European Drug Usage Survey for Amyvid (I6E-MC-AVBF)

Final study report

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PASS information

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Product reference	EU/1/12/805/001-004
Procedure number	EMEA/H/C/002422
Marketing authorisation holder(s)	Eli Lilly Nederland B.V. Papendorpseweg 833528 BJ Utrecht The Netherlands
Joint PASS	No
Research question and objectives	To determine which types of patients are undergoing Amyvid Positron Emission Tomography (PET) scans. In particular, to establish the usage patterns of Amyvid in European clinical practice and assess extent to which Amyvid is being used in off-label indications.
Countries of study	United Kingdom, Spain, Italy
Author	PPD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 United States Telephone: PPD

Marketing authorisation holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V. Papendorpseweg 833528 BJ Utrecht The Netherlands
MAH contact person	PPD Global Patient Safety Epidemiologist Eli Lilly and Company 893 S. Delaware Street Indianapolis, IN 46225 United States Telephone: PPD

Table of Contents

1. Abstract

Title

European Drug Usage Survey for Amyvid (I6E-MC-AVBF).

October 27th, 2017.

PPD Eli Lilly and Company.

Keywords

Alzheimer's disease (AD); dementia; cognitive impairment; positron emission tomography (PET) scans; off-label use.

Rationale and background

Amyvid (florbetapir) is a diagnostic radiopharmaceutical agent that binds to β-amyloid neuritic plaques in the grey matter of the brain and enables them to be imaged via positron emission tomography (PET). A positive scan does not independently establish a diagnosis of Alzheimer's disease (AD) or other cognitive disorder and, for this reason, Amyvid should only be used in conjunction with a clinical evaluation.

On January 2013, the European Commission granted a marketing authorisation for Amyvid for diagnostic use, and a risk management plan was implemented that described the potential for off-label use. At that time, the most likely areas for off-label use were anticipated to be in the setting of physicians looking for the presence of β-amyloid to estimate prognosis in patients with mild cognitive impairment or in monitoring response to anti-AD therapy. To further assess potential off-label uses, the Committee for Medicinal Products for Human Use requested Eli Lilly and Company to investigate the understanding of the indication, usage pattern, and level of off-label use of Amyvid in European clinical practice. A European Drug Usage Survey was therefore developed.

Research question and objectives

The overall goal was to understand the actual use of Amyvid PET scans in the everyday clinical setting in Europe. The specific objectives were to assess the usage patterns, and the level of off-label use of Amyvid in European clinical practice.

Study design

The study was a Prescriber Survey. It was a cross-sectional, non-interventional study conducted among consenting physicians who had referred at least one patient for an Amyvid PET scan in those European Union (EU) countries where Amyvid was first available. The survey was performed between December 2014 and May 2017. Physicians were able to choose among a telephone-assisted interview, a web-based questionnaire, or a paper version of the survey; and were requested to provide information from only their five most recent patients referred for scans.

Setting

EU countries where Amyvid was available: Italy, Spain and the United Kingdom (UK).

Subjects and study size, including dropouts

In total, 20,286 invitations were sent to potential Amyvid prescribing physicians during the study and 203 (1%) were accepted. A total of 109 physicians completed the survey. Due to different enrolment strategies (general approach in UK, targeted approach in Spain and Italy) and dates of availability of Amyvid in the market (June 2013 in UK, January 2014 in Spain and October 2015 in Italy), most respondents (n=85; 78%) were from the UK, whereas 13 (12%) and 11 (10%) were from Spain and Italy, respectively. In total, these physicians provided information on 424 patients referred for Amyvid PET scans; UK physicians referred 326 (76.9%), Spain 61 (14.4%) and Italy 37 (8.7%).

Variables and data sources

The variables, and corresponding survey questions, that addressed study objectives fell into three categories: 1. Characteristics of the referring physicians; 2. Characteristics of the patients who were referred; and 3. Level of off-label use with respect to indication and population.

Results

Physician profile

Overall, 109 voluntary physicians participated in the survey, including 85 (78%) physicians in the UK, 13 (12%) in Spain and 11 (10%) in Italy. They had an average of 14.2 years of current practice experience and were mostly neurologists (n=52; 47.7%) or psychiatrists (n=32; 29.4%).

Amyvid use knowledge

Almost all physicians (n=107; 98.2%) agreed with the approved indication for Amyvid, that is for 'evaluation of patients with cognitive decline for AD or other causes of dementia'. However, three-quarters (n=83; 76.1%) also agreed that the approved indication for Amyvid included 'estimating the risk of mild cognitive impairment (MCI) progression to clinical AD' and nearly half agreed that it included 'for monitoring the response to therapy in patients with AD' (n=53; 48.6%) and 'for risk stratification in asymptomatic individuals, such as relatives of AD patients' (n=52; 47.7%).

While most of the physicians (n=92; 84.4%) agreed that a positive scan may be consistent with AD, but does not independently establish a diagnosis of this disease; some of them (n=8; 7.3%) affirmed that a positive scan would indicate sparse or no plaques, and more than a quarter (n=30; 27.5%) disagreed with the true statement 'a negative scan is not consistent with a diagnosis of AD'.

Referred patient's profile

The physicians reported information on a total of 424 patients, including 326 (76.9%) in the UK, 61 (14.4%) in Spain and 37 (8.7%) in Italy. All patients were adults over the age of 18 years, the distribution by sex was similar across countries, and their mean age was 67.9 years. At the time of the scan referral, only 2.6% (n=11) of the patients referred were reported to be cognitively normal, while 13.7% (n=58) had a cognitive complaint without cognitive impairment on

examination, and 42.7% (n=181) had MCI. The remaining patients (n=174; 41.0%) had some level of dementia.

At the time of the Amyvid PET scan referral, over one-third of the patients (n=163; 38.4%) had impairments in activities of daily living due to cognitive impairment. In addition, a substantial number of patients exhibited atypical symptoms: 22.9% (n=97) had prominent fluctuations in cognition, 22.6% (n=96) had prominent changes in personality, behaviour or comportment, 11.8% (n=50) had visual hallucinations, 10.1% (n=43) had parkinsonism, and 9.9% (n=42) had prominent language disturbance without memory loss. However, 23.3% (n=99) of the patients were referred for an Amyvid PET scan when they were not exhibiting any of the above clinical findings.

Before the scan results, in all but 1.4% (n=6) of cases patients had possible MCI (n=198; 46.7%) or possible dementia. AD was the most common possible etiologic diagnosis (n=258; 60.8%), followed by other neurodegenerative dementia such as Lewy body dementia or frontotemporal dementia (n=123; 29.0%) and vascular dementia (n=87; 20.5%).

Most patients had undergone other clinical assessments prior to the Amyvid PET scan: 97.2% (n=412) had a cognitive test, mainly the Mini Mental State Examination (MMSE) test (n=360; 84.9%), and 80.9% (n=343) had laboratory tests/investigations, mainly clinical imaging (n=286, 67.5%) or blood or urine tests (n=283; 66.7%). Almost 40% (n=169) had received at least one medication for cognitive impairment and 41.7% (n=177) presented at least one comorbidity: 12.3% (n=52) were suffering from renal impairment and 5.9% (n=25) from hepatic impairment.

In 67.2% (n=285) of the patients, the diagnosis or treatment changed based on the Amyvid scan results. Among these patients, scan results increased diagnostic confidence in 80.7% (n=230) and changed the medical management plan in 48.1% (n=137).

According to the physician's answers, more than half of the patients (n=237, 55.9%) were correctly referred for an Amyvid PET scan (i.e., they were referred as part of the evaluation of cognitive decline documented on clinical examination, aligned with the approved indication).

Off-label use

Overall, based on the per protocol analysis, off-label use was reported by physicians in 63.2% (n=268) of the patients. The majority of the off-label use cases (n=266; 62.7%) were related to

the reported use of the scan for a reason other than 'evaluation of cognitive decline documented on clinical examination'.

Although in 55.9% of cases (n=237), physicians correctly included 'As part of the evaluation of a patient with cognitive decline documented on clinical examination' among the reasons for ordering a scan, 44% (n=187) did not. Additionally, regardless of whether the scan was used 'as part of a clinical evaluation of a patient with cognitive decline documented on clinical examination', patient reports were counted off-label when at least one of the following reasons for referral was noted: use of scans to estimate the risk of MCI progression to clinical AD (n=115; 27.1%), to evaluate amyloid status in an asymptomatic individual with either a family history of AD or known to be an apolipoprotein E (ApoE4) carrier (n=31; 7.3%), to monitor response to therapy (n=23; 5.4%), where the reason for scan referral was 'normal cognition' or 'not consistent with use for AD or other cause of cognitive impairment' (n=14; 3.3%), as a substitute for genetic testing (n=13; 3.1%).

A modified analysis of off-label use was conducted, where off-label use was categorized after patients with inconsistent physician responses were excluded (e.g., patient was reported to have normal cognition in one question, but in a different question cognitive impairment was noted) and only clear cases of off-label use (i.e. uses for purpose of monitoring cases or not related to clinical evaluation of the patient) were counted. This modified analysis excluded 81 patients (19.1%), for whom inconsistent responses were reported. Off-label use was reported by physicians in 29.7% (n=102) of the patients in the modified analysis. The majority (n=82; 80.4%) of the 102 off-label use reports in the modified analysis were related to the use of the scan for estimating the risk of MCI progression.

Discussion

Almost all clinicians surveyed correctly agreed with the approved indication for florbetapir, but results from the survey supported two important areas where clinicians reported off-label use: monitoring response to therapy and estimating prognosis in patients with early symptoms of cognitive impairment. Since no approved therapies are currently available, the rationale for using Amyvid to monitor treatment response is unclear. Although three-quarters of physicians agreed that prognostic use of Amyvid, that is, to estimate the risk of MCI progression to clinical AD,

was included in the approved indication, only a little over a quarter actually reported referring patients for this reason.

Despite the almost universal awareness of the Amyvid approved indication, per protocol evaluation of reported reasons for requesting an Amyvid PET scan suggested a high degree of off-label use (n=268; 63.2%). This high proportion of off-label use may suggest that clinicians are familiar with research applications of florbetapir and use these applications in their clinical practice despite the limitation of use in the summary of product characteristics (SmPC), and/or that some clinicians may not have noted the limitations of use currently included in the SmPC.

It is possible that at least some of these responses were affected by misinterpretation of the survey questions. This is supported by the high proportion (n=81; 19.1%) of internally inconsistent responses found across survey questions. When inconsistent responses were excluded and on-label defined more broadly to include information on all cases consistent with the use of the Amyvid as part of a clinical or diagnostic scan, off-label use fell to 29.7% (n=102), but this result should be interpreted cautiously.

Marketing Authorisation Holder(s)

Eli Lilly Nederland B.V.
Papendorpseweg 833528 BJ Utrecht
The Netherlands

Names and affiliations of principal investigators

Not applicable.

2. List of abbreviations

Term	Definition
AD	Alzheimer's Disease
AE	Adverse Event
ApoE4	Apolipoprotein E
AR	Adverse Reaction
CATI	Computer-Assisted Telephone Interview
CAWI	Computer-Assisted Web-Based Interviewing
CHMP	Committee for Medicinal Products for Human Use
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
EphMRA	European Pharmaceutical Market Research Association
EU	European Union
ICC/ESOMAR	International Chamber of Commerce/European Society for Opinion and Marketing Research
Lilly	Eli Lilly
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MRS	Market Research Society
P	Percentile
PET	Positron Emission Tomography
PRAC	Pharmacovigilance Risk Assessment Committee
Q	Question
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
STROBE	Strengthening The Reporting of Observational Studies in Epidemiology
UK	United Kingdom

3. Investigators

Not applicable.

4. Other responsible parties

Sponsor: Eli Lilly and Company

Company Global Patient Safety Epidemiologist

PPD

Global Patient Safety Epidemiologist

Eli Lilly and Company

893 S. Delaware Street

Indianapolis, IN 46225

United States

Telephone: PPD

Company Global Medical Director:

PPD

Chief Medical Officer

Avid Radiopharmaceuticals, Inc., a wholly-owned subsidiary of Eli Lilly and Company

3711 Market Street, 7th Floor

Philadelphia, PA 19104

United States

Telephone: PPD

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	One year after commercial availability, estimated 15 December 2014	17 December 2014	
End of data collection	Collection will end after two years (three years from commercial availability), estimated 15 December 2016	02 May 2017	The period was extended to reach minimum sample size in each country, as acknowledged by the Pharmacovigilance Risk Assessment Committee
Registration in the EU PAS register	Not applicable	12 December 2014	
Final report of study results	Six months from end of data collection, estimated 31 March 2017 for inclusion in PSUR, June 2017	27 October 2017	

6. Rationale and background

6.1. Survey context

In Europe, there are 8.7 million people diagnosed with dementia (1), and Alzheimer's disease (AD), affecting approximately 5% of the European population (2). Accurate diagnosis of AD has been limited by a lack of diagnostic tests, with postmortem biopsy being the main method for confirmation of clinical diagnosis to date.

Amyvid® [florbetapir (18F)] is a diagnostic radiopharmaceutical agent that binds to β-amyloid neuritic plaques in the grey matter of the brain. β-amyloid neuritic plaques occur in patients with AD and some other dementias. By binding to the plaques, Amyvid enables them to be imaged via positron emission tomography (PET). A negative scan indicates sparse or no plaques and is not consistent with a diagnosis of AD, while a positive scan indicates moderate to frequent plaque density which is consistent with the diagnosis of AD. However, a positive scan does not independently establish a diagnosis of AD or other cognitive disorder since neuritic plaque deposition in grey matter may be present in asymptomatic elderly persons and in some neurodegenerative dementias (Lewy body dementia, Parkinson's disease dementia). For this reason, Amyvid should only be used in conjunction with a clinical evaluation (3, 4).

On 14 January 2013, the European Commission granted a marketing authorisation for Amyvid for diagnostic use. As part of the initial marketing authorisation, a risk management plan (RMP) was implemented that described the potential for off-label use, most likely in the setting of physicians looking for the presence of β-amyloid to estimate prognosis in patients with early symptoms of cognitive impairment (i.e., to predict progression of AD) or in monitoring response to anti-AD therapy. As such, Section 4.4 of the summary of product characteristics (SmPC) (3) provides a special warning and precaution statement that the efficacy of Amyvid for predicting development of AD or monitoring response to therapy has not been established. The RMP also describes an extremely low potential for off-label paediatric use, since Amyvid is highly selective for amyloid plaques and the occurrence of amyloid plaques is extremely rare in young populations.

To further assess the potential for off-label use, the Committee for Medicinal Products for Human Use (CHMP) requested Eli Lilly and Company (Lilly) to investigate the understanding of the indication, usage pattern, and level of off-label use of Amyvid in European clinical practice. A European Drug Usage Survey (study I6E-MC-AVBF) was therefore developed, taking into account feedback received from the Pharmacovigilance Risk Assessment Committee (PRAC) (EMEA/H/C/2422 MEA-002.1). The present study was initiated in December 2014 and data collection was completed in May 2017 based on the protocol which was previously discussed and agreed with the PRAC and CHMP.

6.2. Rationale for country selection

The selection of the countries in which the survey was conducted was based on:

- the countries where Amyvid was registered and marketed during the period of the study;
- the extent of active referring physician utilisation of Amyvid, in order to find the required sample of referrers and patients in the designated data collection time period.

Since early adopters of Amyvid PET scans who refer patients in the first six months of availability might not adequately reflect the greater population of clinicians who would refer patients in routine clinical practice, only those countries in which at least 50 scans were undertaken were considered for selection. The number of Amyvid orders served as a proxy measure for the number of Amyvid PET scans performed.

6.3. Rationale for physician selection

This study evaluated cases from physicians who have referred patients for an Amyvid PET scan. This was the sole criterion for establishing physician eligibility for the study.

For United Kingdom (UK), Italy and Spain, information on clinicians likely to refer patients for an Amyvid PET scan was provided by Lilly based on projected use considering, for example, distance from the manufacturing site, association with private clinics or hospitals, etc.

In addition, for the UK, information on expected referring physicians was available through QUINTILESIMS database. This database consists of physicians who have previously agreed to be contacted for surveys and includes physician-related information, such as specialty, which helped to identify potential referrers who were screened for eligibility for this study.

All local privacy laws were observed in the process of identifying potential participants and only physicians who have agreed to be contacted by QUINTILESIMS for purposes consistent with this survey were approached.

7. Research question and objectives

The overall goal of the present study was to understand the actual use of Amyvid PET scans in the everyday clinical setting in Europe. The specific objectives were as follows:

- to assess the usage patterns of Amyvid in European clinical practice;
- to assess the level of off-label use of Amyvid in European clinical practice.

8. Amendments and updates

None.

9. Research methods

9.1. Study design

The study was a Prescriber Survey. It was a cross-sectional, non-interventional study conducted among consenting physicians who had referred at least one patient for an Amyvid PET scan in those European Union (EU) countries where Amyvid was first available: Italy, Spain and the UK.

The survey was performed between December 2014 and May 2017. To increase participation, physicians were able to choose among a telephone-assisted interview, a web-based questionnaire, or a paper version of the survey. At the time of enrolment, physicians were asked about their knowledge of the Amyvid indication, usage and limitations.

Questions from the Survey Questionnaire (see Protocol-Annex 2) Section 1 (Clinician profile), 2 (Awareness of Amyvid) and 3 (Patient referrals) were asked once, with questions from Sections 1 and 2 asked only at baseline, which was the first occasion that the physician participated. Questions from Section 4 (Patient report information) invited clinicians to provide information for their most recent patient referrals for Amyvid PET scans. Participating physicians were encouraged to contribute patient reports on at least a quarterly basis. Physicians were requested to provide information from only their most recent patients referred for scans, with no more than five total patient reports accepted per physician. These questions addressed the study goal of describing the pattern of Amyvid use in routine practice. Overall, the survey questions fell into four categories addressing:

1. characteristics of referring physicians,
2. characteristics of patients who were referred,
3. time elapsed since product availability (calendar period or date of the scan), and
4. on-/off-label use.

No formal a priori hypotheses were tested in this study. Descriptive statistics were generated to describe: the pattern of use of Amyvid with respect to the physician's practice, specialisation and experience in treating patients with cognitive impairment; the patient's cognitive status, severity

of impairment, clinical features related to diagnosis, comorbidities (especially renal/hepatic impairment) and demographic description; and the level of off-label use described by the physician's knowledge of the indication, the patient's age, cognitive status, and suspected diagnosis.

9.2. Setting

This survey analysed the profile of patients referred for Amyvid PET scans by healthcare providers. The survey was carried out among referrers for Amyvid PET scans, that is, physicians in active clinical practice (hospital- or office- based), who practiced in an EU country where Amyvid was available: Italy, Spain and the UK.

The study commenced recruitment at the end of the first year after commercial availability (i.e., December 2014) and continued for more than two years (i.e., until May 2017). Physicians who were included in previously described databases were invited to participate in calendar periods or 'waves' (see Enrolment grid-Annex 2). Enrolled physicians contributed information on patients they had referred in the preceding three months, except for the first time enrolees participated in the survey, when they were invited to provide information on patients referred in the prior six months. Enrolment and data collection continued until at least 100 referring physicians were enrolled (with no fewer than 10 referring physicians from each country) and 300 patient reports were collected. The study continued beyond two years to enable the target enrolment to be achieved in each country.

