participate in the first year period analysis will not be enrolled for the second year period analysis.

Variables: To assess frequency of reading errors in the clinical setting, the key variables will be sensitivity, specificity, and overall percentage of interpretations that are correct compared to the Amyvid expert consensus read as the reference standard. In addition, Fleiss' kappa will be used to estimate inter-reader reliability. Amyvid training methodology (in-person or online), time since Amyvid training, and interpretation history (number of scans read in clinical practice, and time since last routine clinical scan read) will be evaluated as potential explanatory factors. Additional variables will be collected to examine potential for selection bias. To assess understanding of, and compliance with, the indication with respect to scan interpretation, the key variables will be the percentage of occurrences that readers are able to correctly identify scan reports that are consistent or not consistent with the SmPC.

Data sources: Data collection will consist of reader responses on the Clinical Practice Reader Evaluation Form and the Clinical Practice Reader CRFs that will capture their interpretation of each scan. When there are more than 25 eligible readers in a country, randomisation will be stratified in an attempt to enrol an equal distribution of readers trained by live and online training methodologies. A set of 40 Amyvid PET scans will be randomly chosen from the EU sites participating in the ^{18}F-AV-45-A18 clinical study (EudraCT#2012-002595-13; clinicaltrials.gov #NCT01703702). The inclusion/exclusion criteria from this study will result in scans obtained from subjects that are representative of scans expected to be seen in routine EU clinical practice. All efforts will be made to ensure an equal distribution of positive and negative scans.

Study size: The number of qualified physicians may be limited by indirect effects of reimbursement or radiopharmaceutical access. The study will be conducted in the United Kingdom, Spain, and Italy and will include a minimum of 10 readers and a maximum of 25 readers in each participating country. Assuming 85% accuracy and a 10% standard deviation among readers, a minimum sample of 10 readers per country will give an over 90% probability to obtain a 95% confidence interval (CI) of +/- 9% around the point estimation for the mean reader accuracy. In aggregate, a minimum total of 30 readers would give an over 90% probability to obtain a 95% CI of +/- 5% around the point estimation of mean reader accuracy.

Each participant will read an identical set of 40 scans. Assuming 85% accuracy, a sample of 40 scans will give an over 90% probability to obtain a 95% CI of +/- 13% around the point estimation for each individual reader.

Data analysis: There is no formal *a priori* hypothesis being tested in the study. For the analysis of frequency of reader errors, the scan interpretation results from clinical practice readers will be compared to the reading results from the Amyvid expert consensus read on the same scan overall and for each training method as a reference standard. Accuracy, sensitivity, and specificity will be calculated versus the reference standard. Error rate, false negative rate, and false positive rate will also be calculated versus the reference standard. A 95% CI will be calculated for each of the percentages, using the Wilson score method. Mean accuracy across readers and 95% CI will be calculated based on individual reader's accuracy. Fleiss' kappa as a measure of agreement across all readers will also be calculated with 95% CI.

Accuracy results from this study will be compared with accuracy results from completed clinical trials to assess level of consistency; there will be no formal statistical comparison of the results across studies.

For the analysis of reader understanding and compliance with the Amyvid indication with respect to scan interpretation, the percentage of readers responding correctly will be calculated overall and for each training method. Summary statistics will be provided by reader training method (live or online) as well as by country. A 95% CI will be provided for the rate estimation by each reader using the Wilson score method.

Table 4.1. Study Milestones

Milestone	Planned date
Start of data collection (Year 1 assessment)	February 2016 Upon delivery of an Amyvid dose to the 45th unique hospital/institution in the EU
End of data collection (Year 1 assessment)	July 2016 Approximately 6 months after start of data collection for Year 1 assessment
Summary of interim results (Year 1 assessment)	October 2016 Approximately 3 months from end of 1-year data collection period (submitted with first available PSUR or other method as agreed with PRAC)
Start of data collection (Year 2 assessment)	February 2017 1 year after the start of data collection for the Year 1 assessment
End of data collection (Year 2 assessment)	July 2017 Approximately 6 months after start of data collection for Year 2 assessment
Final study results (Year 1 and Year 2 assessments)	October 2017 Approximately 3 months from end of data collection (submitted with first available PSUR or other method as agreed with PRAC)

Abbreviations: EU = European Union; PRAC = Pharmacovigilance Risk Assessment Committee PSUR = Periodic Safety Update Report.