9.3. Subjects

The survey was carried out among physicians who had consented to participate and who had referred patients for at least one Amyvid PET scan. The sole inclusion criterion, that physicians had to have referred a patient for at least one Amyvid PET scan, was verified through the use of a screening question. Only those physicians passing the initial screening were invited to participate in the study. Survey questions were intended to apply only to patients receiving Amyvid PET as part of usual clinical practice, as opposed to subjects in clinical trials. This

survey did not collect information regarding physician participation in clinical trials and it is not known whether such participation may have influenced survey responses.

9.4. Variables

As previously mentioned, the primary objectives of the study were to describe the pattern of use of Amyvid PET scans by referring physicians and referred patients and to evaluate the level of off-label use. The variables, and corresponding survey questions (see Annex 2), that addressed these objectives fell into three categories:

1. Characteristics of the referring physicians;
2. Characteristics of the patients who were referred.
3. Level of off-label use with respect to indication and population.

Variables and questions from the first two categories addressed Objective 1: To assess the usage patterns of Amyvid in European clinical practice, and the category addressed Objective 2: To assess the level of off-label use in European clinical practice.

A summary of the variables addressed by the survey questions is presented below (Table 1).

Table 1. Summary of survey variables

Characteristics of referring physicians (Sections 1, 2 and 3)		
Variable	**Section**	**Question (Q)**
Specialisation (e.g., geriatrician, psychiatrist, neurologist, general practitioner, etc.)	1	1, 2, 5, 6
Experience managing patients with cognitive impairment and dementia	1	2, 3, 4
	2	4, 5
	3	1
Physician awareness of Amyvid indication, usage and limitations	2	1, 2, 3
Characteristics of the referred patients (Section 4)		
Variable	**Section**	**Q**
Demographics		
- Gender	4	1
- Age at time of scan	4	2
Time elapsed since commercial availability (calendar period or date at the time of the scan)	4	3
Cognitive status of patient		
- Severity of cognitive impairment at the time of the referral	4	5
	4	7b
Clinical features related to the diagnosis		
- Time since patient presented	4	4
- Clinical features associated with atypical presentation	4	6
Evidence of evaluation for cognitive impairment		
- Diagnostic procedures	4	10
- Medications indicated for patients with dementia (e.g., acetylcholinesterase inhibitors or memantine)	4	11
Comorbid conditions, especially evidence of hepatic or renal impairment	4	12
Level of off-label use (Section 4)		
Variable	**Section**	**Q**
Patient age at the time of the referral	4	2
Evidence of cognitive impairment at the time of the referral	4	5, 7a, 7b
Physician's clinical question	4	8, 9
Evidence of clinical evaluation for dementia	4	5, 7, 10

9.5. Data sources

In this survey, data on the pattern of Amyvid use in routine clinical practice were collected from participating physicians who completed the survey via web-, post-, or telephone-based methods. The survey questions were tested via pilot interviews (n=6; three in Italy, two in the UK and one in Spain) prior to commencement of the main fieldwork. Physicians who participated in the pilot interviews were specialists in the diagnosis and management of patients with AD who had participated in the clinical development programme of Amyvid.

9.6. Bias

During recruitment, physicians were informed of the survey goal (i.e., to assess the usage patterns of Amyvid and the level of off-label use in the UK, Spain and Italy). To reduce the potential for bias regarding the responses provided, physicians were not informed of Lilly's identity until the end of the survey and only if requested by the individual (only applicable to the UK as this was not possible in Italy or Spain). However, due to the very specific subject matter of the interview, however, it is likely that respondents were aware of the company that commissioned the survey. The effect of this potential knowledge on respondent answers, including on patient case reports, is unknown.

Selection bias

Selection bias is an inherent potential limitation of any study relying on voluntary participation. Selection bias in this survey would exist if physicians who agreed to participate were not representative of the general population of physicians who prescribe Amyvid and, therefore, their responses did not reflect the patterns of use or level of off-label use present among all physicians who refer patients for Amyvid scans.

Non-response was defined as the absence of an answer to a questionnaire and might have included the following situations:

- the physician was not reachable;
- the physician refused to participate;
- the physician withdrew from the survey part way through completion (e.g., had to quit the interview because of an emergency);
- the questionnaire was lost or not analysable.

Participation in the survey was analysed according to different ratios:

- the overall participation;
- the effective proportion of participation among physicians contacted;
- the overall proportion of non-response.

The numerator of the overall proportion of non-response included all possible forms of non-response (including cases when physicians could not be reached by phone).

Missing data

Efforts were made to follow up on surveys with substantial missing information, particularly for participants who elected to respond to the paper form of the survey. However, in case of missing values they were mentioned and treated separately in the analyses. No missing value was replaced.

9.7. Study size

This study aimed to survey at least 100 referring physicians and 300 patient reports for a sampling error margin between 5% and 10%, but in the event of low participation in the survey or lower than anticipated use, a minimum enrolment target was set as 10 physicians per country, i.e., for a minimum total of 30 enrolled physicians and 100 patient reports (for additional details concerning sample size estimation see Statistical Analysis Plan [SAP], Annex 2).

To increase the probability that physicians surveyed would be representative of all physicians who may refer patients for an Amyvid PET scan, recruitment and data collection were only initiated in a country where the number of scans undertaken reached 50. A scan was identified based on an order for Amyvid where each order equated to one scan/patient.

9.8. Data collection

The survey was conducted according to the standard operating procedures (SOPs) of QUINTILESIMS. In each country, recruitment was conducted by QUINTILESIMS dedicated team of native-speaking interviewers.

Respondents' identities were not disclosed. QUINTILESIMS adheres to the Standard Code of Conduct adopted by the European Pharmaceutical Market Research Association (EphMRA), the Market Research Society (MRS), the associations of local market survey organisations and to the International Chamber of Commerce/European Society for Opinion and Marketing Research (ICC/ESOMAR) International Code of Marketing and Social Research Practice. In addition, QUINTILESIMS complied with the terms of the country Data Protection Act in all countries

where the survey was conducted. During recruitment, it was made clear to respondents that all personal data collected during the research project were treated confidentially and used for the purposes of research in an aggregate format only. This might have also reduced the likelihood of respondents only reporting the patients they knew were referred for on-label reasons.

Once a physician agreed to take part in the study they were provided with a method of contributing patient information, either a web-, a paper- or a telephone-based survey. This allowed the collection of details from the physician's last consecutive cases who were referred for an Amyvid PET scan within the previous three months. All data collection was managed by QUINTILESIMS, including the web-based questionnaire, which was hosted via QUINTILESIMS in-house computer-assisted web-based interviewing (CAWI) system. The beginning of the questionnaire provided introductory text that reassured participating physicians about confidentiality, in addition to reminding them of their responsibility regarding adverse reaction (AR) reporting (see Annex 2).

Participating physicians were contacted once every three months to ascertain whether they had referred any additional patients for Amyvid PET scans in the period since the last participation or contact. In the event that they had referred additional patients they were invited to take part in the survey once again, until they had contributed a maximum of five patients. This process was continued throughout the study period to cover at least three years post-commercial availability and until a sufficient number of cases were enrolled to meet the study's sample size requirements with respect to both referring physician numbers and patient reports.

The QUINTILESIMS field team monitored survey initiations and conducted follow-up telephone calls with respondents to encourage completion for all physicians who failed to complete surveys.

Data from completed interviews provided by participating physicians who fulfilled the study entry criteria were included in the analyses. For those physicians who were lost to follow-up, or who dropped out of the study, the analyses included all data up to the point of their last data collection. Data were checked in terms of consistency before the data analysis.

The data collected were stored in a database specific to the survey and the country on a secure QUINTILESIMS server. QUINTILESIMS was responsible for the integrity of the data (i.e.,

accuracy, completeness, legibility, and timeliness) reported to Lilly. Data will be archived and retained as required by applicable laws and regulations.

9.9. Statistical methods

All data analyses were performed using SAS statistics software version 9.1 (SAS Institute Inc., Cary, NC). All analyses were performed in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and applicable sections of the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

9.9.1. Main summary measures

The main summary measures are described in Section 10.

Off-label use was defined as use in a population or for an indication that is not consistent with the label. The level of off-label use of Amyvid PET scans in clinical practice, Objective 2, was assessed by identifying responses that were not consistent with:

a) a clinical evaluation, that is, not monitoring,

b) the indicated population, that is, adults with cognitive impairment (measured objectively or as reported by clinical decline relative to previous performance),

c) AD or other causes of cognitive impairment.

The protocol-defined ('per protocol') criteria for off-label use that were followed for patient-level analyses are listed in Table 2. Based on the protocol, the overall proportion of patients reports indicating off-label use was calculated by dividing the number of reports that met any of the listed criteria, by the total number of valid cases reported. Throughout this section, question numbers always refer to questions from Section 4 of the survey (see Annex 2).

Table 2. Off-label use categories – Analysis per protocol

Off-label category		Criteria indicating off-label use
I.	Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	**Q8**: response will be considered off-label if it does not include 'As part of the evaluation of cognitive decline' Because all of the following are uses for the purpose of monitoring or are uses not related to clinical evaluation of the patient, the following responses to Q8 are off-label, regardless of whether the scan was used as part of evaluation: • monitoring response to therapy • estimating risk of mild cognitive impairment progression to clinical AD • substitute for genetic testing • substitute for clinical evaluation • non-medical use • evaluation of amyloid status in an asymptomatic individual Responses of none/no to Q7a and Q10 do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establishing it
II.	Not consistent with the indicated population	**Q2**: age <= 18 years old OR (**Q5**: "Normal cognition" AND **Q7a/b**: (MMSE) >=27 (if MMSE score available) AND ADAS-Cog <=9 (if ADAS-Cog score available) AND any other reported test result considered normal after medical review, if other test performed)
III.	Not consistent with use of scan for AD or other cause of cognitive impairment	**Q9:** "None of the above"

Abbreviations: AD (Alzheimer's Disease), Q (Question), MMSE (Mini Mental State Examination), ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive).

Because several survey questions collected information concerning the potential off-label use of Amyvid, this allowed respondents to provide inconsistent responses across the survey. To account for this, the proportion of responses to questions 5 and 8 were calculated both as originally defined per the protocol and after excluding inconsistent responses (Table 3). As originally proposed per the protocol, when inconsistent responses were identified based on the criteria listed in Table 3, all responses given by the respondent to that question were excluded for that case. The case was also then excluded from the numerator and denominator for the purpose of calculating the proportion of patients considered as valid for that question.

Table 3. Inconsistent responses to questions defining off-label use

Survey question affected	Inconsistent response leading to exclusion	Exclusion criteria
Q5	**Reported normal cognitive status does not match cognitive test score or other responses** Q5 cognitive normal but Q7 reports abnormal cognitive score Q5 cognitive normal but Q9 response indicates presence of cognitive impairment Q5 cognitive normal but Q11 indicates treatment for cognitive impairment	Q5 response = "Normal Cognition" AND one or more of the following: Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review Q9 includes any response except "none of the above" Q11 response = "Yes" for either medication
Q8	**"Asymptomatic" reasons were checked but symptoms reported** Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score	Q8 = see footnote AND one or both of the following: Q5 response NOT "Normal Cognition" Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review
Q8	**Estimating risk of progression of mild cognitive impairment to dementia when the subject is already demented** Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia	Q8 response = "For estimating risk of mild cognitive impairment progression to clinical Alzheimer's disease" AND Q5 response = mild or moderate or severe dementia

Footnote: **Q8** "asymptomatic" reasons include any of the following:
- As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a Apolipoprotein E4 carrier.
- As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or amyloid precursor protein).
- As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors.

Abbreviations: AD (Alzheimer's Disease), Q (Question), MMSE (Mini Mental State Examination), ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive).

Additionally, responses to particular questions might not have clearly indicated off-label use. Specifically, for the off-label category 'Not consistent with use of scan as part of a clinical evaluation for cognitive impairment', some physicians may have provided a response to question 8 that was consistent with the label (see Table 4), but may then also have selected question 8 responses which were off-label. In such a situation, it is unclear whether such use was truly off-label use. For off-label category II 'Not consistent with the indicated population', responses to question 9 about the inclusion of dementia in the differential diagnosis and question 11, about treatment of the patient with medication for cognitive impairment, should also be considered. Therefore, the algorithm to define off-label use was revised to take into account the existence of

inconsistent patient reports and potential lack of clarity in the responses used for some off-label use categories.

Table 4 provides this modified analysis of potential off-label use that may more accurately assess the level of off-label use in EU countries' practice than the per protocol analysis. The modified analysis based on the criteria in Table 4, defines only clear cases of off-label use (i.e., for the purpose of monitoring or unrelated to the clinical evaluation of the patient) and only defines a case as off-label use if the patient report by the respondent was internally consistent.

Table 4. Off-label use analysis criteria – Modified analysis

Off-label category		Criteria	Difference compared to analysis per protocol (Table 2)
MI	Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	**Q8**: Only the following responses are off-label: • monitoring response to therapy • estimating risk of mild cognitive impairment progression to clinical AD • substitute for genetic testing • substitute for clinical evaluation • nonmedical use • evaluation of amyloid status in an asymptomatic individual Q7a and Q10: responses of none/no to do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establishing it.	**Q8**: responses that include 'As part of the evaluation of cognitive decline' will be considered on-label, regardless of the other responses selected
MII	Not consistent with the indicated population	**Q2**: age <= 18 years old OR **Q5**: "Normal cognition" AND **Q7a/b**: MMSE >=27 AND ADAS-Cog <=9 AND any other reported test result considered normal after medical review AND **Q9**: none AND **Q11**: no	Both Q5 and Q7a/b must be true in addition to other requirements: **Q9**: "None of the above" must be present to indicate off-label use. Other responses would indicate that dementia is included in the possible diagnoses (and that use is therefore potentially not off-label) **Q11**: No for each treatment; otherwise physician is reporting treatment for cognitive impairment
MIII	Not consistent with use of scan for AD or other cause of cognitive impairment	**Q9**: "None of the above" AND **Q8**: not off-label as described above	No change from Table 2

Abbreviations: AD (Alzheimer's Disease), Q (Question), MMSE (Mini Mental State Examination), ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive).

9.9.2. Main statistical methods

All analyses were performed by descriptive statistical methods. Continuous variables were described with number of patients with valid, mean, standard deviation, median, first and third

quintile, minimum and maximum values. Categorical variables were described by frequencies and related percentages per class level.

The response rates for each question of the survey were tracked in the results by country, overall, by experience with management of cognitive impaired patients, by the number of previous Amyvid PET scans and per specialty as per stratifications defined in the next section.

Calculations were performed on raw data. Thus, no projection factor was applied to generalise the results to the entire referrers' universe. As a consequence, the report only shows the results observed on the total sample.

No statistical tests were performed; stratifications were presented only on a descriptive level. All variables were reported at country level according to the referrers' characteristics, provided that the physicians' anonymity was not compromised. Moreover, results were analysed according to experience with management of cognitive impaired patients, according to the number of previous Amyvid PET scans and according to prescribers' specialty to check for possible recruitment bias.

9.9.3. Missing values

Based on the study objective, unavailable information was analysed as missing values. No methods to impute values to missing data were used.

9.9.4. Sensitivity analyses

Not applicable.

9.9.5. Amendments to the statistical analysis plan

The SAP was originally approved in 2014 following wording in the protocol. Since there was no detailed definition of off-label use in the protocol, an algorithm was developed in line with the protocol language, to allow the overall proportion of off-label use to be quantified. Therefore, prior to the start of statistical analyses, the SAP was amended to incorporate this algorithm. Table 2 describes the criteria used to define off-label use per the protocol for the patient-level analyses.

During development of the off-label use criteria, the existence of internally inconsistent responses that could impact the validity and reliability of the results was detected. Therefore, an

additional modified analysis which excluded inconsistent survey responses were included; these are presented in Table 3 and Table 4:

- Table 3 provides a modified analysis that presents the proportion of responses to questions 5 and 8, after revision of the off-label criteria to exclude internally inconsistent responses.
- Table 4 provides a modified analysis of off-label use criteria after exclusion of both internally inconsistent responses and responses to particular questions that might not have indicated clear off-label use.

9.10. Quality control

Quality control for the collection of data through the web and telephone-based surveys included the programming of key controls into the CAWI and computer-assisted telephone interview (CATI) systems to ensure that respondents were not able to submit responses which were not relevant to the question for any pre-coded and closed-ended questions. The information provided via paper surveys was entered via the CAWI/CATI system. Certain checks were implemented to some open-ended questions requiring a numeric response. Answers to questions requiring a free-text response were checked once the completed survey was submitted by the respondent. In the event that there were queries, the respondent was contacted by telephone or e-mail to provide clarification. Any surveys which did not meet the quality control standards set for the project, for example, >50% missing or illegible information, were excluded from the final analysis (n=0).

All survey data were stored electronically on a secure server, with the original data maintained as originally entered by the clinician who participated in the survey. Coding of the data collected followed a predetermined and documented process, with verification of coding confirmed by double data entry. The final analytical dataset and statistical programmes used for cleaning and analysing data are preserved and maintained in electronic format and are available for auditing at all times. All information collected through the survey is traceable to specific login or participant identifiers, provided to each clinician at the time of their enrolment into the study. In order to preserve anonymity and confidentiality of the respondents, this information was not shared with the client, Lilly, but used internally by QUINTILESIMS to collate data provided by each

physician. All records, survey data, and analytical programmes have been securely maintained by QUINTILESIMS throughout the period of the study or longer, but may be shared with Lilly as long as this does not compromise participant anonymity or confidentiality.

9.10.1. Safeguards, security and traceability of calls

Interviewers, specialised in health surveys, were assigned to the project and briefed on the methodology prior to commencement of recruitment. Teams of interviewers undertaking telephone recruitment or data collection were supervised at all times.

The data collected was stored on a secure server and all telephone calls made were logged.

All aspects of the survey from protocol development to the reporting of the results were conducted following QUINTILESIMS SOPs.

9.11. Protection of human subjects

This study was conducted in accordance with applicable laws and regulations of the region and countries where the study was conducted.

The survey was non-interventional and entirely anonymous. No identifying information about patients was collected and data from physician participants were de-identified. In addition, data collected remains confidential and only aggregate data was communicated or presented.

Physicians participating in the survey were informed about the survey objectives, the type of data transmitted, the intended use of data, recipients of this data, and their right of access and rectification, and their right to object according to the European and national regulations.

Physicians were compensated for time they spent participating in this survey, based on fair market value in their region for their specialisation and seniority during the period of this study. National guidance on reimbursement and remuneration of physicians was followed for each country.

9.12. Management and reporting of adverse events (AEs)/ adverse reactions (ARs)

This study was a cross-sectional, non-interventional survey. No Amyvid doses were administered for the specific purposes of this study. Hence any suspected AE/AR uncovered during the evaluation of case files for collection or analysis of data for this study was submitted directly to Lilly Pharmacovigilance personnel for tabulation in the ongoing post-marketing dataset and was not recorded as part of this study.