5. Amendments and Updates

Changes made in Version 1.0 incorporating comments from PRAC final assessment report dated 05 December 2013:

- Interim and final results will be submitted to PRAC using a method agreed with PRAC in advance.
- Study design ensures that a minimum of 20% of cases included in Phase 1 are considered difficult due to image noise, atrophy with a thinned cortical ribbon, or image blur.
- Study design allows participation by remote readers using an internet-based platform.
- Reasons for physicians not participating in the study will be collected and analysed.
- Separate analyses will be provided for accuracy results (including sensitivity and specificity) for each of the participating countries.
- Added language noting that national guidance on reimbursement and remuneration of physicians will be followed.
- Updated milestones per agreements with PRAC
- Minor changes were made for clarity and correctness throughout the protocol.

6. Milestones

The study milestones are outlined in Table 6.1. As requested during Pharmacovigilance Risk Assessment Committee (PRAC) review of the protocol, physician readers will be enrolled from 3 European Union (EU) countries (United Kingdom, Spain, and Italy). Physicians participating in the first period will be excluded from participating in the second period. It is possible that the number of physicians who are actively interpreting Amyvid scans may be lowered by delays in reimbursement or commercial radiopharmaceutical access. As agreed between the sponsor and PRAC, recruitment of readers will commence when 45 unique hospitals/institutions in the EU have placed commercial orders for Amyvid. A summary of the interim results based on data collected from readers identified in the first year period of the study is targeted for submission approximately 9 months after the first reader identification period closes. This will allow 6 months for recruitment and scheduling reader participation (ie, data collection) and 3 months to analyse the data and generate the interim report. This summary will be submitted in the first available PSUR after the interim results are finalised. As noted in Section 9.9, in the case of limited recruitment, the study recruitment period will be extended until the stated minimums are met. The final report will contain data from the second 1-year period of the study as well as the aggregate data from both periods, and will be provided approximately 3 months after the end of data collection for the Year 2 assessment.

Table 6.1. Study Milestones

Milestone	Planned date
Start of data collection (Year 1 assessment)	February 2016 Upon delivery of an Amyvid dose to the 45th unique hospital/institution in the EU
End of data collection (Year 1 assessment)	July 2016 Approximately 6 months after start of data collection for Year 1 assessment
Summary of interim results (Year 1 assessment)	October 2016 Approximately 3 months from end of 1-year data collection period (submitted with first available PSUR or other method as agreed with PRAC)
Start of data collection (Year 2 assessment)	February 2017 1 year after the start of data collection for the Year 1 assessment
End of data collection (Year 2 assessment)	July 2017 Approximately 6 months after start of data collection for Year 2 assessment
Final study results (Year 1 and Year 2 assessments)	October 2017 Approximately 3 months from end of data collection (submitted with first available PSUR or other method as agreed with PRAC)

Abbreviations: EU = European Union; PRAC = Pharmacovigilance Risk Assessment Committee PSUR = Periodic Safety Update Report.

7. Rationale and Background

Amyvid® (florbetapir ^{18}F) is a member of a new class of diagnostic radiopharmaceuticals for positron emission tomography (PET) imaging. Because some physicians may be unfamiliar with Amyvid scan interpretation, reader training programmes have been developed and tested, and will be provided as a component of the risk management system for the product. The Amyvid Summary of Product Characteristics (SmPC) Section 4.2 states that "Amyvid images should only be interpreted by readers trained in the interpretation of PET images with florbetapir (^{18}F)." In accordance with the approved Risk Management Plan (RMP) for Amyvid, the company will make available the training materials in both in-person and online (web-based) programmes (see Annex 1 for the Key Principles of Amyvid Interpretation Training). Although there are 2 different training methodologies (in-person and online), the training materials are identical and will include an educational presentation, demonstration, and practice scan review using a standard nuclear medicine viewer, and a reader trainee evaluation procedure. The intended audience for the reader training programme is physicians trained in nuclear medicine or physicians trained in radiology with additional training or commensurate experience in nuclear medicine. While such programmes have been successful in training readers within the setting of clinical trials, it is important to assess the effectiveness of these reader training methods when used by physicians as part of routine clinical practice in EU to ensure that accuracy in routine practice is in line with expected accuracy from the clinical trials. The overall outline of the proposed study was discussed and agreed with the Committee for Medicinal Products for Human Use (CHMP) (see Annex 1 for Study Synopsis 1 – Evaluation of Effectiveness of Amyvid Reader Training).