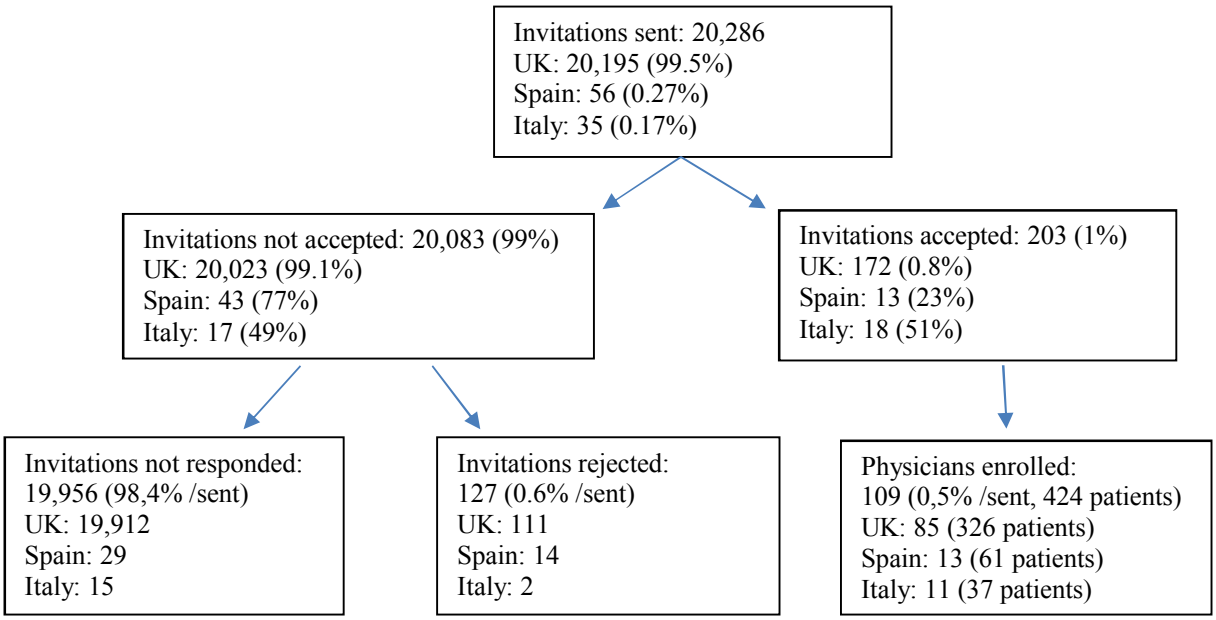
10. Results

10.1. Participants

In total, 20,286 invitations were sent to potential Amyvid prescribing physicians during the study and 203 (1%) were accepted. A total of 109 physicians completed the survey, providing information on 424 patients (see Enrolment grid-Annex 2).

Due to different enrolment strategies (general approach in UK, targeted approach in Spain and Italy) and dates of availability of Amyvid in the market (June 2013 in UK, January 2014 in Spain and October 2015 in Italy), most respondents (n=85; 78%) were from the UK, whereas 13 (12%) and 11 (10%) were from Spain and Italy, respectively. In total, these physicians provided information on 424 patients referred for Amyvid PET scans; UK physicians referred 326 (76.9%), Spain 61 (14.4%) and Italy 37 (8.7%) (see Figure 1).

Figure 1. Enrolment flow chart



10.2. Descriptive data

10.2.1. Physician profile

Among the 109 physicians who participated, the vast majority (n=92; 84.4%) received additional specialty training related to the management of patients with cognitive impairment. Neurology was the most commonly reported specialty (n=52; 47.7%). Psychiatry was the second most frequently reported specialty (n=32; 29.4%). This was driven by reports from UK where geriatric psychiatrists specialize in care for patients with AD and other types of cognitive impairment (Table 5 and Table 6).

Table 5. Physician's specialty

Question[a,b]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
General Practitioner			3 (3.5%)	3 (2.8%)
Geriatrics/Care of the Elderly	1 (9.1%)		17 (20.0%)	18 (16.5%)
Neurology	9 (81.8%)	11 (84.6%)	32 (37.6%)	52 (47.7%)
Psychiatry			32 (37.6%)	32 (29.4%)
Other	1 (9.1%)	2 (15.4%)	1 (1.2%)	4 (3.7%)
Nuclear Medicine		2 (15.4%)	1 (1.2%)	3 (2.8%)
Internal Medicine	1 (9.1%)			1 (0.9%)

[a]Question 1, Section 1: Please confirm your specialty by selecting one discipline from the list below. If you work across disciplines, please select that which takes the most of your time.
[b]Multiple response question, a physician can report more than one specialty.

Table 6. Additional specialist training received related to the management of patients with cognitive impairment

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
No	5 (45.5%)		8 (9.4%)	13 (11.9%)
Yes[b]	5 (45.5%)	12 (92.3%)	75 (88.2%)	92 (84.4%)
Geriatrics/Care of the Elderly	3 (60.0%)		26 (34.7%)	29 (31.5%)
Neurology	4 (80.0%)	10 (83.3%)	39 (52.0%)	53 (57.6%)
Psychiatry	2 (40.0%)		37 (49.3%)	39 (42.4%)
Other				
Internal Medicine	1 (20.0%)			1 (1.1%)
Cerebrovascular specialty	1 (20.0%)			1 (1.1%)
Nuclear Medicine		1 (8.3%)		1 (1.1%)
Positron emission tomography (PET)		1 (8.3%)		1 (1.1%)
Don't know/ recall	1 (9.1%)	1 (7.7%)	2 (2.4%)	4 (3.7%)

[a]Question 2, Section 1: Did you receive specialty training such as a fellowship in an area that relates to the management of patients with cognitive impairment? (Yes/No, Don't know). If yes, please indicate for which sub-specialty/specialties you received additional formal training.
[b]Multiple response question, a physician can report more than one specialty training received.

Almost all (n=107; 98.2%) physicians reported managing patients with AD or other forms of dementia. Of these, 68 (63.6%) spent more than half of their time managing these patients. (Table 7).

Table 7. Management of patients with Alzheimer's disease or other causes of dementia

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
No			2 (2.4%)	2 (1.8%)
Yes	11 (100.0%)	13 (100.0%)	83 (97.6%)	107 (98.2%)
0-25% of time	2 (18.2%)	2 (15.4%)	12 (14.5%)	16 (15.0%)
26-50% of time	3 (27.3%)	2 (15.4%)	18 (21.7%)	23 (21.5%)
51-75% of time	4 (36.4%)	3 (23.1%)	30 (36.1%)	37 (34.6%)
76-100% of time	2 (18.2%)	6 (46.2%)	23 (27.7%)	31 (29.0%)

[a]Question 3, Section 1: Does physician's practice include the management of patients with AD or other causes of dementia?

Table 8 summarises the number of patients with cognitive complaints that physicians had in their practices. Overall, nearly half (n=49; 45.0%) had more than 100 patients with cognitive complaints under care in their practices, and 12 (11.0%) reported having ten patients or fewer with cognitive complaints.

Table 8. Number of patients with cognitive complaints that physicians currently have in their practices

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
0 patients[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1-10 patients	1 (9.1%)	2 (15.4%)	9 (10.6%)	12 (11.0%)
11-50 patients	3 (27.3%)	1 (7.7%)	11 (12.9%)	15 (13.8%)
51-100 patients			33 (38.8%)	33 (30.3%)
>100 patients	7 (63.6%)	10 (76.9%)	32 (37.6%)	49 (45.0%)

[a]Question 4, Section 2: Approximately how many patients with cognitive complaints do you currently have in your practice? We are only interested in those patients who visit your office and receive a face-to-face consultation with you.
[b] Only physicians who referred at least one patient were eligible.

Overall, physicians had been in current practice for a mean of 14.2 (SD=5.5) years (Table 9). In Spain, physicians spent 55.8% (SD=35.5) of their time in a hospital, whereas in Italy they spent in a hospital an average of 85.5% (SD=21.6). UK physicians were not assessed since standard practice is hospital-based (Table 10).

Table 11 summarises the physicians' grades in each country.

Table 9. Years spent in current practice

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
Mean	12.8	14.3	14.4	14.2
(SD)	(6.3)	(7.1)	(5.2)	(5.5)
Median	15.0	15.0	15.0	15.0
(P25;P75)	(5.0; 19.0)	(10.0; 20.0)	(11.0; 16.0)	(10.0; 16.5)
(Min; Max)	(4.0; 20.0)	(5.0; 29.0)	(3.0; 30.0)	(3.0; 30.0)

[a]Question 4, Section 1: How many years have you spent in this practice?

Table 10. Proportion of time spent in each setting

Question[a]	Italy (n=11)	Spain (n=13)	Total (n=24)
Hospital practice			
Mean	85.5	55.8	69.4
(SD)	(21.6)	(35.5)	(33.0)
Median	100.0	60.0	80.0
(P25;P75)	(80.0; 100.0)	(20.0; 80.0)	(42.5; 100.0)
(Min; Max)	(40.0; 100.0)	(0.0; 100.0)	(0.0; 100.0)
Private office practice			
Mean	9.1	36.2	23.8
(SD)	(15.8)	(31.2)	(28.4)
Median	0.0	30.0	20.0
(P25;P75)	(0.0; 20.0)	(20.0; 60.0)	(0.0; 37.5)
(Min; Max)	(0.0; 50.0)	(0.0;100.0)	(0.0; 100.0)
Other			
Mean	5.5	8.1	6.9
(SD)	(15.1)	(16.3)	(15.5)
Median	0.0	0.0	0.0
(P25;P75)	(0.0; 0.0)	(0.0; 0.0)	(0.0; 0.0)
(Min; Max)	(0.0; 50.0)	(0.0; 50.0)	(0.0; 50.0)

[a]Question 5, Section 1: Please indicate the proportion of your time that you spend in each of the following settings.

Table 11. Physicians' grades

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)
Consultant			72 (84.7%)
Specialist Registrar			12 (14.1%)
Jefe de Servicio		1 (7.7%)	
Jefe de Sección		3 (23.1%)	
Adjunto		8 (61.5%)	
Dirigente di II livello / Primario	3 (27.3%)		
Dirigente di I livello / Aiuto	6 (54.5%)		
Other			
Staff Grade			1 (1.2%)
Investigador Predoctoral		1 (7.7%)	
Libero professionista/ private doctor	2 (18.2%)		

[a]Question 6, Section 1: What is your grade?

Table 12 summarises the number of patients that physicians had ever referred for an Amyvid PET scan. The majority of physicians (n= 66; 61%) had referred more than five patients.

Table 12. Number of patients referred for an Amyvid PET scan

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
0 patients	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
1-2 patients	1 (9.1%)	2 (15.4%)	20 (23.5%)	23 (21.1%)
3-5 patients	1 (9.1%)	1 (7.7%)	18 (21.2%)	20 (18.3%)
6-10 patients	3 (27.3%)	3 (23.1%)	19 (22.4%)	25 (22.9%)
11-20 patients	3 (27.3%)	3 (23.1%)	18 (21.2%)	24 (22.0%)
>20 patients	3 (27.3%)	4 (30.8%)	10 (11.8%)	17 (15.6%)

[a]Question 5, Section 2: To date, approximately how many patients in total have you ever personally referred for an Amyvid PET scan? We are only interested in those patients who visit your office and receive a face-to-face consultation with you.

10.2.2. Awareness of Amyvid indication

Physicians were asked several questions to evaluate their knowledge about the Amyvid indication. Almost all physicians (n=107; 98.2%) agreed with the approved indication for Amyvid, that is for 'evaluation of patients with cognitive decline for AD or other causes of dementia'. However, three-quarters (n=83; 76.1%) also agreed that the approved indication for Amyvid included 'estimating the risk of mild cognitive impairment (MCI) progression to clinical AD' and nearly half agreed that it included 'for monitoring the response to therapy in patients with AD' (n= 53; 48.6%) and 'for risk stratification in asymptomatic individuals, such as relatives of AD patients' (n=52; 47.7%) (Table 13).

Table 13. Indication for Amyvid in Europe knowledge

Question[a]	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
For evaluation of patients with cognitive decline for AD or other causes of dementia				
Agree	11 (100.0%)	12 (92.3%)	84 (98.8%)	107 (98.2%)
Disagree		1 (7.7%)		1 (0.9%)
Don't know			1 (1.2%)	1 (0.9%)
For risk stratification in asymptomatic individuals, such as relatives of AD patients				
Agree	3 (27.3%)	3 (23.1%)	46 (54.1%)	52 (47.7%)
Disagree	6 (54.5%)	10 (76.9%)	34 (40.0%)	50 (45.9%)
Don't know	2 (18.2%)		5 (5.9%)	7 (6.4%)
For estimating the risk of MCI progression to clinical AD				
Agree	9 (81.8%)	12 (92.3%)	62 (72.9%)	83 (76.1%)
Disagree	1 (9.1%)	1 (7.7%)	16 (18.8%)	18 (16.5%)
Don't know	1 (9.1%)		7 (8.2%)	8 (7.3%)
For monitoring response to therapy in patients with AD				
Agree	4 (36.4%)		49 (57.6%)	53 (48.6%)
Disagree	6 (54.5%)	12 (92.3%)	30 (35.3%)	48 (44.0%)
Don't know	1 (9.1%)	1 (7.7%)	6 (7.1%)	8 (7.3%)

[a]Question 1, Section 2: Based on your understanding of Amyvid, we are interested in whether you agree or disagree that the approved indication for Amyvid in Europe includes (Agree) or does not include (Disagree) the following.
Abbreviations: AD (Alzheimer's Disease), Mild Cognitive Impairment (MCI).

Table 14 summarises how physicians interpreted the result of an Amyvid PET scan. The vast majority of physicians (n=92; 84.4%) correctly agreed that a positive scan result may be consistent with AD but does not independently establish a diagnosis of AD, and more than half (n=57; 52.3%) agreed that a positive scan result would be consistent with having moderate to frequent plaques. Nevertheless, some (n=8; 7.3%) incorrectly agreed with the statement that a positive scan would indicate sparse or no plaques.

Moreover, when physicians were asked about their agreement with the true statement 'a negative scan is not consistent with a diagnosis of AD', more than one quarter (n=30; 27.5%) disagreed.

Table 14. Scan diagnosis knowledge

	Italy (n=11)	Spain (n=13)	UK (n=85)	Total (n=109)
A positive scan indicates[a]:				
Sparse or no plaques			8 (9.4%)	8 (7.3%)
Moderate to frequent plaques	8 (72.7%)	8 (61.5%)	41 (48.2%)	57 (52.3%)
May be consistent with AD, but does not independently establish a diagnosis of AD	9 (81.8%)	12 (92.3%)	71 (83.5%)	92 (84.4%)
A negative scan is not consistent with a diagnosis of Alzheimers disease:				
False	2 (18.2%)	2 (15.4%)	26 (30.6%)	30 (27.5%)
True	9 (81.8%)	11 (84.6%)	58 (68.2%)	78 (71.6%)
Don't know			1 (1.2%)	1 (0.9%)

[a]Questions 2 and 3, Section 2. Multiple response question.
Abbreviations: AD (Alzheimer's Disease).

10.2.3. Patient information

In total, 424 patients were referred by the 109 participating physicians, including 326 (76.9%) in the UK, 61 (14.4%) in Spain and 37 (8.7%) in Italy. All were adults over the age of 18 years and the distribution by sex was similar across countries, although some differences were observed. The proportion of female patients was higher in Italy (n=23; 62.2%), whereas in Spain there was a higher proportion of male patients (n=33, 54.1%). Overall, the mean age of patients was 67.9 (SD=11.2) years, similar in the three countries (Table 15).

Table 15. Patient sociodemographic information

Question[a]	Italy	Spain	UK	Total
Sex				
Female	23 (62.2%)	28 (45.9%)	164 (50.3%)	215 (50.7%)
Male	14 (37.8%)	33 (54.1%)	161 (49.4%)	208 (49.1)
Don't know/ recall			1 (0.3%)	1 (0.2%)
valid n	*37*	*61*	*326*	*424*
Age (at the time of having Amyvid PET scan)				
Mean	67.8	67.5	68.0	67.9
(SD)	(8.0)	(9.4)	(11.8)	(11.2)
Median	69.0	70.0	68.0	68.0
(P25;P75)	(63.0; 73.0)	(59.0; 75.0)	(60.0; 76.0)	(60.0; 76.0)
(Min; Max)	(51.0; 84.0)	(51.0; 84.0)	(30.0; 100.0)	(30.0; 100.0)
valid n	*37*	*61*	*311*	*409*

[a]Questions 1 and 2, section 4: What is the patient's gender? / How old was the patient at the time of having the Amyvid PET scan? Please write exact age, in years or Do Not Know.
Abbreviations: Positron emission tomography (PET).

10.3. Outcome data

Not applicable.

10.4. Main results

10.4.1. Clinical features related to the Amyvid PET scan

Table 16 summarises the time elapsed since the patient first presented to physician with the complaint or symptom that led to Amyvid PET scan referral and the date the scan was performed. Overall, patients were referred after a mean of 10.0 (SD=10.5) months. The elapsed time was shorter in the UK (mean of 8.4 [SD=9.0] months), and longer in Spain (mean of 13.8 [SD=13.8] months) and Italy (mean of 15.9 [SD=11.7] months).

Table 16. Time elapsed, in months, since the patient first presented to physician and Amyvid PET scan referral

Question[a]	Italy (n=32)	Spain (n=56)	UK (n=253)	Total (n=341)
Mean	15.9	13.8	8.4	10.0
(SD)	(11.7)	(13.8)	(9.0)	(10.5)
Median	12.0	10.0	6.0	6.0
(P25;P75)	(7.0; 24.0)	(5.0; 19.5)	(3.0; 11.0)	(3.0; 12.0)
(Min; Max)	(0.0; 42.0)	(0.0; 60.0)	(0.0; 60.0)	(0.0; 60.0)

[a]Question 4, Section 4: How much time (months) has elapsed since the patient first presented to you with the complaint/symptom that led to your referral for an Amyvid scan?

Table 17 summarises patients' cognitive status at the time of Amyvid PET scan. Only 2.6% (n=11) of the patients referred were reported to be cognitively normal, while 13.7% (n=58) had a cognitive complaint without cognitive impairment on examination, and 42.7% (n=181) had MCI. The remaining patients (n=174, 41.0%) had some level of dementia. The 'total, per protocol' (raw) data were consistent with the data from the modified analysis that excluded inconsistent responses.

Table 17. Patient's cognitive status at the time of the Amyvid PET scan

	Modified analysis excluding inconsistent responses[b]				Per protocol analysis[b]
Question[a]	**Italy (n=37)**	**Spain (n=61)**	**UK (n=319)**	**Total (n=417)**	**Total (n=424)**
Normal cognition			4 (1.3%)	4 (1.0%)	11 (2.6%)
Cognitive complaint without cognitive impairment on examination	4 (10.8%)	4 (6.6%)	50 (15.7%)	58 (13.9%)	58 (13.7%)
Mild cognitive impairment	19 (51.4%)	41 (67.2%)	121 (37.9%)	181 (43.4%)	181 (42.7%)
Mild dementia	4 (10.8%)	14 (23.0%)	105 (32.9%)	123 (29.5%)	123 (29.0%)
Moderate dementia	9 (24.3%)	2 (3.3%)	31 (9.7%)	42 (10.1%)	42 (9.9%)
Severe dementia	1 (2.7%)		8 (2.5%)	9 (2.2%)	9 (2.1%)

[a]Question 5, Section 4: At the time of the Amyvid PET scan, what was the patient's cognitive status?
[b]The column 'Total, per protocol' shows the raw data. The other columns report the data after removing inconsistent reponses (see Table 28).

Table 18 summarises the clinical findings at the time of the Amyvid PET scan. Over one-third of the patients (n=163; 38.4%) had impairments in activities of daily living due to cognitive impairment, while 22.9% (n=97) had prominent fluctuations in cognition, 22.6% (n=96) had prominent changes in personality, behaviour or comportment, 11.8% (n=50) had visual hallucinations, 10.1% (n=43) had parkinsonism and 9.9% (n=42) had prominent language disturbance without memory loss. However, 23.3% (n=99) of the patients were referred for an Amyvid PET scan when they were not exhibiting any of the above clinical findings.