8. Research Question and Objectives

The reader training methods developed by the company were proven effective for training the readers who participated in the Amyvid clinical studies. The present study will assess the effectiveness of reader training on a broader scale, by enroling physician readers who have been trained by the company and have used Amyvid in actual clinical practice. The overall objective of the study is to assess the effectiveness of reader training methods (in-person and online) agreed in the European clinical setting. This will be accomplished by investigating 2 primary objectives:

(1) to assess the frequency of reading errors in routine clinical practice after training implementation, and

(2) to assess reader understanding of, and compliance with, the indication with respect to image interpretation after training implementation.

The first primary objective will be achieved by calculating reader accuracy (ie, sensitivity, specificity, error rate, and false negative/false positive rates) using a consensus expert panel as the standard of truth for image interpretation. The sensitivity and specificity results from this study will be compared with sensitivity and specificity results observed in the clinical trials that supported the approval of Amyvid. The second primary objective will be achieved by scoring readers on their ability to correctly identify statements in hypothetical PET scan reports as consistent or not consistent with the approved SmPC.

9. Research Methods

9.1. Study Design

This study will recruit clinical practice readers ("readers") from that group who have completed Amyvid training, either online or in-person, have used Amyvid PET in actual clinical practice, and can be identified from the company's training records. The overall aim of the study is to assess the effectiveness of reader training.

The study will consist of 2 phases, conducted at the same session: the first phase will assess reading errors and the second phase will assess compliance with the indication with respect to scan interpretation. Each physician reader will be asked to participate in both phases.

Study Phase 1:

To assess reading errors, each clinical practice reader will interpret an identical set of 40 Amyvid PET scans that have been randomly chosen from the EU sites participating in 18F-AV-45-A18 clinical study (Study A18; EudraCT#2012-002595-13; clinicaltrials.gov #NCT01703702), in which scans obtained from subjects are representative of scans expected to be seen in routine EU clinical practice. Cases will be selected such that at least 8 (20%) of the scans will be considered in the opinion of the sponsor's medical director to be more difficult due to image noise, atrophy with a thinned cortical ribbon, or image blur. Scans from Study A18 will be read by an expert consensus panel consisting of 3 Amyvid expert readers (see Section 9.4). To ensure equal distribution of positive and negative scans, randomisation of scans will be stratified based on the Study A18 expert consensus read interpretation. Having all clinical practice readers interpret the same 40 randomised scans will allow for a larger sample size per reader, rather than the limited number that is expected at their own imaging centre, and produce more robust statistical analyses. Visual interpretation of scans by the readers will occur remotely via an internet-based platform. All interpretations will be recorded on a case report form (CRF). Clinical practice readers will be asked to certify that they received no assistance in performing the study-required scan interpretations. All study materials will be translated into the local language of each country participating.

The clinical practice reader will interpret each scan for cortical grey matter tracer uptake as positive (consistent with more than sparse amyloid plaques), or negative (indicating sparse or no plaques) in accordance with the approved SmPC. This interpretation will be recorded on the Clinical Practice Reader CRF (Annex 3).

Study Phase 2:

In the second phase, each reader will complete a Clinical Practice Reader Evaluation to gauge their understanding of, and compliance with, the Amyvid indication with respect to scan interpretation, and to ensure readers' comprehension of the 3 key concepts outlined below:

1. Indication: Florbetapir should be used in patients who have cognitive impairment and are being evaluated for suspected Alzheimer's disease (AD). Florbetapir should be used in conjunction with a clinical evaluation.