Table 18. Findings at the time of the Amyvid PET scan

Question[a]	Italy (n=37)	Spain (n=61)	UK (n=326)	Total (n=424)
Impairment in activities of daily living due to cognitive impairment	17 (45.9%)	23 (37.7%)	123 (37.7%)	163 (38.4%)
Parkinsonism	2 (5.4%)	4 (6.6%)	37 (11.3%)	43 (10.1%)
Visual hallucinations	4 (10.8%)	1 (1.6%)	45 (13.8%)	50 (11.8%)
Prominent fluctuations in cognitive function	7 (18.9%)	2 (3.3%)	88 (27.0%)	97 (22.9%)
Prominent changes in personality, behaviour or comportment	15 (40.5%)	9 (14.8%)	72 (22.1%)	96 (22.6%)
Prominent language disturbance without memory loss	3 (8.1%)	8 (13.1%)	31 (9.5%)	42 (9.9%)
Substantial concomitant cerebrovascular disease	4 (10.8%)	2 (3.3%)	22 (6.7%)	28 (6.6%)
None of the above	9 (24.3%)	27 (44.3%)	63 (19.3%)	99 (23.3%)

[a]Question 6, Section 4: At the time of the Amyvid PET scan, did the patient have any of the following findings (Mark all that apply)?
[b]Multiple response question, one patient can have more than one finding.

Table 19 summarises the tests designed specifically to measure cognitive function that were performed prior to the Amyvid PET scan. Almost all patients (n=412; 97.2%) had undergone cognitive function tests. Among those patients, 87.4% (n=360) had undergone a Mini Mental State Examination (MMSE), with different percentages across the countries: 85.2% (n=271) of patients in the UK, 91.2% (n=52) in Spain and 100.0% (n=37) in Italy. Patients scored a median of 25.0 points in this test, corresponding to a possible cognitive impairment (5), and 67.8% (n=219) of patients presented an MMSE score < 27.

In addition, 17.2% (n=71) of patients had been tested with an Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) test, all of them in the UK. They scored a median 21.5 points, suggesting some cognitive impairment (6), and 88.2% (n=30) of patients with valid results (n=34) had an ADAS-Cog score > 9.

Table 19. Description of tests performed specifically to measure cognitive function

Question[a]	Italy	Spain	UK	Total
No		4 (6.6%)	8 (2.5%)	12 (2.8%)
Yes	37 (100.0%)	57 (93.4%)	318 (97.5%)	412 (97.2%)
Valid n	*37*	*61*	*326*	*424*
Type of test performed				
MMSE	37 (100.0%)	52 (91.2%)	271 (85.2%)	360 (87.4%)
Mean	24.8	24.7	23.7	23.9
(SD)	(4.9)	(4.2)	(4.4)	(4.4)
Median	27.0	25.0	24.0	25.0
(P25;P75)	(23.0; 28.0)	(23.5; 28.0)	(22.0; 27.0)	(22.0; 27.0)
(Min; Max)	(8.0; 29.0)	(9.0; 30.0)	(3.0; 30.0)	(3.0; 30.0)
MMSE < 27	16 (47.1%)	32 (61.5%)	171 (72.2%)	219 (67.8%)
MMSE ≥ 27	18 (52.9%)	20 (38.5%)	66 (27.8%)	104 (32.2%)
Valid n	*34*	*52*	*237*	*323*
ADAS-cog			71 (22.3%)	71 (17.2%)
Mean			28.5	28.5
(SD)			(19.1)	(19.1)
Median			21.5	21.5
(P25;P75)			(15.0; 45.0)	(15.0; 45.0)
(Min; Max)			(5.0; 66.0)	(5.0; 66.0)
ADAS-cog > 9			30 (88.2%)	30 (88.2%)
ADAS-cog ≤ 9			4 (11.8%)	4 (11.8%)
Valid n			*34*	*34*
Other	12 (32.4%)	32 (56.1%)	67 (21.1%)	111 (26.9%)
ACE			37 (11.6%)	37 (9.0%)
Memory tests	10 (27.0%)	7 (12.3%)	13 (4.1%)	30 (7.3%)
NPS battery		8 (14.0%)	5 (1.6%)	13 (3.2%)
Stroop	3 (8.1%)	8 (14.0%)		11 (2.7%)
Orientation tests	4 (10.8%)	4 (7.0%)		8 (1.9%)
Boston Naming Test		7 (12.3%)		7 (1.7%)
Other	8 (21.6%)	20 (35.1%)	24 (7.5%)	52(12.6 %)
valid n	*37*	*57*	*318*	*412*

[a]Questions 7a and 7b, Section 4: Prior to the Amyvid PET scan, did the patient have any tests which were designed specifically to measure cognitive function? If yes, please specify below/What was the result of this test?

Abbreviations: MMSE (Mini Mental Scale Examination), ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive), ACE (Addenbrooke's Cognitive Examination), NPS (Neuropsychiatric Syndromes).

Table 20 summarises the reasons why patients were referred for an Amyvid PET scan (physicians were allowed to select multiple answers). In more than half of cases (n=237; 55.9%) the physician reported that at least one of the reasons for referral was 'as part of the evaluation of cognitive decline documented on clinical examination'.

Table 20. Reasons for referring the patient for an Amyvid PET scan

	Modified analysis excluding inconsistent responses[b]				Per protocol analysis[b]
Question[a]	Italy (n=34)	Spain (n=59)	UK (n=256)	Total (n=349)	Total (n=424)
As part of the evaluation of a patient with cognitive decline documented on clinical examination	15 (44.1%)	34 (57.6%)	154 (60.2%)	203 (58.2%)	237 (55.9%)
As part of an evaluation of the severity of dementia	3 (8.8%)		50 (19.5%)	53 (15.2%)	72 (17.0%)
As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be an apolipoprotein E4 carrier			2 (0.8%)	2 (0.6%)	31 (7.3%)
For monitoring response to therapy			16 (6.3%)	16 (4.6%)	23 (5.4%)
As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination	5 (14.7%)	4 (6.8%)	50 (19.5%)	59 (16.9%)	83 (19.6%)
For estimating risk of mild cognitive impairment progression to clinical Alzheimer's disease	12 (35.3%)	22 (37.3%)	49 (19.1%)	83 (23.8%)	115 (27.1%)
To establish a diagnosis of Alzheimer's disease based on a positive scan result	17 (50.0%)	33 (55.9%)	106 (41.4%)	156 (44.7%)	180 (42.5%)
As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or amyloid precursor protein)					13 (3.1%)
As a substitute for clinical evaluation			1 (0.4%)	1 (0.3%)	3 (0.7%)
As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors	2 (5.4%)		1 (0.4%)	3 (0.9%)	22 (5.2%)
For a non-medical use (e.g., insurance coverage, legal or employment-related reasons)			3 (1.2%)	3 (0.9%)	4 (0.9%)

	Modified analysis excluding inconsistent responses[b]				Per protocol analysis[b]
Question[a]	**Italy (n=34)**	**Spain (n=59)**	**UK (n=256)**	**Total (n=349)**	**Total (n=424)**
Other		6 (10.2%)	2 (0.8%)	8 (2.3%)	9 (2.1%)
Investigation		5 (8.5%)	1 (0.4%)	6 (1.7%)	7 (1.7%)
Differential diagnosis		1 (1.7%)	1 (0.4%)	2 (0.6%)	2 (0.5%)

[a] Question 8, Section 4. Multiple response question: When you referred the patient for an Amyvid PET scan, what was the reason for the referral? Mark all that apply.

[b]The column 'Total, per protocol' reports the raw data (original count of responses for each question without regard to the internal consistency of responses for a patient). All other columns report counts after removing inconsistent responses (see Table 28).

Table 21 summarises the differential diagnoses of patients at the time of the Amyvid PET scan but before receiving the scan results. In all but 1.4% (n=6) of cases (where physician response was 'none of the above'), patients had possible MCI (n=198; 46.7%) or possible dementia. AD was the most common possible etiologic diagnosis before the results of the scan (n=258; 60.8% of the entire patient population), followed by MCI (n=198; 46.7%) and other neurodegenerative dementia such as Lewy body dementia or frontotemporal dementia (n=123; 29.0%) and vascular dementia (n=87; 20.5%). Of note, other dementia diagnoses, such as depressive pseudodementia, depression, alcoholism or anxiety, accounted for 4.5% (n=19) of the possible diagnoses.

Table 21. Possible diagnosis at the time of the Amyvid PET scan before receiving the scan results

Question[a,b]	Italy (n=37)	Spain (n=61)	UK (n=326)	Total (n=424)
Mild cognitive impairment	14 (37.8%)	36 (59.0%)	148 (45.4%)	198 (46.7%)
Vascular dementia	3 (8.1%)	1 (1.6%)	83 (25.5%)	87 (20.5%)
Alzheimer's disease	29 (78.4%)	35 (57.4%)	194 (59.5%)	258 (60.8%)
Other neurodegenerative dementia , (e.g., Lewy body dementia, frontotemporal dementia)	14 (37.8%)	15 (24.6%)	94 (28.8%)	123 (29.0%)
Dementia with unknown/uncertain diagnosis	3 (8.1%)	12 (19.7%)	71 (21.8%)	86 (20.3%)
Other dementia diagnosis	4 (10.8%)	7 (11.5%)	8 (2.5%)	19 (4.5%)
Depressive Pseudodementia	4 (10.8%)	4 (6.6%)	2 (0.6%)	10 (2.4%)
Depression		1 (1.6%)	6 (1.8%)	7 (1.7%)
Alcoholism			2 (0.6%)	2 (0.5%)
Anxiety			2 (0.6%)	2 (0.5%)
Cerebral Amyloid Angiopathy		1 (1.6%)		1 (0.2%)
Limbic encephalitis		1 (1.6%)		1 (0.2%)
None of the above			6 (1.8%)	6 (1.4%)

[a]Question 9, Section 4: At the time of the Amyvid PET scan, but before receiving the scan results, which of the following were included in your possible diagnosis? (Mark all that apply.)
[b]Multiple response question.

Table 22 summarises the laboratory tests /investigations that physicians ordered for a patient prior to an Amyvid PET scan. Most patients (n=343; 80.9%) had at least one laboratory test/investigation prior to the scan. Among these, the three most commonly requested were clinical imaging (n=286; 83.4% of the subjects that had laboratory tests/investigations, 67.5% of the entire patient population), laboratory tests from blood or urine (n=283; 82.5% of the subjects that had laboratory tests/investigations, 66.7% of the entire patient population) and neuropsychological testing (n=218; 63.6% of the subjects that had laboratory tests, 51.4% of the entire patient population). Of note, 14.2% (n=60) of patients had not undergone any laboratory test/investigation prior to the Amyvid PET scan.

Table 22. Laboratory tests/investigations ordered prior to the Amyvid PET scan

Question[a,b]	Italy	Spain	UK	Total
No	1 (2.7%)	10 (16.4%)	49 (15.0%)	60 (14.2%)
Yes	33 (89.2%)	50 (82.0%)	260 (79.8%)	343 (80.9%)
Don't know/ recall	3 (8.1%)	1 (1.6%)	17 (5.2%)	21 (5.0%)
valid n	*37*	*61*	*326*	*424*
Type of laboratory tests ordered[b]				
Clinical imaging e.g., CT, MRI	30 (90.9%)	50 (100.0%)	206 (79.2%)	286 (83.4%)
Scan using an imaging agent, e.g., PET or SPECT scan	20 (60.6%)	28 (56.0%)	59 (22.7%)	107 (31.2%)
Lumbar puncture	5 (15.2%)	16 (32.0%)	65 (25.0%)	86 (25.1%)
Lab tests from blood or urine, e.g., CBC, B12, serum chemistry, etc.	29 (87.9%)	46 (92.0%)	208 (80.0%)	283 (82.5%)
Genetic testing, e.g., ApoE or other	6 (18.2%)	4 (8.0%)	33 (12.7%)	43 (2.5%)
Neuropsychological testing	26 (78.8%)	49 (98.0%)	143 (55.0%)	218 (63.6%)
valid n	*33*	*50*	*260*	*343*

[a]Question 10, Section 4: Regarding your intended management plan for this patient prior to the Amyvid scan, did you order any laboratory tests? (Y/N). If yes, please mark the tests you ordered.
[b]Multiple response question. Percentages shown are percent of patients that had lab tests ordered (i.e., n for denominator is 343; thus 83.4%, 286/343, subjects that had lab tests ordered underwent clinical imaging). A smaller percentage of the whole population (n=424) received each test (e.g., 67.5%, 286/424 underwent clinical imaging).
Abbreviations: CT (computed tomography), MRI (magnetic resonance imaging), PET (photon emission tomography), SPECT (single photon emission computed tomography), CBC (complete blood count), B12 (vitamin B12), ApoE4 (apolipoprotein E4).

Table 23 summarises the medications for cognitive impairment that patients had received since they first sought treatment. Overall, almost 40% percent of the patients (n=169) had taken at least one AD medication.

Table 23. Medications received since first seeking treatment for cognitive impairment

Question[a]	Italy (n=37)	Spain (n=61)	UK (n=326)	Total (n=424)
Acetylcholinesterase inhibitor [donepezil (Aricept), rivastigmine (Exelon), or galantamine (Nivalin, Lycoremine, Razadyne)]				
No	20 (54.1%)	42 (68.9%)	197 (60.4%)	259 (61.1%)
Yes	16 (43.2%)	19 (31.1%)	117 (35.9%)	152 (35.8%)
Don't know/ recall	1 (2.7%)		12 (3.7%)	13 (3.1%)
Memantine (Namenda, Axura, Akatinol, Ebixa, Abixa, Memox)				
No	27 (73.0%)	55 (90.2%)	266 (81.6%)	348 (82.1%)
Yes	9 (24.3%)	5 (8.2%)	44 (13.5%)	58 (13.7%)
Don't know/ recall	1 (2.7%)	1 (1.6%)	16 (4.9%)	18 (4.2%)

[a]Question 11, Section 4: Prior to the Amyvid PET scan, had the patient received any of the following medications since they first sought treatment for cognitive impairment? Indicate "Yes", "No", or "Do Not Know" for each treatment below.

Table 24 summarises the patients' comorbidities at the time of the Amyvid PET scan. Overall, less than half of the patients (n=177; 41.7%) had comorbidities at the time of the scan, although some differences were observed across countries: in the UK 45.7% (n=149), in Italy 40.5% (n=15) and in Spain only 21.3% (n=13). Among all patients, 12.3% (n=52) were suffering from renal impairment and 5.9% (n=25) from hepatic impairment. Clinically meaningful cerebrovascular disease and other psychiatric morbidities, such as depression, anxiety, schizoaffective disorders or alcoholism, were commonly reported (n=47 [11.1%] and n=61 [14.4%)] of the entire sample of patients, respectively).

Table 24. Patient comorbidities at the time of the Amyvid PET scan

Question[a]	Italy	Spain	UK	Total
No	14 (37.8%)	37 (60.7%)	159 (48.8%)	210 (49.5%)
Yes	15 (40.5%)	13 (21.3%)	149 (45.7%)	177 (41.7%)
Don't know/ recall	8 (21.6%)	11 (18.0%)	18 (5.5%)	37 (8.7%)
Valid n	*37*	*61*	*326*	*424*
Co-morbidities[b]				
Clinically meaningful cerebrovascular disease	6 (40.0%)	4 (30.8%)	37 (24.8%)	47 (26.6%)
Renal impairment	4 (26.7%)		48 (32.2%)	52 (29.4%)
Hepatic impairment	1 (6.7%)	1 (7.7%)	23 (15.4%)	25 (14.1%)
Other psychiatric morbidities	8 (53.3%)	7 (53.8%)	46 (30.9%)	61 (34.5%)
Depression	8 (100.0%)	5 (71.4%)	31 (67.4%)	44 (72.1%)
Anxiety	1 (12.5%)		8 (17.4%)	9 (14.8%)
Schizoaffective disorders		1 (14.3%)	6 (13.0%)	7 (11.5%)
Alcoholism			5 (10.9%)	5 (8.2%)
Personality disorder			3 (6.5%)	3 (4.9%)
Mood swings			2 (4.3%)	2 (3.3%)
Anger outburst			1 (2.2%)	1 (1.6%)
Depressive Pseudodementia		1 (14.3%)		1 (1.6%)
Insomnia			1 (2.2%)	1 (1.6%)
Irritability			1 (2.2%)	1 (1.6%)
Other neurological morbidities	3 (20.0%)	2 (15.4%)	12 (8.1%)	17 (9.6%)
Epilepsy		1 (50.0%)	2 (16.7%)	3 (17.6%)
Parkinson disease			3 (25.0%)	3 (17.6%)
Brain cancer	2 (66.7%)			2 (11.8%)
Dysarthria			2 (16.7%)	2 (11.8%)
Limbic encephalitis	1 (33.3%)	1 (50.0%)		2 (11.8%)
Traumatic brain injury			2 (16.7%)	2 (11.8%)
Confusion			1 (8.3%)	1 (5.9%)
Desorientation			1 (8.3%)	1 (5.9%)
Disturbance of gait			1 (8.3%)	1 (5.9%)
Post herpetic trigeminal neuralgia			1 (8.3%)	1 (5.9%)
Supranuclear palsy			1 (8.3%)	1 (5.9%)
Don't know/ recall			1 (8.3%)	1 (5.9%)
Valid n	*15*	*13*	*149*	*177*

[a]Question 12, Section 4: At the time of the Amyvid PET scan, did the patient have any of the following comorbidities? Please mark all that apply.
[b]Multiple response question.

Table 25 summarises the changes in the diagnosis or treatment resulting from Amyvid PET scans. In 67.2% (n=285 out of 424) of the patients, the diagnosis or treatment changed based on the Amyvid scan results. Among these patients, scan results increased diagnostic confidence in

80.7% (n=230 out of 285; 54.2% of the entire study population) and changed the medical management plan in 48.1% (n=137 out of 285; 32.3% of the entire study population). The diagnosis or treatment did not change after the scan results in 24.8% (n=105 out of 424) of the patients (sum of those who initially answered 'no' and those who initially answered 'yes' but then answered 'did not change my diagnosis or treatment').

Table 25. Changes on the diagnosis or treatment after Amyvid scan results

Question[a,b]	Italy	Spain	UK	Total
Yes	27 (73.0%)	50 (82.0%)	208 (63.8%)	285 (67.2%)
No	10 (27.0%)	9 (14.8%)	81 (24.8%)	100 (23.6%)
Don't know/ recall		2 (3.3%)	37 (11.3%)	39 (9.2%)
valid n	*37*	*61*	*326*	*424*
If 'Yes,' then details of change:				
Increased diagnostic confidence	15 (55.6%)	46 (92.0%)	169 (81.2%)	230 (80.7%)
Decreased diagnostic confidence	1 (3.7%)	1 (2.0%)	14 (6.7%)	16 (5.6%)
Changed the medical management plan	20 (74.1%)	35 (70.0%)	82 (39.4%)	137 (48.1%)
Changed plans for referral to other specialists	7 (25.9%)	6 (12.0%)	38 (18.3%)	51 (17.9%)
Changed plan for counseling the patient or caregiver	6 (22.2%)	28 (56.0%)	73 (35.1%)	103 (37.5%)
Changed planned use of other diagnostic tests	4 (14.8%)	12 (24.0%)	37 (17.8%)	53 (18.6%)
Did not change my diagnosis or management	1 (3.7%)		4 (1.9%)	5 (1.8%)
Don't know/ recall	2 (7.4%)			2 (0.7%)
valid n	*27*	*50*	*208*	*285*

[a]Questions 13a and 13b, Section 4: Has/Will the Amyvid scan result changed the diagnosis or treatment of this patient? / In what way has the Amyvid scan result changed the diagnosis or management of this patient? Please mark all that apply.
[b]Multiple response question.