2. Protocol: Patients should be imaged in accordance with the SmPC image acquisition directions.
3. Impression: A binary read methodology has been developed and validated where a negative scan indicates sparse or no plaques and a positive scan indicates moderate-to-frequent density. A positive florbetapir scan does not independently establish a diagnosis of AD. The efficacy of florbetapir scans for predicting development of AD or monitoring response to therapy has not been established.

The evaluation consists of a series of 12 hypothetical, pre-prepared written Amyvid PET scan reports (Annex 3) containing scan interpretations that are consistent or not consistent with the indication concepts listed above, presented in random order. Readers will be asked to read the reports and indicate which reports are not consistent with the SmPC. No images will be provided in this phase, only the hypothetical, written scan reports.

There is no formal *a priori* hypothesis to be tested in this study. Data analysis will report reader accuracy compared with the Amyvid expert consensus read overall and for each training method and the observed error rates in identification of scan reports that are consistent with or not consistent with the SmPC with respect to the key concepts listed above. Reader accuracy results from Phase 1 of the study will be compared to accuracy results from completed clinical trials to assess level of consistency; there will be no formal statistical comparison of the results across studies. The proposed comparison across studies is described in more detail in the data analysis subsection (Section 9.7).

9.2. Setting

This study will include readers who meet the following criteria:

- have completed an Amyvid reader training programme provided by the company
- have agreed to be contacted by the company (in accordance with EU privacy laws)
- have interpreted Amyvid scans in their own clinical practice setting

Qualified physicians from countries where Amyvid is commercially available will be invited to participate in the study. Physicians who are participating as investigators in Study A18 will be excluded. If there are more than the maximum number of qualified physicians available for contact in a given country (i.e., > 25), the order of the invitations will be randomised. Physicians will be recruited for the study until the list is exhausted or the maximum number is reached.

Readers who agree to participate in the Year 1 assessment will not be enrolled in the Year 2 assessment.

9.3. Variables

As part of the selection to participate in the study, the Amyvid training methodology, the date of training, interpretation history, including number of Amyvid scans read in routine clinical practice, and the date of the last routine clinical scan read, research experience interpreting scans with any amyloid imaging agents (yes/no), and total number of amyloid scans evaluated with either qualitative or quantitative techniques (including Amyvid and other research experience)

will be recorded for each reader and will be evaluated as potential explanatory factors. To evaluate potential selection bias, these basic characteristics will be compared between physicians who participate and those who decline to participate. In order to collect information to better evaluate potential selection bias, readers who decline to participate will be asked to provide a reason. In addition, the number of physicians contacted and the number of physicians unwilling to participate will be recorded, including those who do not respond.

For the analysis of frequency of reader errors, the scan interpretation results from the readers will be compared to the results from the company's Amyvid expert consensus panel read on the same scan. Accuracy results from this study will be compared with accuracy results from completed clinical trials to assess the overall level of consistency (see Section 9.7)

Reader understanding of and compliance with the Amyvid indication with respect to scan interpretation will be assessed through the Clinical Practice Reader Evaluation. The percentage of readers responding correctly will be reported overall and for each training method.

9.4. Data Sources

Primary data will be collected directly from the readers, who will complete the study assessments remotely via an internet-based platform. Data collection will consist of reader responses on the Clinical Practice Reader CRF that will capture their interpretation of each scan and a Clinical Practice Reader Evaluation Forms (Annex 3). When there are more than 25 eligible readers in a country, randomisation will be stratified in an attempt to enrol an equal distribution of readers trained by live and online training methodologies. A pilot study was conducted to ensure the validity of the Clinical Practice Reader Evaluation. Pilot reader feedback has been incorporated into the forms in the protocol annex and is summarized at the beginning of the annex.

A set of 40 Amyvid PET scans will be randomly chosen from the EU sites participating in the ^{18}F-AV-45-A18 clinical study (EudraCT#2012-002595-13; clinicaltrials.gov #NCT01703702). The inclusion/exclusion criteria from this study will result in scans obtained from subjects that are representative of scans expected to be seen in routine EU clinical practice. All efforts will be made to ensure an equal distribution of positive and negative scans. Additionally, cases will be selected such that at least 8 (20%) of the scans will be considered in the opinion of the sponsor's medical director to be more difficult due to image noise, atrophy with a thinned cortical ribbon, or image blur.

The blinded read of the Study A18 scans will be performed by a consensus panel of 3 Amyvid expert readers to be used as the comparator/reference standard for evaluating reader accuracy in this study. The members of the expert consensus panel will meet the following minimum requirements (members are listed in Annex 4):

- Board certification in nuclear medicine and/or radiology
- Expert-level knowledge about amyloid PET imaging as certified by the Chief Medical Officer at Avid Radiopharmaceuticals

- Experienced interpreter of Amyvid PET scans and has interpreted at least 100 Amyvid scans using the approved visual interpretation method.

The members of the expert panel will independently interpret all 40 scans visually. For scans where all 3 readers do not agree, a consensus discussion requiring all members of the expert panel will take place to determine the final interpretation. The final consensus read by the expert panel will be recorded in the database and used as the reference standard for accuracy calculations.

9.5. Study Size

The number of qualified physicians available to participate in this study may be limited by indirect effects of reimbursement or radiopharmaceutical access. The study will be conducted in the United Kingdom, Italy, and Spain and will include a minimum of 10 readers completing the study in each of the participating countries and a maximum of 25 readers in each country. For the first year interim analysis, selection will continue until approximately 10 to 25 readers per country have agreed to participate in aggregate. The reliability of the point estimation accuracy can be estimated for the proposed minimum sample size as follows:

From Study PT01, which was included in the initial Marketing Authorisation Application (MAA), the average accuracy of participating readers was 86%, with a standard deviation of 6%. Assuming 85% accuracy and a 10% standard deviation, a minimum sample of 10 readers per country would give an over 90% probability to obtain a 95% confidence interval (CI) of +/-9 % around the point estimation of mean reader accuracy. Similarly, in aggregate, a minimum sample of 30 readers overall would give an over 90% probability to obtain a 95% CI of +/- 5% around the point estimation of mean reader accuracy.

A total of 40 scans will be read by each participant. From Study PT01, the average accuracy with neuropathologist's diagnosis as truth standard is 86%. Assuming an 85% accuracy, a sample of 40 scans will give an over 90% probability to obtain a 95% CI of +/- 13% around the point estimation of individual reader accuracy.

9.6. Data Management

The Clinical Practice Readers will be supplied with a CRF. At the completion of their read session, the clinical practice readers will transfer the CRFs to the sponsor. The Sponsor will review the CRFs, and queries will be issued to the clinical practice readers for illegible, inconsistent or missing data.

Final datasets will be stored and archived according to the sponsor's quality assessment requirements and applicable laws and regulations.

9.7. Data Analysis

There is no formal *a priori* hypothesis being tested in the study.

For the analysis of frequency of reader errors, the scan interpretation results from clinical practice readers will be compared to the reading results from the expert consensus panel on the

same scan. With the expert readers' consensus interpretation serving as the truth standard, the accuracy (percent of agreement) will be calculated in the following ways:

$$Accuracy = \frac{\text{number of scans interpreted the same between reader and expert panel}}{total\ number\ of\ scans\ read} \times 100\%$$

$$Sensitivity = \frac{\text{number of scans interpreted as positive by both reader and expert panel}}{number\ of\ scans\ interpreted\ as\ positive\ by\ expert\ panel} \times 100\%$$

$$Specificity = \frac{\text{number of scans interpreted as negative by both reader and expert panel}}{number\ of\ scans\ interpreted\ as\ negative\ by\ expert\ panel} \times 100\%$$

$$Error\ Rate = \frac{\text{number of scans interpreted differently between reader and expert panel}}{total\ number\ of\ scans\ read} \times 100\%$$

$$False\ Negative\ Rate = \frac{\text{number of scans interpreted as negative by reader and positive by expert panel}}{number\ of\ scans\ interpreted\ as\ positive\ by\ expert\ panel} \times 100\%$$

$$False\ Positive\ Rate = \frac{\text{number of scans interpreted as positive by reader and negative by expert panel}}{number\ of\ scans\ interpreted\ as\ negative\ by\ expert\ panel} \times 100\%$$

A 95% CI will be calculated for each of the percentages using the Wilson score method. Mean accuracy and 95% CI across readers will be calculated based on individual readers' accuracy. Fleiss' kappa as a measure of agreement across all readers will also be calculated with 95% CI. Results will be reported for each training method (live or online).