10.4.2. Off-label use of the Amyvid PET scan

Table 26 summarises the off-label use of the Amyvid PET scan according to the per protocol analysis. Overall, based on the per protocol analysis, off-label use was reported by physicians in 63.2% (n=268) of the patients. In Spain, off-label use was reported in 59% (n=36) of the patients, while higher proportions were observed in the UK (n=205; 62.9%) and Italy (n=27; 73.0%).

The majority of the off-label use cases (n=266; 62.7% of the entire study population) were related to the reported use of the scan for a reason other than 'evaluation of cognitive decline documented on a clinical examination'.

Table 26. Off-label use of the Amyvid PET scan – Per protocol analysis

	Italy (n=37)	Spain (n=61)	UK (n=326)	Total[d] (n=424)
Total patients indicating on-label use	10 (27.0%)	25 (41.0%)	121 (37.1%)	156 (36.8%)
Total patients indicating off-label use	27 (73.0%)	36 (59.0%)	205 (62.9%)	268 (63.2%)
Categories of off-label use				
I. Not consistent with use of scan as part of a clinical evaluation for cognitive impairment[a]	**27 (73.0%)**	**36 (59.0%)**	**203 (62.3%)**	**266 (62.7%)**
Q8 response does not include "As part of the evaluation of cognitive decline"	20 (54.1%)	26 (42.6%)	141 (43.3%)	187 (44.1%)
Q8 response includes uses for the purpose of monitoring or not related to clinical evaluation of the patient	14 (37.8%)	24 (39.3%)	128 (39.3%)	166 (39.2%)
Monitoring response to therapy	0 (0.0%)	0 (0.0%)	23 (7.1%)	23 (5.4%)
Estimating risk of MCI progression to clinical AD	13 (35.1%)	23 (37.7%)	79 (24.2%)	115 (27.1%)
Substitute for genetic testing	0 (0.0%)	0 (0.0%)	13 (4.0%)	13 (3.1%)
Substitute for clinical evaluation	0 (0.0%)	0 (0.0%)	3 (0.9%)	3 (0.7%)
Nonmedical use	0 (0.0%)	0 (0.0%)	4 (1.2%)	4 (0.9%)
Evaluation of amyloid status in an asymptomatic individual	1 (2.7%)	1 (1.6%)	29 (8.9%)	31 (7.3%)
II. Not consistent with the indicated population[b]	**0 (0.0%)**	**0 (0.0%)**	**8 (2.5%)**	**8 (1.9%)**
Q2 age <= 18 years old	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal cognition	0 (0.0%)	0 (0.0%)	8 (2.5%)	8 (1.9%)
III. Not consistent with use of scan for AD or other cause of cognitive impairment[c]	0 (0.0%)	0 (0.0%)	6 (1.8%)	6 (1.3%)

[a] **Not consistent with use of scan as part of a clinical evaluation for cognitive impairment**: Q8: response was considered off-label if it did not include "As part of the evaluation of cognitive decline documented on clinical examination".

Because all of the following are uses for the purpose of monitoring or are uses not related to clinical evaluation of the patient, the following responses to Q8 resulted in the case being counted as off-label, regardless of whether the scan was used as part of evaluation: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/evaluation of amyloid status in an asymptomatic individual. Responses of none/no to Q7a (if cognitive function tests were performed prior to the scan) and Q10 (if other laboratory tests were performed prior to the scan) do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establishing it.

[b] **Not consistent with the indicated population:** Q2 age <= 18 years old normal cognition defined as OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 (if MMSE score available) AND ADAS-Cog <=9 (if ADAS-Cog score available) AND any other reported test result considered normal after medical review (if other test performed)

[c] **Not consistent with use of scan for AD or other cause of cognitive impairment**: Q9 = "none of the above".

[d] the following counts are reported for each category and reflect percentages out of the total n=424.

Table 27 summarises the off-label use of the Amyvid PET scan according to the modified analysis, where inconsistent responses were excluded and only clear cases of off-label use (i.e., uses for purpose of monitoring cases or not related to clinical evaluation of the patient) were counted. Overall, according to these criteria, off-label use was reported by physicians in 29.7% (n=102) of the patients. The majority (n=82) of the 102 off-label use reports were related to the use of the scan for estimating the risk of MCI progression.

Table 27. Off-label use of the Amyvid PET scan - Modified analysis

	Italy (n=34)	Spain (n=59)	UK (n=250)	Total[d] (n=343)
Total patients indicating on-label use (modified analysis)	22 (64.7%)	37 (62.7%)	182 (72.8%)	241 (70.3%)
Total patients indicating off-label use (modified analysis)	12 (35.3%)	22 (37.3%)	68 (27.2%)	102 (29.7%)
Categories of off-label use				
I- Not consistent with use of scan as part of a clinical evaluation for cognitive impairment[a]	**12 (35.3%)**	**22 (37.3%)**	**66 (26.4%)**	**100 (29.2%)**
Q8 response includes uses for the purpose of monitoring or not related to clinical evaluation of the patient	12 (35.3%)	22 (37.3%)	66 (26.4%)	100 (29.2%)
Monitoring response to therapy	0 (0.0%)	0 (0.0%)	15 (6.0%)	15 (4.4%)
Estimating risk of MCI progression	12 (35.3%)	22 (37.3%)	48 (19.2%)	82 (23.9%)
Substitute for genetic testing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Substitute for clinical evaluation	0 (0.0%)	0 (0.0%)	1 (0.4%)	1 (0.3%)
Nonmedical use	0 (0.0%)	0 (0.0%)	3 (1.2%)	3 (0.9%)
Evaluation of amyloid status in an asymptomatic individual	0 (0.0%)	0 (0.0%)	2 (0.8%)	2 (0.6%)
II- Not consistent with the indicated population[b]	**0 (0.0%)**	**0 (0.0%)**	**4 (1.6%)**	**4 (1.2%)**
Q2 age <= 18 years old	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal cognition	0 (0.0%)	0 (0.0%)	4 (1.6%)	4 (1.2%)
III- Not consistent with use of scan for AD or other cause of cognitive impairment[c]	**0 (0.0%)**	**0 (0.0%)**	**4 (1.6%)**	**4 (1.2%)**

[a]**Not consistent with use of scan as part of a clinical evaluation for cognitive impairment:** Q8: Only the following responses are off-label: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/ evaluation of amyloid status in an asymptomatic individual

[b]**Not consistent with the indicated population:** Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 AND ADAS-Cog <=9 AND any other reported test result considered normal after medical review AND Q9 = none AND Q11 = no

[c]**Not consistent with use of scan for AD or other cause of cognitive impairment:** Q9 = "none of the above" AND Q8 not off-label as described above.

[d] The following counts are reported for each category and reflect percentages out of the total n=343.

Table 28 summarises the inconsistent responses related to off-label use. Overall, inconsistent responses were reported in 81 patient reports (19.1%).

Specifically, inconsistent responses were identified in 58 (13.7%) patient reports, for which in Q8 the patient was reported to receive an Amyvid PET scan for asymptomatic reasons but then symptoms were reported for that patient. This inconsistency was more common in the UK (n=54; 16.6%) than in Italy (n=3; 8.1%) or Spain (n=1; 1.6%). As an example, some physicians reported non-normal cognitive status in Q5 (n=57; 13.4% of all patient reports) or an abnormal cognitive score in Q7 (n=34; 8.0% of all patient reports) for a patient that was classified as having an Amyvid PET scan prescribed for asymptomatic reasons (as indicated in Q8). Inconsistent responses were also identified in seven (1.7%) patient reports, for which the patients were reported to have normal cognitive status in Q5 but the cognitive test scores or other responses in other questions did not match the answer in Q5. For example, some patients were reported to have an abnormal cognitive score in Q7 (n=3; 0.7% of all patient reports), cognitive impairment in Q9 (n=7; 1.7% of all patient reports) or treatment for cognitive impairment in Q11 (n=5; 1.2%).

Additionally, inconsistent responses were identified in 20 (4.7%) patient reports, for which in Q8 the physician indicated the estimation of the risk of progression of MCI to dementia as a reason for referral, but the patient was already reported to be suffering from dementia in Q5.

Table 28. Summary of inconsistent responses related to off-label

Inconsistent responses	Italy	Spain	UK	Total
Q5 Reported normal cognitive status does not match cognitive test score or other responses	0 (0.0%)	0 (0.0%)	7 (2.1%)	7 (1.7%)
Q5 cognitive normal but Q7 reports abnormal cognitive score	0 (0.0%)	0 (0.0%)	3 (0.9%)	3 (0.7%)
Q5 cognitive normal but Q9 response indicates presence of cognitive impairment	0 (0.0%)	0 (0.0%)	7 (2.1%)	7 (1.7%)
Q5 cognitive normal but Q11 response indicates treatment for cognitive impairment	0 (0.0%)	0 (0.0%)	5 (1.5%)	5 (1.2%)
Q8 "asymptomatic" reasons but symptoms reported	3 (8.1%)	1 (1.6%)	54 (16.6%)	58 (13.7%)
Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment	3 (8.1%)	1 (1.6%)	53 (16.3%)	57 (13.4%)
Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score	0 (0.0%)	0 (0.0%)	34 (10.4%)	34 (8.0%)
Q8 Estimating risk of progression of MCI to dementia when the subject is already demented	0 (0.0%)	1 (1.6%)	19 (5.8%)	20 (4.7%)
Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia	0 (0.0%)	1 (1.6%)	19 (5.8%)	20 (4.7%)

Exclusion of case from Q5 - Reported normal cognitive status does not match cognitive test score or other responses - Q5 cognitive normal but Q7 reports abnormal cognitive score: Q5 response = "Normal Cognition" AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review; Q5 cognitive normal but Q9 response indicates presence of cognitive impairment: Q5 response = "Normal Cognition" AND Q9 includes any response except "none of the above"; Q5 cognitive normal but Q11 indicates treatment for cognitive impairment: Q5 response = "Normal Cognition" AND Q11 response = "Yes" for either medication

Exclusion of case from Q8 - "Asymptomatic" reasons were checked but symptoms reported - Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment: Q8 = see footnote* AND Q5 response NOT "Normal Cognition"; Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score: Q8 = see footnote* AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review

Exclusion of case from Q8 - Estimating risk of progression of MCI to dementia when the subject is already demented - Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia: Q8 response = "For estimating risk of MCI progression to clinical Alzheimer's disease" AND Q5 response = mild or moderate or severe dementia

*Footnote: Q8 "asymptomatic" reasons include any of the following:

-As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier.

-As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin 1, presenilin 2 or amyloid precursor protein).
-As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors.

10.5. Other analyses

Refer to Annex 1. Other analyses.

10.6. Adverse events/adverse reactions

No information on AEs/ARs was specifically collected as part of the study.

11. Discussion

11.1. Key results

This physician survey was implemented to assess the usage patterns of Amyvid and the level of off-label use in European clinical practice. The results presented below reflect the per protocol analysis (raw data) unless stated otherwise.

Physician profile

Overall, 109 physicians volunteered to participate in the survey, including 85 (78%) physicians in the UK, 13 (12%) in Spain and 11 (10%) in Italy. On average, they had 14.2 years of experience in current practice and were mostly neurologists (n=52; 47.7%) or psychiatrists (n= 32; 29.4%). The vast majority (n=92; 84.4%) had formal training on management of patients with cognitive impairment and almost all (n=107; 98.2%) managed patients with AD or other causes of dementia as part of their practice.

Awareness of Amyvid indication

Almost all physicians (n=107; 98.2%) correctly stated that the Amyvid approved indication included the evaluation of patients with cognitive decline for AD or other causes of dementia. However, the majority also agreed with the statement that the approved indication included: 'for estimating the risk of MCI progression to clinical AD' (n=83; 76.1%), and nearly half agreed that it included 'for monitoring the response to therapy in patients with AD' (n=53; 48.6%) and 'for risk stratification in asymptomatic individuals, such as relatives of AD patients' (n= 52; 47.7%).

Referred patient's profile

Only a small proportion of patients referred for an Amyvid PET scan were reported to be cognitively normal (n=11; 2.6%), although 13.7% (n=58) were reported to have expressed cognitive complaints without cognitive impairment on examination. The remaining patients had an objectively verified impairment ranging from MCI through severe dementia (n=355; 83.7%). Consistent with a role for Amyvid in differential diagnosis (to rule out AD), the majority of off-label findings were reported among patients who were consistent with an atypical AD or non-AD syndrome, including prominent fluctuations in cognition (n=97; 22.9%), prominent changes in

personality, behaviour or comportment (n=96; 22.6%), prominent language disturbance without memory loss (n=42; 9.9%), visual hallucinations (n=50; 11.8%) and parkinsonism (n=43; 10.1%).

Possible diagnoses prior to PET scan included both AD (n=258; 60.8%) and non-AD sources of impairment (e.g., vascular dementia [n=87; 20.5%], other neurodegenerative dementia [n=123; 29.0%], dementia with uncertain diagnosis [n=86; 20.3%]). Importantly, only 1.4% (n=6) of subjects had possible diagnoses not consistent with one of the listed potential causes of cognitive impairment.

Use of the Amyvid PET scan

Among the 424 patients reported in this survey, 63.2% (n=268) of referrals for an Amyvid scan did not meet the protocol-defined criteria for on-label use. Although in 55.9% (n=237) of cases the reasons reported for the referrals correctly included 'As part of the evaluation of a patient with cognitive decline documented on clinical examination', other response options were checked instead of this option in a substantial number of cases (44.1%; n=187). Additionally, responses not meeting the per protocol definition of on-label use, such as 'Estimating risk of MCI progression to clinical AD', checked in addition to, or instead of, 'As part of the evaluation of a patient with cognitive decline documented on clinical examination' also contributed to the observed level of off-label use. When internally inconsistent responses were removed (Modified analysis) and additional information (i.e., responses to Q9 and Q11) considered to include all cases consistent with the use of the Amyvid PET scan as part of a clinical or diagnostic evaluation in adult symptomatic individuals, 29.7% (n=102) of the reported referrals did not meet the modified criteria for on-label use. Within this modified definition of off-label use, the single greatest reason accounting for the 23.9% total off-label use (n=82) was the reported use of the scan to estimate risk of MCI progression.

In addition to the primary objectives, this survey also collected information on changes in diagnosis and management after Amyvid PET. Physicians reported changing their diagnosis or treatment 67.2% of the time (n=285) and changing their medical management plan in 32.3% of the time (n=137).

11.2. Limitations

Due to its nature and many challenges faced for identifying and enrolling new pharmaceutical products' prescribers, this study has several limitations.

First, the representativeness of the physician sample who responded to the survey and the subsequent generalisability of the results is difficult to evaluate. This is a well-known limitation of studies that rely on volunteer participants. Volunteer bias occurs if the responses provided differ in an important way from the responses that would have been provided by those who chose note to participate. The direction of any potential volunteer bias on the results could lead to the sample not being representative, or exaggerating some findings of the study (7). In this survey, we noticed that the patients reported appeared to be younger and have fewer comorbidities than the typical AD community sample or AD clinical trial subjects (19, 20). Ultimately, since information on non-participants was not available, and because of the very small sample size in two of the three countries (Spain and Italy), the potential for selection bias cannot be discarded.

Second, the design of some of the questions of the survey may have led to some inconsistent responses that could have impacted the validity and reliability of the survey. Although the questionnaire was based on the Amyvid SmPC, some questions may have been interpreted differently by respondents than it was intended. This seems especially likely given the high proportion of internally inconsistent answers detected. Inconsistent responses were found in up to 19% (n=81/424) of the reports of patients referred. For example, in Q8 physicians reported 'asymptomatic' reasons for scan referral but they also reported cognitive symptoms for the same patient in Q5 or Q7. In addition, in an effort to increase sensitivity, some key questions for the identification of off-label use allowed multiple responses when there was only one on-label response (e.g., in Q8). This may have led physicians to provide additional responses beyond the response consistent with the 'correct' indication. This could be interpreted as a bias caused by a leading question, i.e., different wordings of the same question could guide or direct respondents towards a different answer (8). The presence of these internal inconsistencies suggests the possibility of a significant misclassification bias, but we cannot ascertain the direction, i.e., some off-label reported uses might have been on-label, or the opposite.

11.3. Interpretation

Awareness of Amyvid indication

Almost all physicians (n=107; 98.2%) correctly agreed with the approved indication for Amyvid: the evaluation of patients with cognitive decline for AD or other causes of dementia. However, 76.1% (n=83) also erroneously agreed that the Amyvid approved indication included: 'for estimating the risk of MCI progression to clinical AD', and nearly half agreed with other non-approved indications: 'for monitoring the response to therapy in patients with AD' (n=53; 48.6%), despite the lack of existence of approved therapies with an impact on β-amyloid, and 'for risk stratification in asymptomatic individuals, such as relatives of AD patients' (n=52; 47.7%).

Amyvid is indicated in patients with cognitive impairment and the warning and precautions section of the SmPC states that the efficacy of Amyvid for predicting development of AD has not been established. The finding that a majority of physicians agreed with the statement that Amyvid may also be used for estimating the risk of MCI progression to clinical AD and for risk stratification in asymptomatic individuals may reflect a lack of knowledge/misunderstanding of the label, but it could possibly also reflect physicians' awareness of evolving scientific literature on differing rates of progression of cognitive impairment in amyloid positive and amyloid negative patients (9-12). Given the complexity and multiplicity of factors that may influence the expression of cognitive decline in elderly individuals with AD pathology (13, 14) and the relatively slow rate of progression from clinically normal or MCI to dementia (estimated as 10 to 20 years [15, 21]), it is unlikely that any diagnostic test or combination of tests will achieve a level of sensitivity and specificity to predict the development of AD in individual patients. However, the survey responses may reflect an evidence-based belief that, when used as part of a comprehensive evaluation, and particularly when taken together with biomarker evidence of neurodegeneration, the result of amyloid PET scans may be helpful in estimating the probability and likely future rate of cognitive deterioration (9, 10, 12, 14).

It is important to note that, in contrast to their awareness of the indication, only 27.1% (n=115) of physicians reported referring patients for Amyvid PET for predicting risk of development of AD in clinical practice. Use of Amyvid was reported in a modest proportion of asymptomatic patients in clinical practice (only 2.6% [n=11] of subjects referred for Amyvid PET scan were

reported to have normal cognition and 13.7% (n=58) were reported to have a cognitive complaint without cognitive impairment on examination).

The finding that 48.6% of physicians agreed with the statement that amyloid PET may be used to monitor response to therapy is unexpected, given the lack of approved therapies with an impact on β-amyloid. The warning and precautions section of the SmPC states that the efficacy of Amyvid for monitoring response to therapy has not been established. Indeed, there is no evidence that amyloid PET is of any value in monitoring efficacy of approved therapeutics such as cholinesterase inhibitors and memantine. However, during the period that this survey was conducted, considerable media attention focused on the finding from a small Phase II study (22), that experimental anti-amyloid therapies, such as aducanumab, can reduce amyloid plaque load as assessed by Amyvid PET, and there was some question whether this reduction in plaque load was associated with a reduction in rate of cognitive deterioration. During the same period, serial amyloid imaging was incorporated into a number of other prominent anti-amyloid therapeutic trials. The results of this survey could reflect confusion between these research uses with appropriate clinical use. Again, reported use of Amyvid PET for this purpose in clinical practice was substantially lower than what might have been suggested by the percent of physicians agreeing to this use (5.4% [n=23] of physicians reported that at least one of the reasons for referring a patient was 'for monitoring response to therapy').

When the understanding of PET scan results was assessed, 84.4% (n=92) of physicians correctly agreed with the statement that a positive scan may be consistent with AD, but does not independently establish a diagnosis of this disease, and 72.5% (n=79) also agreed with the true statement that a negative scan is not consistent with a diagnosis of AD. These results follow the trend seen in previous clinical trials, toward a change in diagnosis after positive and negative scans, in which physicians were more willing to endorse an AD diagnosis after a positive amyloid scan, than to reject an AD diagnosis after a negative scan, regardless of the initial diagnosis (16, 17). This may seem counter-intuitive since the absence of amyloid at autopsy is sufficient to rule out AD, whereas the presence of amyloid is not itself sufficient to rule in AD. The observed result may reflect a greater technical confidence in a positive than in a negative scan interpretation; e.g., the physicians may assume that sometimes a negative scan occurs because the patient is in early stages of disease and pathophysiology, and is just below the threshold for detection on an amyloid PET scan. It is also important to note that in this study, this

interpretation is from the referring physician, rather than from the imaging physician, who may have a higher confidence and better understanding of the PET results.

In contrast to the relatively high correct evaluation of the clinical/diagnostic implications of an amyloid PET scan, only 52.3% (n=57) of respondents endorsed the correct statement that a positive scan indicates moderate to frequent plaques and 7.3% (n=8) incorrectly agreed with the statement that a positive scan would indicate sparse or no plaques. Together these findings suggest that although practicing physicians have a good understanding of the clinical implications of amyloid burden as assessed by a PET scan (e.g., a positive scan indicates an amyloid plaque burden that may be consistent with AD), their understanding of the histologic criteria for AD pathology may be more limited. This result is not completely unexpected since the practicing dementia specialists will only be required to interpret the positive or negative scan results provided by the nuclear imaging physicians.

Referred patient's profile

Physicians reported information on a total of 424 patients, including 326 (76.9%) in the UK, 61 (14.4%) in Spain and 37 (8.7%) in Italy. All patients were adults (i.e., no evidence of use in paediatric subjects) and their mean age was 67.9 years. A mean of ten months elapsed since patients first presented to the physician with the complaint or symptom until they were referred for an Amyvid PET scan. Only 2.6% (n=11) of subjects referred for Amyvid PET scan were reported to be cognitively normal. The remaining patients either had an objectively verified impairment ranging from MCI through severe dementia (n=355; 83.7%) or expressed cognitive complaints without cognitive impairment on examination (n=58; 13.7%). Consistent with a role of Amyvid in differential diagnosis (to rule out AD), the majority of off-label findings were reported in patients who were consistent with an atypical AD or non-AD syndrome, including prominent fluctuations in cognition (n=97; 22.9%), prominent changes in personality, behaviour or comportment (n=96; 22.6%), prominent language disturbance without memory loss (n=42; 9.9%), visual hallucinations (n=50; 11.8%) and parkinsonism (n=43; 10.1%).

Possible diagnoses prior to PET scan included both AD (n=258; 60.8%) and non-AD sources of impairment (e.g., vascular dementia [n=87; 20.5%], other neurodegenerative dementia [n=123; 29.0%], dementia with uncertain diagnosis [n=86; 20.3%]). Importantly, only 1.4% (n=6) of

subjects had possible diagnoses not consistent with one of the listed potential causes of cognitive impairment.

Most patients had undergone other clinical assessments prior to the Amyvid PET scan: 97.2% (n=412) had a cognitive test, mainly the MMSE test (87.4%), and 80.9% (n=343) had laboratory tests, mainly clinical imaging (83.4% of the patients who had a laboratory test performed; n=286) or blood or urine tests (82.5% of the patients who had a laboratory test performed; n=283). Thus, the reported patient characteristics suggest that the vast majority of patients who received Amyvid PET scans in clinical practice had some type of cognitive impairment (97.4% [n=413] had either cognitive complaint or objectively verified cognitive impairment, 98.6% [n=418] had a working diagnosis consistent with cognitive impairment, and 80.9% [n=343] had received neuropsychological evaluation and laboratory tests/investigations consistent with a diagnostic evaluation). Taken together, these results suggest that the majority of patients had a clinical profile in line with the approved label; i.e., as part of a clinical evaluation for adult patients with cognitive impairment who are being evaluated for AD and other causes of cognitive impairment.

Off-label use of the Amyvid PET scan

The most likely reasons for off-label use of Amyvid were expected to result from physicians using Amyvid for monitoring response to anti-AD therapy or for estimating β-amyloid density to predict prognosis in patients with early symptoms of cognitive impairment (i.e., to predict progression of AD). At the time this survey was designed, Lilly anticipated that a treatment for AD that targeted β-amyloid would have become available to patients. No such therapy is currently available, however, so the potential to use Amyvid to monitor response to treatment in clinical practice is limited. Interestingly, even in the absence of such a therapy, 48.6% of physicians (n=53) agreed that the indication included monitoring response to therapy in patients with AD. When the reasons for referring patients for an Amyvid PET scan were reported, though, only 5.4% (n=23) of patient reports were off-label as a result of selecting monitoring as the reason for the referral. The survey did not collect information about what therapy this would have been in regards to.

The second reason for concern over off-label use was the potential that physicians might use Amyvid to estimate progression in patients with early symptoms of cognitive impairment.

Although 76.1% of physicians (n=83) incorrectly agreed that estimating the risk of MCI progression to clinical AD was part of the approved indication for Amyvid, only in 27.1% (n=115) of patients' records it was noted that estimating the risk of MCI progression to clinical AD was the reason for referring patients for Amyvid scans. With regard to off-label use, based on the protocol-defined criteria for off-label use, physicians who responded to the survey reported off-label use in 63.2% (268/424) of patients they referred for Amyvid PET scans. Considering the experience and awareness of the indication of the referring physicians and the evidence that appropriate patients were being referred for an Amyvid scan, it is surprising that in 63.2% of cases the physician-reported reason for ordering an Amyvid scan did not meet the protocol-defined criteria for on-label use. One explanation may be an overly strict protocol definition of on-label use (only referral as part of the evaluation of cognitive decline documented on clinical examination was considered on-label per protocol and if additional uses not related to clinical evaluation were reported the case was considered off-label). Alternatively, there may have been a difference between the interpretation of the response alternatives anticipated by the protocol and the interpretations used by the survey respondents. Examination of individual reasons for scan referral revealed that in 55.9% of cases (n=237) physicians correctly included 'As part of the evaluation of a patient with cognitive decline documented on a clinical examination' among the reasons for ordering a scan. However, other response options were checked instead of this option in a substantial number of cases (44.1%; n=187/424). Additionally, responses not meeting the per protocol definition of on-label use, such as 'Estimating risk of MCI progression to clinical AD', checked in addition to, or instead of, the correct indication 'As part of the evaluation of a patient with cognitive decline documented on a clinical examination' also contributed to the observed level of off-label use. For example the response option, 'As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination' was endorsed as at least one of the reasons for referral in 19.6% of cases (n=83). This option was considered off-label in the protocol because it was intended to identify scans performed in subjects who had cognitive complaints, but were determined to be cognitively normal. However, since working diagnoses at the time of the scan endorsed some form/aetiology of cognitive impairment in 98.6% of cases (n=418), it seems likely the physicians did not interpret this option in the way that was anticipated. This option may have been used

instead for patients with cognitive decline from previous levels, but still within normal limits in objective tests, which would have been considered on-label by the protocol.

The response option 'As part of an evaluation of the severity of dementia' was endorsed as at least one of the reasons for referrals in 17.0% of cases (n=72). This option was intended to reflect inappropriate use of an Amyvid scan as a measure of severity of disease, however, the survey language was not that specific, i.e., 'as part of an evaluation of', and physicians may have endorsed this response in cases where they were trying to make a diagnosis in patients at the border between MCI and dementia/AD. Consistent with this hypothesis, physicians reported ordering scans to 'establish a diagnosis of AD based on a positive scan result' in 42.5% of cases (n=180). A positive Amyvid scan does not independently establish a diagnosis of AD; however, when used as directed, in conjunction with clinical evaluation, a positive Amyvid scan may provide diagnostically important information, specifically confirming the presence of moderate to frequent neuritic plaques. Given that the patient profiles as described above suggest that the vast majority of patients were in fact undergoing a clinical evaluation (97.2% [n=412] underwent cognitive testing and 80.9% [n=343] underwent laboratory testing) these results may reflect the use of the Amyvid scan to aid in diagnosis in the context of a clinical evaluation, in accordance with recent diagnostic guidelines (18).

Physicians also reported ordering Amyvid PET scans 'As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be an apoE4 carrier' in 7.3% of cases (n=31), 'As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease' in 3.1% of cases (n=13), and 'As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors' in 5.2% of cases (n=22). Although these are clearly off-label as written, it is again curious how 3-7% cases (n=13-31) (or more cumulatively) could be considered asymptomatic when 98.6% (n=418) of cases had a working diagnosis indicating some form or etiology of cognitive impairment.

Finally, a small number of physicians reported ordering the scan 'as a substitute for clinical evaluation' in 0.7% (n=3), and 'for a non-medical use' in 0.9% (n=4) of cases. These uses are clearly not consistent with the label but represent a small minority of the total cases.

A modified analysis was also conducted where cases with internally inconsistent responses (19.1%; n=81) were excluded, and on-label use was defined more broadly to include all cases consistent with the use of the amyloid PET scan as part of a clinical or diagnostic evaluation in adult symptomatic individuals. In this modified analysis the proportion of off-label use decreased from 63.2% (n=268) in the original per protocol analysis to 29.7% (n=102). The largest proportion of total off-label use in this modified analysis (23.9%; n=82) was attributable to estimating risk of MCI progression, which as discussed above may reflect physician's awareness of the evolving literature.

Although not the primary objective of the study, the survey also collected information on changes in diagnosis and management after Amyvid PET. The physicians reported overall change in diagnosis or treatment in 285 of 424 cases (67.2%) and changing medical management plan post-scan in 137 of 424 cases (32.3%). These results are also consistent with the previous findings regarding impact of amyloid PET in prospective clinical trials and clinical use (16, 17, 23). Together, these results suggest amyloid PET may have an important utility in influencing clinical decision making and patient care.

11.4. Generalisability

The generalisability of this survey is limited by the ability to sample the population of physicians who are eligible to prescribe Amyvid in each EU country. In the UK, the survey sampled a large proportion of the referring physicians during the period of the survey, therefore the results may be reasonably generalizable to other UK physicians who are referring patients for Amyvid scans. As physicians in Italy and Spain represented only a small portion of all referring physicians available, the applicability of the survey results to physicians in those regions is unclear. In all countries, the survey is limited by the requirement to invite only physicians who have previously agreed to be contacted. Finally, this survey relied on volunteer participation. The responses of volunteers may differ from those who did not participate in the survey, but no information is available on those who declined to participate so this difference cannot be assessed. Overall, the results obtained from this survey may be generally representative of UK referring physicians but generalisability to other European referrers cannot be ensured.

12. Other Information

Not applicable.

13. Conclusion

Almost all clinicians surveyed correctly agreed with the approved indication for florbetapir, but results from the survey revealed two important areas where clinicians reported off-label use: monitoring response to therapy and estimating prognosis in patients with early symptoms of cognitive impairment. Since no approved therapies are currently available, the rationale for using Amyvid to monitor treatment response is unclear. Although three-quarters of physicians agreed that prognostic use of Amyvid, that is, to estimate the risk of MCI progression to clinical AD, was included in the approved indication, only a little over a quarter actually reported referring patients for this reason.

Despite the almost universal awareness of the Amyvid approved indication, per protocol evaluation of reported reasons for requesting an Amyvid PET scan suggested a high degree of off-label use (n=268; 63.2%). This high proportion of off-label use may suggest that clinicians are familiar with research applications of florbetapir and use these applications in their clinical practice despite the limitation of use in the SmPC, and/or that some clinicians may not have noted the limitations of use currently included in the SmPC.

It is possible that at least some of these responses were affected by misinterpretation of the survey questions. This is supported by the high proportion (n=81; 19.1%) of internally inconsistent responses found across survey questions. When inconsistent responses were excluded and on-label defined more broadly to include information on all cases consistent with the use of the Amyvid as part of a clinical or diagnostic scan, off-label use fell to 29.7% (n=102), but this result should be interpreted cautiously.

14. References

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Annex 1. Other analyses

Additional tables were developed stratifying by physician´s characteristics including: physician´s specialty, proportion of time dedicated by the physicians to the management of patients with Alzheimer's disease (AD) or other causes of dementia, number of patients with cognitive complaints that the physicians have in their practices, and number of patients ever referred by the physicians for and Amyvid PET scan. Tables are presented below in sections 1, 2, 3, 4, respectively.

Additionally, a listing showing patient cases considered to be off-label use for no clinical evaluation as per protocol with evidence of ongoing evaluation from detailed analysis is presented further below (see section 5).

1. Stratification by physician´s specialty

Table 29. Patient sociodemographic information

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Sex						
Female	7 (46.7%)	38 (54.3%)	116 (54.5%)	49 (46.2%)	5 (25.0%)	215 (50.7%)
Male	8 (53.3%)	32 (45.7%)	97 (45.5%)	56 (52.8%)	15 (75.0%)	208 (49.1%)
Don't know/ recall				1 (0.9%)		1 (0.2%)
valid n	*15*	*70*	*213*	*106*	*20*	*424*
Age (at the time of having Amyvid PET scan)						
Mean	73.5	72.6	68.0	63.0	70.5	67.9
(SD)	(8.2)	(9.0)	(12.2)	(8.5)	(10.5)	(11.2)
Median	72.0	72.0	69.0	63.0	72.0	68.0
(P25;P75)	(69.0; 78.0)	(67.0; 79.0)	(60.0; 76.0)	(58.0; 68.5)	(61.0; 80.5)	(60.0; 76.0)
(Min; Max)	(60.0; 90.0)	(52.0; 92.0)	(30.0; 100.0)	(39.0; 81.0)	(52.0; 84.0)	(30.0; 100.0)
valid n	*14*	*68*	*211*	*96*	*20*	*409*

[a]Question: What is the patient's gender? / How old was the patient at the time of having the Amyvid PET scan? Please write exact age, in years or Do Not Know.

Table 30. Time elapsed, in months, since the patient first presented to physician with the complaint/ symptom that led to physician referral for an Amyvid PET scan presented

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Mean	8.1	7.9	10.4	9.2	15.9	10.0
(SD)	(7.5)	(8.0)	(11.2)	(10.1)	(11.5)	(10.5)
Median	4.0	6.0	6.0	6.0	12.0	6.0
(P25;P75)	(3.0; 12.0)	(3.0; 12.0)	(3.0; 12.0)	(4.0; 9.0)	(8.0; 24.0)	(3.0; 12.0)
(Min; Max)	(2.0;24.0)	(1.0; 36.0)	(0.0; 60.0)	(0.0; 60.0)	(1.0; 36.0)	(0.0; 60.0)
valid n	*15*	*45*	*193*	*71*	*17*	*341*

[a]Question: How much time (months) has elapsed since the patient first presented to you with the complaint/ symptom that led to your referral for an Amyvid scan?

Table 31. Patient's cognitive status at the time of the Amyvid PET scan

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)	Overall, as reported[b] (n=424)
Normal cognition			4 (1.9%)			4 (1.0%)	11 (2.6%)
Cognitive complaint without cognitive impairment on examination	1 (6.7%)	17 (24.3%)	17 (8.2%)	18 (17.1%)	5 (25.0%)	58 (13.9%)	58 (13.7%)

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)	Overall, as reported[b] (n=424)
Mild cognitive impairment	6 (40.0%)	21 (30.0%)	95 (45.9%)	48 (45.7%)	11 (55.0%)	181 (43.4%)	181 (42.7%)
Mild dementia	6 (40.0%)	20 (28.6%)	67 (32.4%)	28 (26.7%)	2 (20.0%)	123 (29.5%)	123 (29.0%)
Moderate dementia	2 (13.3%)	9 (12.9%)	19 (9.2%)	10 (9.5%)	2 (20.0%)	42 (10.1%)	42 (9.9%)
Severe dementia		3 (4.3%)	5 (2.4%)	1 (1.0%)		9 (2.2%)	9 (2.1%)
valid n	*15*	*70*	*207*	*105*	*20*	*417*	*424*

[a]Question: At the time of the Amyvid PET scan, what was the patient's cognitive status?
[b]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 42)

Table 32. Findings at the time of the Amyvid PET scan

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Impairment in activities of daily living due to cognitive impairment	4 (26.7%)	20 (28.6%)	78 (36.6%)	53 (50.0%)	8 (40.0%)	163 (38.4%)
Parkinsonism	3 (20.0%)	6 (8.6%)	25 (11.7%)	8 (7.5%)	1 (5.0%)	43 (10.1%)
Visual hallucinations	2 (13.3%)	10 (14.3%)	26 (12.2%)	12 (11.3%)		50 (11.8%)
Prominent fluctuations in cognitive function	2 (13.3%)	16 (22.9%)	46 (21.6%)	30 (28.3%)	3 (15.0%)	97 (22.9%)
Prominent changes in personality, behavior or comportment	3 (20.0%)	12 (17.1%)	49 (23.0%)	26 (24.5%)	6 (30.0%)	96 (22.6%)
Prominent language disturbance without memory loss	3 (20.0%)	7 (10.0%)	21 (9.9%)	10 (9.4%)	1 (5.0%)	42 (9.9%)
Substantial concomitant cerebrovascular disease	1 (6.7%)	4 (5.7%)	17 (8.0%)	4 (3.8%)	2 (10.0%)	28 (6.6%)
None of the above	2 (13.3%)	22 (31.4%)	42 (19.7%)	24 (22.6%)	9 (45.0%)	99 (23.3%)

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following findings (Mark all that apply)?
[b]Multiple response question; one patient can have more than one finding

Table 33. Description of tests performed specifically to measure cognitive function

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
No	4 (26.7%)	1 (1.4%)	2 (0.9%)	1 (0.9%)	4 (20.0%)	12 (2.8%)
Yes	11 (73.3%)	69 (98.6%)	211 (99.1%)	105 (99.1%)	16 (80.0%)	412 (97.2%)
Valid n	*15*	*70*	*213*	*106*	*20*	*424*
Type of test performed						
MMSE	10 (66.7%)	56 (80.0%)	196 (92.0%)	83 (78.3%)	15 (75.0%)	360 (84.9%)
Mean	21.1	23.5	24.6	22.3	26.8	23.9
(SD)	(2.2)	(5.7)	(3.6)	(5.0)	(2.3)	(4.4)
Median	20.0	25.0	25.0	22.0	27.0	25.0
(P25;P75)	(20.0; 22.0)	(20.0;28.0)	(24.0; 27.0)	(20.6; 26.0)	(25.0; 29.0)	(22.0; 27.0)
(Min; Max)	(18.0; 25.0)	(3.0; 30.0)	(8.0; 30.0)	(5.0; 30.0)	(23.0; 30.0)	(3.0; 30.0)
Valid n	*9*	*54*	*177*	*68*	*15*	*323*
ADAS-cog	1 (6.7%)	9 (12.9%)	31 (14.6%)	30 (28.3%)		71 (16.7%)
Mean	15.0	34.9	29.2	17.0		28.5
(SD)	(0.0)	(22.1)	(19.0)	(8.8)		(19.1)
Median	15.0	32.0	23.0	18.0		21.5
(P25;P75)	(15.0; 15.0)	(15.0; 55.0)	(18.0; 54.0)	(8.0; 24.0)		(15.0; 45.0)
(Min; Max)	(15.0; 15.0)	(9.0; 66.0)	(5.0; 63.0)	(8.0; 27.0)		(5.0; 66.0)
Valid n	*1*	*9*	*19*	*5*		*34*
Other		11 (15.9%)	62 (29.4%)	37 (35.2%)	1 (6.3%)	111 (26.9%)
ACE		4 (5.7%)	6 (2.8%)	27 (25.5%)		37 (9.0%)
Memory tests			25 (11.7%)	5 (4.7%)		30 (7.3%)
NPS battery			8 (3.8%)	5 (4.7%)		13 (3.2%)
Stroop			11 (5.2%)			11 (2.7%)
Orientation tests			8 (3.8%)			8 (1.9%)
Boston Naming Test			7 (3.3%)			7 (1.7%)
Other		7 (10.1%)	33 (15.6%)	11 (10.5%)	1 (6.3%)	52 (12.6%)
Valid n	*11*	*69*	*211*	*105*	*16*	*412*

[a]Question: Prior to the Amyvid PET scan, did the patient have any tests which were designed specifically to measure cognitive function? If yes, please specify below / What was the result of this test?