Accuracy results from this study will be compared with accuracy results from completed clinical trials to assess the overall level of consistency; there will be no formal statistical comparison of the results across studies. Study PT01 that was included in the MAA recruited 5 readers who received Amyvid interpretation training via the online method. A secondary analysis of this study examined sensitivity and specificity using autopsy diagnosis as the standard of truth.

Pooled sensitivity of the 5 readers was 82% (95% CI: 70.9% – 89.6%); pooled specificity was 93% (95% CI: 78.4% – 98.0%). The consensus interpretation proposed as the truth standard in the present study would be expected to closely reflect autopsy diagnosis. Therefore, the sensitivity and specificity results of the present study will be compared with the pooled sensitivity and specificity results of Study PT01. It is expected that the effect estimate for sensitivity and specificity from the present study will be within the 95% CIs reported in Study PT01.

For the final report, data obtained from Year 1 and Year 2 will be analysed in aggregate and separately as a sensitivity analysis.

Accuracy results, including sensitivity and specificity, will also be analysed by the other explanatory variables present in the study with regard to their possible relationship with high or low performance readers. These explanatory variables include the country of practice, Amyvid training methodology, the date of training, interpretation history, including number of Amyvid scans read in routine clinical practice, and the date of the last routine clinical scan read, research experience interpreting scans with any amyloid imaging agents (yes/no), and total number of amyloid scans evaluated with either qualitative or quantitative techniques (including Amyvid and other research experience).

Information regarding the number of physicians contacted and the number of physicians not willing to participate will be presented by basic characteristics available from the dataset (for example, country, specialty, type of practice) and will be evaluated as part of a discussion of selection bias.

For the analysis of reader understanding of, and compliance with the Amyvid indication, the following analyses will be performed across all readers:

- average percent correctly identifying which sections are not consistent with SmPC (box is correctly checked “no”)
- average percent correctly identifying which sections are consistent with SmPC (box is correctly checked “yes”)

Results will be presented overall and by reader training method (live or online), as well as by country. Summary statistics (mean, standard deviation) will be used to describe these rates across all readers. A 95% CI will be provided for the rate estimation by each reader, which will be calculated using the Wilson score method.

9.8. Quality Control

Sponsor personnel will monitor the completed reader evaluation forms and scan interpretation CRFs to ensure legibility and completeness before the reader’s participation ends. If CRFs received are illegible or incomplete, efforts will be made to contact the reader to clarify their entries.

9.9. Limitations of the Research Methods

This study will not obtain information on accuracy of scan interpretation from scans performed in actual routine clinical practice in the EU and the participating readers may not be representative of the total reader population. In addition, although Study A18 is intended to evaluate PET imaging in usual clinical practice, the patients who agree to participate in a clinical study may differ from the population at large. Nevertheless, patient privacy issues in the EU, as well as the possibility that insufficient numbers of scans would be contributed, especially from participating readers during the first year after product availability in the EU, support the approach proposed in this study. In addition, having the same 40 scans from the A18 clinical study interpreted by all readers allows for more robust statistical analyses to assess reader accuracy.

The overall sample size of the study may be limited due to reimbursement or radiopharmaceutical access, which could result in too few readers trained by one of the methods to enrol in the study to allow for meaningful comparison between the 2 training methods. In the case of limited recruitment (<10 in any country, or <3 trained by a particular method), the study recruitment period will be extended until the above-stated minimums are met. The PRAC will be consulted if the study is to be terminated with a limited sample size due to difficulties in physician recruitment.