Table 34. Reasons for referring the patient for an Amyvid PET scan

Question[a,b]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)	Overall, as reported (n=424)[c]
As part of the evaluation of a patient with	6 (60.0%)	37 (66.1%)	95 (51.9%)	56 (66.7%)	9 (56.3%)	203 (58.2%)	237 (55.9%)

Question[a,b]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)	Overall, as reported (n=424)[c]
cognitive decline documented on clinical examination							
As part of an evaluation of the severity of dementia	3 (30.0%)	15 (26.8%)	24 (13.1%)	10 (11.9%)	1 (6.3%)	53 (15.2%)	72 (17.0%)
As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier			2 (1.1%)			2 (0.6%)	31 (7.3%)
For monitoring response to therapy		4 (7.1%)	8 (4.4%)	4 (4.8%)		16 (4.6%)	23 (5.4%)
As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination	1 (10.0%)	15 (26.8%)	19 (10.4%)	20 (23.8%)	4 (25.0%)	59 (16.9%)	83 (19.6%)
For estimating risk of MCI progression to clinical Alzheimer's disease	1 (10.0%)	14 (25.0%)	49 (26.8%)	18 (21.4%)	1 (6.3%)	83 (23.8%)	115 (27.1%)
To establish a diagnosis of Alzheimer's disease based on a positive scan result	3 (30.0%)	17 (30.4%)	88 (48.1%)	40 (47.6%)	8 (50.0%)	156 (44.7%)	180 (42.5%)
As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)							13 (3.1%)
As a substitute for clinical evaluation			1 (0.5%)			1 (0.3%)	3 (0.7%)
As part of an assessment of Alzheimer's disease in an asymptomatic			1 (0.5%)			1 (0.3%)	22 (5.2%)

Question[a,b]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)	Overall, as reported (n=424)[c]
individual without other risk factors							
For a non-medical use (e.g., insurance coverage, legal or employment-related reasons)			1 (0.5%)	2 (2.4%)		3 (0.9%)	4 (0.9%)
Other		1 (1.8%)	6 (3.3%)	1 (1.2%)		8 (2.3%)	9 (2.1%)
Investigation			5 (2.7%)	1 (1.2%)		6 (1.7%)	7 (1.7%)
Differential diagnosis		1 (1.8%)	1 (0.5%)			2 (0.6%)	2 (0.5%)
valid n	*10*	*56*	*183*	*84*	*16*	*349*	*424*

[a]Question: When you referred the patient for an Amyvid PET scan, what was the reason for the referral? Mark all that apply.
[b]Multiple response question
[c]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 42)

Table 35. Possible diagnosis at the time of the Amyvid PET scan before receiving the scan results

Question[a,b]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Mild cognitive impairment	6 (40.0%)	36 (51.4%)	88 (41.3%)	54 (50.9%)	14 (70.0%)	198 (46.7%)
Vascular dementia	3 (20.0%)	17 (24.3%)	39 (18.3%)	22 (20.8%)	6 (30.0%)	87 (20.5%)
Alzheimer's disease	6 (40.0%)	38 (54.3%)	132 (62.0%)	68 (64.2%)	14 (70.0%)	258 (60.8%)
Other neurodegenerative dementia , (e.g., Lewy body dementia, frontotemporal dementia)	2 (13.3%)	17 (24.3%)	69 (32.4%)	30 (28.3%)	5 (25.0%)	123 (29.0%)
Dementia with unknown/uncertain diagnosis		12 (17.1%)	40 (18.8%)	32 (30.2%)	2 (10.0%)	86 (20.3%)
Other dementia diagnosis			16 (7.5%)	2 (1.9%)	1 (5.0%)	19 (4.5%)
Depressive Pseudodementia			8 (3.8%)	1 (0.9%)	1 (5.0%)	10 (2.4%)

Question[a,b]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Depression			6 (2.8%)	1 (0.9%)		7 (1.7%)
Alcoholism			2 (0.9%)			2 (0.5%)
Anxiety			2 (0.9%)			2 (0.5%)
Cerebral Amyloid Angiopathy			1 (0.5%)			1 (0.2%)
Limbic encephalitis			1 (0.5%)			1 (0.2%)
None of the above	1 (6.7%)		4 (1.9%)	1 (0.9%)		6 (1.4%)

[a]Question: At the time of the Amyvid PET scan, but before receiving the scan results, which of the following were included in your possible diagnosis? (Mark all that apply.)
[b]Multiple response question.

Table 36. Laboratory tests ordered prior to the Amyvid PET scan

Question[a,b]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
No	4 (26.7%)	9 (12.9%)	19 (8.9%)	14 (13.2%)	14 (70.0%)	60 (14.2%)
Yes	8 (53.3%)	61 (87.2%)	183 (85.9%)	86 (81.1%)	5 (25.0%)	343 (80.9%)
Don't know/ recall	3 (20.0%)		11 (5.2%)	6 (5.7%)	1 (5.0%)	21 (5.0%)
valid n	*15*	*70*	*213*	*106*	*20*	*424*
Type of Laboratory tests ordered[b]						
Clinical imaging e.g., CT, MRI	2 (25.0%)	54 (88.5%)	157 (85.8%)	68 (79.1%)	5 (100.0%)	286 (83.4%)
Scan using an imaging agent, e.g., PET or SPECT scan	3 (37.5%)	9 (14.8%)	70 (38.3%)	20 (23.3%)	5 (100.0%)	107 (31.2%)
Lumbar puncture	3 (37.5%)	15 (24.6%)	64 (35.0%)	4 (4.7%)		86 (25.1%)
Lab tests from blood or urine, e.g., CBC, B12, serum chemistry, etc.	6 (75.0%)	49 (80.3%)	139 (76.0%)	84 (97.7%)	5 (100.0%)	283 (82.5%)
Genetic testing, e.g., ApoE or other		4 (6.6%)	26 (14.2%)	13 (15.1%)		43 (12.5%)
Neuropsychological testing	3 (37.5%)	21 (34.4%)	116 (63.4%)	73 (84.9%)	5 (100.0%)	218 (63.6%)
valid n	*8*	*61*	*183*	*86*	*5*	*343*

[a]Question: Regarding your intended management plan for this patient prior to the Amyvid scan, did you order any laboratory tests? (Y/N) If yes, please mark the tests you ordered

[b]Multiple response question.

Table 37. Medication received since they first sought treatment for cognitive impairment

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Acetylcholinesterase inhibitor [donepezil (Aricept), rivastigmine (Exelon), or galantamine (Nivalin, Lycoremine, Razadyne)]						
No	11 (73.3%)	45 (64.3%)	108 (50.7%)	80 (75.5%)	15 (75.0%)	259 (61.1%)
Yes	4 (26.7%)	24 (34.3%)	100 (46.9%)	19 (17.9%)	5 (25.0%)	152 (35.8%)
Don't know/ recall		1 (1.4%)	5 (2.3%)	7 (6.6%)		13 (3.1%)
Memantine (Namenda, Axura, Akatinol, Ebixa, Abixa, Memox)						
No	11 (73.3%)	58 (82.9%)	169 (79.3%)	95 (89.6%)	15 (75.0%)	348 (82.1%)
Yes	3 (20.0%)	10 (14.3%)	37 (17.4%)	4 (3.8%)	4 (20.0%)	58 (13.7%)
Don't know/ recall	1 (6.7%)	2 (2.9%)	7 (3.3%)	7 (6.6%)	1 (5.0%)	18 (4.2%)

[a]Question: Prior to the Amyvid PET scan, had the patient received any of the following medications since they first sought treatment for cognitive impairment? Indicate "Yes", "No", or "Do Not Know" for each treatment below

Table 38. Patient's comorbidities at the time of the Amyvid PET scan

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
No	7 (46.7%)	33 (47.1%)	98 (46.0%)	63 (59.4%)	9 (45.0%)	210 (49.5%)
Yes	8 (53.3%)	33 (47.1%)	98 (46.0%)	32 (30.2%)	6 (30.0%)	177 (41.7%)
Don't know/ recall		4 (5.7%)	17 (8.0%)	11 (10.4%)	5 (25.0%)	37 (8.7%)
Valid n	*15*	*70*	*213*	*106*	*20*	*424*
Co-morbidities[b]						
Clinically meaningful cerebrovascular disease	2 (25%)	15 (45.5%)	24 (24.5%)	4 (12.5%)	2 (33.3%)	47 (26.6%)
Renal impairment	2 (25%)	12 (36.4%)	32 (32.7%)	4 (12.5%)	2 (33.3%)	52 (29.4%)
Hepatic impairment	2 (25%)	2 (6.1%)	18 (18.4%)	2 (6.3%)	1 (16.7%)	25 (14.1%)
Other psychiatric morbidities	1 (12.5%)	6 (18.2%)	27 (27.6%)	24 (75%)	3 (50%)	61 (34.5%)
Depression	1 (100.0%)	5 (83.3%)	21 (77.8%)	15 62.5%)	2 (66.7%)	44 (72.1%)

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Anxiety		1 (16.7%)	6 (22.2%)	2 (8.3%)		9 (14.8%)
Schizoaffective disorders			3 (11.1%)	4 (16.7%)		7 (11.5%)
Alcoholism			2 (7.4%)	3 (12.5%)		5 (8.2%)
Personality disorder			2 (7.4%)	1 (4.2%)		3 (4.9%)
Mood swings				2 (8.3%)		2 (3.3%)
Anger outburst				1 (4.2%)		1 (1.6%)
Depressive Pseudodementia					1 (33.3%)	1 (1.6%)
Insomnia				1 (4.2%)		1 (1.6%)
Irritability				1 (4.2%)		1 (1.6%)
Valid n	*1*	*6*	*27*	*24*	*3*	*61*
Other neurological morbidities	1 (12.5%)	3 (9.1%)	8 (8.2%)	4 (12.5%)	1 (16.7%)	17 (9.6%)
Epilepsy		1 (33.3%)	1 (12.5%)	1 (25.0%)		3 (17.6%)
Parkinson disease		1 (33.3%)	1 (12.5%)	1 (25.0%)		3 (17.6%)
Brain cancer			1 (12.5%)		1 (100.0%)	2 (11.8%)
Dysarthria	1 (100.0%)			1 (25.0%)		2 (11.8%)
Limbic encephalitis			2 (25.0%)			2 (11.8%)
Traumatic brain injury			2 (25.0%)			2 (11.8%)
Confusion				1 (25.0%)		1 (5.9%)
Desorientation				1 (25.0%)		1 (5.9%)
Disturbance of gait				1 (25.0%)		1 (5.9%)
Post herpetic trigeminal neuralgia		1 (33.3%)				1 (5.9%)
Supranuclear palsy				1 (25.0%)		1 (5.9%)
Don't know/ recall			1 (12.5%)			1 (5.9%)
Valid n	*1*	*3*	*8*	*4*	*1*	*17*
Valid n	*8*	*33*	*98*	*32*	*6*	*177*

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following comorbidities? Please mark all that apply.
[b]Multiple response question.

Table 39. Changes on the diagnosis or treatment after Amyvid scan results

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Yes	7 (46.7%)	51 (72.9%)	138 (64.8%)	69 (65.1%)	20 (100.0%)	285 (67.2%)
No	3 (20.0%)	15 (21.4%)	58 (27.2%)	24 (22.6%)		100 (23.6%)
Don't know/ recall	5 (33.3%)	4 (5.7%)	17 (8.0%)	13 (12.3%)		39 (9.2%)
valid n	*15*	*70*	*213*	*106*	*20*	*424*

Question[a]	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Increased diagnostic confidence	5 (71.4%)	43 (84.3%)	96 (69.6%)	67 (97.1%)	19 (95.0%)	230 (80.7%)
Decreased diagnostic confidence	1 (14.3%)	1 (2.0%)	14 (10.1%)			16 (5.6%)
Changed the medical management plan	1 (14.3%)	20 (39.2%)	71 (51.4%)	34 (49.3%)	11 (55.0%)	137 (48.1%)
Changed plans for referral to other specialists	2 (28.6%)	8 (15.7%)	22 (15.9%)	17 (24.6%)	2 (10.0%)	51 (17.9%)
Changed plan for counseling the patient or caregiver	2 (28.6%)	17 (33.3%)	54 (39.1%)	32 (46.4%)	2 (10.0%)	107 (37.5%)
Changed planned use of other diagnostic tests	1 (14.3%)	4 (7.8%)	33 (23.9%)	13 (18.8%)	2 (10.0%)	53 (18.6%)
Did not change my diagnosis or management		4 (2.9%)	1 (1.4%)			5 (1.8%)
Don't know/ recall			2 (1.4%)			2 (0.7%)
valid n	*7*	*51*	*138*	*69*	*20*	*285*

[a]Question: Has/Will the Amyvid scan result change(d) the diagnosis or treatment of this patient? /. In what way has the Amyvid scan result changed the diagnosis or management of this patient? Please mark all that apply
[b]Multiple response question

Table 40. Off-label use of the Amyvid PET scan – Per protocol Analysis

	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Total number of patient cases indicating off-label use (per protocol analysis)	10 (66.7%)	42 (60.0%)	141 (66.2%)	64 (60.4%)	11 (55.0%)	268 (63.2%)
Reasons for Amyvid PET scan off-label use						
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	10 (66.7%)	42 (60.0%)	140 (65.7%)	63 (59.4%)	11 (55.0%)	266 (62.7%)
Not consistent with the indicated population	0 (0.0%)	0 (0.0%)	8 (3.8%)	0 (0.0%)	0 (0.0%)	8 (1.9%)
Not consistent with use of scan for AD or other cause of cognitive impairment	1 (6.7%)	0 (0.0%)	4 (1.9%)	1 (0.9%)	0 (0.0%)	6 (1.4%)

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: response will be considered off-label if it does not include "As part of the evaluation of cognitive decline documented on clinical examination".

Because all of the following are uses for the purpose of monitoring or are uses not related to clinical evaluation of the patient, the following responses to Q8 would result in the case being counted as off-label, regardless of whether the scan was used as part of evaluation: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/evaluation of amyloid status in an asymptomatic individual. Responses of none/no to Q. 7a (if cognitive function tests were performed prior to the scan) and 10 (if other laboratory tests were performed prior to the scan) do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establish it.

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 (if MMSE score available) AND ADAS-Cog <=9 (if ADAS-Cog score available) AND any other reported test result considered normal after medical review (if other test performed)

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above"

Table 41. Off-label use of the Amyvid PET scan – Modified per protocol Analysis

	General Practitioner	Geriatrics/ Care of the Elderly	Neurology	Psychiatry	Other	Total
Total number of patient cases with off-label use (modified per protocol analysis)	1 (10.0%)	17 (30.4%)	59 (33.3%)	24 (28.6%)	1 (6.3%)	102 (29.7%)
Reasons for Amyvid PET scan off-label use						
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	1 (10.0%)	17 (30.4%)	57 (32.2%)	24 (28.6%)	1 (6.3%)	100 (29.2%)
Not consistent with the indicated population	0 (0.0%)	0 (0.0%)	4 (2.3%)	0 (0.0%)	0 (0.0%)	4 (1.2%)
Not consistent with use of scan for AD or other cause of cognitive impairment	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
valid n	*10*	*56*	*177*	*84*	*16*	*343*

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: Only the following responses are off-label: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/ evaluation of amyloid status in an asymptomatic individual

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 AND ADAS-Cog <=9 AND any other reported test result considered normal after medical review AND Q9 = none AND Q11 = no

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above" AND Q8 not off-label as described above

Table 42. Summary of Inconsistent Responses related to Off-label

	General Practitioner (n=15)	Geriatrics/ Care of the Elderly (n=70)	Neurology (n=213)	Psychiatry (n=106)	Other (n=20)	Total (n=424)
Inconsistent responses	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Q5 Reported normal cognitive status does not match cognitive test score or other responses	0 (0.0%)	0 (0.0%)	6 (2.8%)	1 (0.9%)	0 (0.0%)	7 (1.7%)
Q5 cognitive normal but Q7 reports abnormal cognitive score	0 (0.0%)	0 (0.0%)	2 (0.9%)	1 (0.9%)	0 (0.0%)	3 (0.7%)
Q5 cognitive normal but Q9 response indicates presence of cognitive impairment	0 (0.0%)	0 (0.0%)	6 (2.8%)	1 (0.9%)	0 (0.0%)	7 (1.7%)
Q5 cognitive normal but Q11 response indicates treatment for cognitive impairment	0 (0.0%)	0 (0.0%)	5 (2.3%)	0 (0.0%)	0 (0.0%)	5 (1.2%)
Q8 “asymptomatic” reasons but symptoms reported	5 (33.3%)	11 (15.7%)	20 (9.4%)	19 (17.9%)	3 (15.0%)	58 (13.7%)
Q8 response is “asymptomatic” reason but Q5 reports cognitive impairment	5 (33.3%)	11 (15.7%)	20 (9.4%)	18 (17.0%)	3 (15.0%)	57 (13.4%)
Q8 response is “asymptomatic” reason but Q7 reports abnormal cognitive score	5 (33.3%)	6 (8.6%)	10 (4.7%)	13 (12.3%)	0 (0.0%)	34 (8.0%)
Q8 Estimating risk of progression of MCI to dementia when the subject is already demented	0 (0.0%)	3 (4.3%)	11 (5.2%)	5 (4.7%)	1 (5.0%)	20 (4.7%)
Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia	0 (0.0%)	3 (4.3%)	11 (5.2%)	5 (4.7%)	1 (5.0%)	20 (4.7%)

Exclusion of case from question 5 - Reported normal cognitive status does not match cognitive test score or other responses - Q5 cognitive normal but Q7 reports abnormal cognitive score: Q5 response = “Normal Cognition” AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review; Q5 cognitive normal but Q9 response indicates presence of cognitive impairment: Q5 response = “Normal Cognition” AND Q9 includes any response except “none of the above”; Q5 cognitive normal but Q11 indicates treatment for cognitive impairment: Q5 response = “Normal Cognition” AND Q11 response = “Yes” for either medication

Exclusion of case from question 8 - "Asymptomatic" reasons were checked but symptoms reported - Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment: Q8 = see footnote* AND Q5 response NOT "Normal Cognition"; Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score: Q8 = see footnote* AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review

Exclusion of case from question 8 - Estimating risk of progression of MCI to dementia when the subject is already demented - Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia: Q8 response = "For estimating risk of MCI progression to clinical Alzheimer's disease" AND Q5 response = mild or moderate or severe dementia

*Footnote: Q8 "asymptomatic" reasons include any of the following:

- As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier
- As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)
- As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors

2. Stratification by the proportion of time dedicated by the physician to the management of patients with AD or other causes of dementia

Table 43. Patient sociodemographic information

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Sex					
Female	25 (47.2%)	44 (45.8%)	84 (57.5%)	61 (49.6%)	214 (51.2%)
Male	28 (52.8%)	51 (53.1%)	62 (42.5%)	62 (50.4%)	203 (48.6%)
Don't know/ recall		1 (1.0%)			1 (0.2%)
valid n	*53*	*96*	*146*	*123*	*418*
Age (at the time of having Amyvid PET scan)					
Mean	65.6	68.7	69.7	65.8	67.8
(SD)	(8.8)	(10.0)	(11.4)	(12.3)	(11.2)
Median	65.5	70.0	70.0	66.5	68.0
(P25;P75)	(57.5; 71.5)	(62.0; 76.0)	(62.5; 78.0)	(58.0; 73.5)	(60.0; 76.0)
(Min; Max)	(51.0; 83.0)	(41.0; 92.0)	(43.0; 100.0)	(30.0; 100.0)	(30.0; 100.0)
valid n	*52*	*91*	*140*	*120*	*403*

[a]Question: What is the patient's gender? / How old was the patient at the time of having the Amyvid PET scan? Please write exact age, in years or Do Not Know.