9.10. Other Aspects

Readers will be compensated for their time related to participation in the study. Readers will be paid a fee per scan interpreted and for their time to complete the clinical practice reader evaluation (estimated 1 hour). Fees/rates will be set in accordance with established company fair market valuation processes to ensure compliance with national guidance on reimbursement and remuneration of physicians in each country. No other compensation will be provided to the participants.

10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all prospective observational studies will be submitted to at least one independent body (e.g., ERB) for review and to confirm that the study is considered noninterventional. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

All subjects participating in Study A18 in the EU (image source for PET scans that will be used to assess reader accuracy) have provided informed consent for the use of their PET scan for other medical research purposes in addition to use of their information for the purposes of the A18 study. Company procedures will ensure that no private health information is transmitted in the PET scan metadata.

Additionally, company procedures, which are in-line with EU data protection law, will ensure the privacy of data gathered from participating physicians. These procedures cover the following topics: obtaining authorisation for processing personal information, collection of personal information, use of personal information, access to personal information, and security and transfer of personal information.

11. Management and Reporting of Adverse Events/Adverse Reactions

During the course of this study, information pertaining to adverse reactions may be identified by individuals who administer the protocol. All study personnel will be trained on Lilly's Adverse Event/Product Complaint reporting procedures. An Adverse Drug Reaction (ADR) form for submission to Lilly Pharmacovigilance personnel will be made available to physicians participating in the study.

12. Plans for Disseminating and Communicating Study Results

In accordance with the milestone dates provided in Section 6, a summary of the interim results of the Year 1 assessment data will be provided, when available, in a scheduled PSUR submission or other method as agreed with PRAC. A final report including the Year 2 assessment data and the aggregated 1- and 2-year data will be provided, when available, in a scheduled PSUR submission or other method as agreed with PRAC. Publications may result from this study.

If the accuracy of scan interpretations by the physicians in this study is not consistent with completed clinical trials, and it is determined that changes to the Amyvid Reader Training Programme are needed, the company will consult PRAC/CHMP before submitting these changes for country-level competent authority review/approval and subsequent implementation.

13. References

Not Applicable.

Annex 1. List of Stand-Alone Documents

1. Key Principles of Amyvid Interpretation Training (Annex 8 to Approved Amyvid Risk Management Plan 07 Nov 2012)
2. Study Synopsis 1 – Evaluation of Effectiveness of Amyvid Reader Training (Appendix 5 to Approved Amyvid Risk Management Plan 07 Nov 2012)

Annex 2. ENCePP Checklist for Study Protocols

Study title: Evaluation of Effectiveness of Amyvid® Reader Training

Study reference number: I6E-AV-AVBE

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Start of data collection is considered the first contact to potential readers. Registration in EU PAS register not described in protocol. Study has been registered in EU PAS register with the following identifier: ENCEPP/SDPP/11867

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	15
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	20

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	20-21
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	20-21

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				12
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	18-19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	18-19

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	18
8.1.3 Covariates?	☒	☐	☐	18
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17-18
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17-18
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	20-21
10.3 Are descriptive analyses included?	☒	☐	☐	20-21
10.4 Are stratified analyses included?	☒	☐	☐	20-21
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	19
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☒	☐	☐	22
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	22
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	25

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases?	☒	☐	☐	18,20
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	18,20
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19
12.3 Does the protocol address other limitations?	☒	☐	☐	22

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	23
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	23

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	11

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	25
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	25

Comments:

Name of main author of the protocol: **<name redacted for privacy purposes>**

Date: / / [DD/MM/YYYY]

Signature: Signature on file

Annex 3. Case Report Form (CRF) and Clinical Practice Reader Evaluation Forms

Florbetapir ^{18}F PET Image Case Report Form (CRF)

Case ID: _____ Date of Read _____

Name of Reader: _____

1. Provide an assessment of the amyloid burden:	
Aβ – (negative – indicating the absence of β-amyloid plaque)	☐
Aβ + (positive – indicating the presence of β-amyloid plaque)	☐

_____

Signature of Reader

<Clinical Practice Reader Evaluation Forms redacted to preserve study integrity>

Annex 4. Expert Panel Member List

<Expert panel member names redacted to protect confidentiality>