Table 44. Time elapsed, in months, since the patient first presented to physician with the complaint/ symptom that led to physician referral for an Amyvid PET scan presented

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Mean	13.3	11.4	8.0	10.1	10.0
(SD)	(12.9)	(11.1)	(8.9)	(10.6)	(10.6)
Median	12.0	6.0	6.0	6.5	6.0
(P25;P75)	(2.0; 24.0)	(4.0; 14.0)	(2.0; 10.0)	(4.0; 12.0)	(3.0; 12.0)
(Min; Max)	(1.0; 60.0)	(0.0; 48.0)	(1.0; 60.0)	(0.0; 60.0)	(0.0; 60.0)
valid n	*44*	*66*	*121*	*106*	*337*

[a]Question: How much time (months) has elapsed since the patient first presented to you with the complaint/ symptom that led to your referral for an Amyvid scan?

Table 45. Patient's cognitive status at the time of the Amyvid PET scan

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)	Overall, as reported[b] (n=418)
Normal cognition	3 (5.8%)		1 (0.7%)		4 (1.0%)	11 (2.6%)
Cognitive complaint without cognitive impairment on examination	8 (15.4%)	13 (13.5%)	20 (14.1%)	14 (11.6%)	55 (13.4%)	55 (13.2%)

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)	Overall, as reported[b] (n=418)
Mild cognitive impairment	22 (42.3%)	46 (47.9%)	54 (38.0%)	58 (47.9%)	180 (43.8%)	180 (43.1%)
Mild dementia	13 (25.0%)	28 (29.2%)	51 (35.9%)	31 (25.6%)	123 (29.9%)	123 (29.4%)
Moderate dementia	6 (11.5%)	8 (8.3%)	13 (9.2%)	13 (10.7%)	40 (9.7%)	40 (9.6%)
Severe dementia		1 (1.0%)	3 (2.1%)	5 (4.1%)	9 (2.2%)	9 (2.2%)
valid n	52	96	142	*121*	*411*	*418*

[a]Question: At the time of the Amyvid PET scan, what was the patient's cognitive status?
[b]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 56)

Table 46. Findings at the time of the Amyvid PET scan

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Impairment in activities of daily living due to cognitive impairment	27 (50.9%)	41 (42.7%)	50 (34.2%)	40 (32.5%)	158 (37.8%)
Parkinsonism	3 (5.7%)	7 (7.3%)	19 (13.0%)	14 (11.4%)	43 (10.3%)
Visual hallucinations	6 (11.3%)	6 (6.2%)	25 (17.1%)	12 (9.8%)	49 (11.7%)
Prominent fluctuations in cognitive function	15 (28.3%)	20 (20.8%)	34 (23.3%)	24 (19.5%)	93 (22.2%)
Prominent changes in personality, behavior or comportment	19 (35.8%)	22 (22.9%)	34 (23.3%)	20 (16.3%)	95 (22.7%)
Prominent language disturbance without memory loss	3 (5.7%)	12 (12.5%)	17 (13.0%)	10 (8.1%)	42 (10.0%)
Substantial concomitant cerebrovascular disease	7 (13.2%)	7 (7.3%)	9 (6.2%)	5 (4.1%)	28 (6.7%)
None of the above	13 (24.5%)	27 (28.1%)	25 (17.1%)	34 (27.6%)	99 (23.7%)

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following findings (Mark all that apply)?
[b]Multiple response question; one patient can have more than one finding

Table 47. Description of the tests specially designed to measure cognitive function performed

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
No	4 (7.5%)	7 (7.3%)	1 (0.7%)		12 (2.9%)
Yes	49 (92.5%)	89 (92.7%)	145 (99.3%)	123 (100.0%)	406 (97.1%)
Valid n	*53*	*96*	*146*	*123*	*418*
Type of test performed					
MMSE	47 (88.7%)	87 (90.6%)	123 (84.2%)	97 (78.9%)	354 (84.7%)
Mean	24.1	24.4	23.5	24.4	24.1
(SD)	(4.1)	(3.2)	(4.9)	(4.3)	(4.3)
Median	24.0	25.0	25.0	25.0	25.0
(P25;P75)	(22.0; 28.0)	(22.0; 27.0)	(21.0; 27.0)	(22.0; 28.0)	(22.0; 27.0)
(Min; Max)	(15.0; 30.0)	(17.0; 29.0)	(3.0; 30.0)	(8.0; 30.0)	(3.0; 30.0)
Valid n	*42*	*71*	*111*	*93*	*317*
ADAS-cog	4 (7.5%)	14 (14.6%)	27 (18.5%)	26 (21.1%)	71 (17.0%)
Mean	23.0	59.0	25.7	17.7	28.5
(SD)	(4.6)	(3.7)	(18.4)	(7.6)	(19.1)
Median	24.0	60.0	20.0	19.0	21.5
(P25;P75)	(18.0; 27.0)	(55.0; 62.0)	(15.0; 32.0)	(10.0; 23.5)	(15.0; 45.0)
(Min; Max)	(18.0; 27.0)	(54.0; 63.0)	(9.0; 66.0)	(5.0;27.0)	(5.0; 66.0)
Valid n	*3*	*6*	*13*	*12*	*34*
Other	9 (18.4%)	17 (19.1%)	29 (20.0%)	56 (45.6%)	111 (27.3%)
ACE	1 (1.9%)	3 (3.1%)	9 (6.2%)	24 (19.5%)	37 (8.9%)
Memory tests	5 (9.4%)	12 (12.5%)	7 (4.8%)	6 (4.9%)	30 (7.2%)
NPS battery				13 (10.6%)	13 (3.1%)
Stroop		2 (2.1%)	4 (2.7%)	5 (4.1%)	11 (2.6%)
Orientation tests	1 (1.9%)	3 (3.1%)	3 (2.1%)	1 (0.8%)	8 (1.9%)
Boston Naming Test			4 (2.7%)	3 (2.4%)	7 (1.7%)
Other	7 (14.3%)	6 (6.7%)	19 (13.1%)	20 (16.3%)	52 (12.8%)
Valid n	*49*	*89*	*145*	*123*	*406*

[a]Question: Prior to the Amyvid PET scan, did the patient have any tests which were designed specifically to measure cognitive function? If yes, please specify below / What was the result of this test?

Table 48. Reasons for referring the patient for an Amyvid PET scan

Question[a,b]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)	Overall, as reported (n=418)[c]
As part of the evaluation of a	25 (52.1%)	51 (61.4%)	74 (62.2%)	52 (53.6%)	202 (58.2%)	236 (56.5%)

Question[a,b]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)	Overall, as reported (n=418)[c]
patient with cognitive decline documented on clinical examination						
As part of an evaluation of the severity of dementia	2 (4.2%)	19 (22.9%)	19 (16.0%)	13 (13.4%)	53 (15.3%)	71 (17.0%)
As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier	1 (2.1%)		1 (0.8%)		2 (0.6%)	29 (6.9%)
For monitoring response to therapy		2 (2.4%)	11 (9.2%)	3 (3.1%)	16 (4.6%)	23 (5.5%)
As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination	7 (14.6%)	22 (26.5%)	14 (11.8%)	15 (15.5%)	58 (16.7%)	81 (19.4%)
For estimating risk of MCI progression to clinical Alzheimer's disease	6 (12.5%)	25 (30.1%)	20 (16.8%)	30 (30.9%)	81 (23.3%)	111 (26.6%)
To establish a diagnosis of Alzheimer's disease based on a positive scan result	29 (60.4%)	41 (49.4%)	34 (28.6%)	52 (53.6%)	156 (45.0%)	179 (42.8%)
As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)						13 (3.1%)
As a substitute for clinical evaluation	1 (2.1%)				1 (0.3%)	3 (0.7%)
As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors	1 (2.1%)				1 (0.3%)	21 (5.0%)
For a non-medical use (e.g., insurance coverage, legal or employment-related reasons)	1 (2.1%)		1 (0.8%)	1 (1.0%)	3 (0.9%)	3 (0.7%)
Other		1 (1.2%)	6 (5.0%)	1 (1.0%)	8 (2.3%)	9 (2.2%)
Investigation		1 (1.2%)	5 (4.2%)		6 (1.7%)	7 (1.7%)
Differential diagnosis			1 (0.8%)	1 (1.0%)	2 (0.6%)	2 (0.5%)

Question[a,b]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)	Overall, as reported (n=418)[c]
valid n	*48*	*83*	*119*	*97*	*347*	*418*

[a]Question: When you referred the patient for an Amyvid PET scan, what was the reason for the referral? Mark all that apply.
[b]Multiple response question
[c]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 56)

Table 49. Possible diagnosis at the time of the Amyvid PET scan before receiving the scan results

Question[a,b]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Mild cognitive impairment	22 (41.5%)	53 (55.2%)	57 (39.0%)	66 (53.7%)	198 (47.4%)
Vascular dementia	16 (30.2%)	20 (20.8%)	35 (24.0%)	15 (12.2%)	86 (20.6%)
Alzheimer's disease	36 (67.9%)	52 (54.2%)	91 (62.3%)	75 (61.0%)	254 (60.8%)
Other neurodegenerative dementia , (e.g., Lewy body dementia, frontotemporal dementia)	27 (50.9%)	25 (26.0%)	34 (23.3%)	33 (26.8%)	119 (28.5%)
Dementia with unknown/uncertain diagnosis	12 (22.6%)	18 (18.8%)	30 (20.5%)	25 (20.3%)	85 (20.3%)
Other dementia diagnosis	1 (1.9%)	6 (6.3%)	6 (4.1%)	6 (4.9%)	19 (4.5%)
Depressive Pseudodementia	1 (1.9%)	1 (1.0%)	3 (2.1%)	5 (4.1%)	10 (2.4%)
Depression		5 (5.2%)	2 (1.4%)		7 (1.7%)
Alcoholism		2 (2.1%)			2 (0.5%)
Anxiety		2 (2.1%)			2 (0.5%)
Cerebral Amyloid Angiopathy				1 (0.8%)	1 (0.2%)
Limbic encephalitis			1 (0.7%)		1 (0.2%)
None of the above	3 (5.7%)	2 (2.1%)	1 (0.7%)		6 (1.4%)

[a]Question: At the time of the Amyvid PET scan, but before receiving the scan results, which of the following were included in your possible diagnosis? (Mark all that apply.)
[b]Multiple response question.

Table 50. Laboratory tests ordered prior to the Amyvid PET scan

Question[a,b]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)

Question[a,b]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
No	17 (32.1%)	7 (7.3%)	24 (16.4%)	12 (9.8%)	60 (14.4%)
Yes	33 (62.3%)	79 (82.3%)	116 (79.5%)	109 (88.6%)	337 (80.6%)
Don't know/ recall	3 (5.7%)	10 (10.4%)	6 (4.1%)	2 (1.6%)	21 (5.0%)
valid n	*53*	*96*	*146*	*123*	*418*
Type of Laboratory tests ordered[b]					
Clinical imaging e.g., CT, MRI	30 (90.9%)	69 (87.3%)	83 (71.6%)	101 (92.7%)	283 (84.0%)
Scan using an imaging agent, e.g., PET or SPECT scan	11 (33.3%)	23 (29.1%)	43 (37.1%)	30 (27.5%)	107 (31.8%)
Lumbar puncture	11 (33.3%)	25 (31.6%)	32 (27.6%)	18 (16.5%)	86 (25.5%)
Lab tests from blood or urine, e.g., CBC, B12, serum chemistry, etc.	28 (84.8%)	74 (93.7%)	79 (68.1%)	96 (88.1%)	277 (82.2%)
Genetic testing, e.g., ApoE or other	9 (27.3%)	3 (3.8%)	12 (10.3%)	16 (14.7%)	40 (11.9%)
Neuropsychological testing	27 (81.8%)	46 (58.2%)	55 (47.4%)	87 (79.8%)	215 (63.8%)
valid n	*33*	*79*	*116*	*109*	*337*

[a]Question: Regarding your intended management plan for this patient prior to the Amyvid scan, did you order any laboratory tests? (Y/N) If yes, please mark the tests you ordered

[b]Multiple response question.

Table 51. Medication received since they first sought treatment for cognitive impairment

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Acetylcholinesterase inhibitor [donepezil (Aricept), rivastigmine (Exelon), or galantamine (Nivalin, Lycoremine, Razadyne)]					
No	40 (75.5%)	60 (62.5%)	70 (47.9%)	84 (68.3%)	254 (60.8%)
Yes	9 (17.0%)	30 (31.2%)	75 (51.4%)	37 (30.1%)	151 (36.1%)
Don't know/ recall	4 (7.5%)	6 (6.2%)	1 (0.7%)	2 (1.6%)	13 (3.1%)
Memantine (Namenda, Axura, Akatinol, Ebixa, Abixa, Memox)					
No	46 (86.8%)	76 (79.2%)	113 (77.4%)	107 (87.0%)	342 (81.8%)
Yes	4 (7.5%)	12 (12.5%)	30 (20.5%)	12 (9.8%)	58 (13.9%)
Don't know/ recall	3 (5.7%)	8 (8.3%)	3 (2.1%)	4 (3.3%)	18 (4.3%)

[a]Question: Prior to the Amyvid PET scan, had the patient received any of the following medications since they first sought treatment for cognitive impairment? Indicate "Yes", "No", or "Do Not Know" for each treatment below

Table 52. Patient's comorbidities at the time of the Amyvid PET scan

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
No	27 (50.9%)	53 (55.2%)	52 (35.6%)	74 (60.2%)	206 (49.3%)
Yes	17 (32.1%)	35 (36.4%)	83 (56.8%)	40 (32.5%)	175 (41.9%)
Don't know/ recall	9 (17.0%)	8 (8.3%)	11 (7.5%)	9 (7.3%)	37 (8.9%)
Valid n	*53*	*96*	*146*	*123*	*418*
Co-morbidities[b]					
Clinically meaningful cerebrovascular disease	6 (35.3%)	10 (28.6%)	18 (21.7%)	13 (32.5%)	47 (26.9%)
Renal impairment		9 (25.7%)	32 (38.6%)	10 (25.0%)	51 (29.1%)
Hepatic impairment	1 (5.9%)	3 (8.6%)	18 (21.7%)	3 (7.5%)	25 (14.3%)
Other psychiatric morbidities	12 (70.6%)	12 (34.3%)	18 (21.7%)	17 (42.5%)	59 (33.7%)
Depression	5 (41.7%)	11 (91.7%)	15 (83.3%)	13 (76.5%)	44 (74.6%)
Anxiety	2 (16.7%)	3 (25.0%)	2 (11.1%)	2 (11.8%)	9 (15.3%)
Schizoaffective disorders	2 (16.7%)	1 (8.3%)	2 (11.1%)	1 (5.9%)	6 (10.2%)
Alcoholism	2 (16.7%)	2 (16.7%)		1 (5.9%)	5 (8.5%)
Personality disorder	1 (8.3%)			2 (11.8%)	3 (5.1%)
Mood swings	1 (8.3%)				1 (1.7%)
Anger outburst					

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Depressive Pseudodementia	1 (8.3%)				1 (1.7%)
Insomnia					
Irritability					
Valid n	*12*	*12*	*18*	*17*	*59*
Other neurological morbidities	1 (5.9%)	8 (22.9%)	5 (6.0%)	3 (7.5%)	17 (9.7%)
Epilepsy		2 (25%)	1 (20.0 %)		3 (17.6%)
Parkinson disease		1 (12.5%)	1 (20.0%)	1 (33.3%)	3 (17.6%)
Brain cancer		1 (12.5%)		1 (33.3%)	2 (11.8%)
Dysarthria	1 (100.0%)	1 (12.5%)			2 (11.8%)
Limbic encephalitis			2 (40.0%)		2 (11.8%)
Traumatic brain injury		2 (25.0%)			2 (11.8%)
Confusion	1 (100.0%)				1 (5.9%)
Desorientation	1 (100.0%)				1 (5.9%)
Disturbance of gait	1 (100.0%)				1 (5.9%)
Post herpetic trigeminal neuralgia			1 (20.0%)		1 (5.9%)
Supranuclear palsy				1 (33.3%)	1 (5.9%)
Don't know/ recall		1 (12.5%)			1 (5.9%)
Valid n	*1*	*8*	*5*	*3*	*17*
Valid n	*17*	*35*	*83*	*40*	*175*

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following comorbidities? Please mark all that apply.
[b]Multiple response question.

Table 53. Changes on the diagnosis or treatment after Amyvid scan results

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Yes	34 (64.2%)	68 (70.8%)	88 (60.3%)	90 (73.2%)	280 (67.0%)
No	16 (30.2%)	15 (15.6%)	44 (30.1%)	25 (20.3%)	100 (23.9%)
Don't know/ recall	3 (5.7%)	13 (13.5%)	14 (9.6%)	8 (6.5%)	38 (9.1%)
valid n	*53*	*96*	*146*	*123*	*418*
Increased diagnostic confidence	25 (73.5%)	59 (86.8%)	62 (70.5%)	79 (87.8%)	225 (80.4%)
Decreased diagnostic confidence	1 (2.9%)	1 (1.5%)	8 (9.1%)	6 (6.7%)	16 (5.7%)
Changed the medical management plan	13 (38.2%)	40 (58.8%)	34 (38.6%)	48 (53.3%)	135 (48.3%)
Changed plans for referral to other specialists	8 (23.5%)	12 (17.6%)	11 (12.5%)	20 (22.2%)	51 (18.2%)
Changed plan for counseling the patient or caregiver	6 (17.6%)	34 (50.0%)	25 (28.4%)	42 (46.7%)	107 (38.2%)
Changed planned use of other diagnostic tests	6 (17.6%)	19 (27.9%)	14 (15.9%)	12 (13.3%)	51 (18.2%)
Did not change my diagnosis	2 (5.9%)	2 (2.9%)		1 (1.1%)	5 (1.8%)

Question[a]	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
or management					
Don't know/ recall		2 (2.9%)			2 (0.7%)
valid n	*34*	*68*	*88*	*90*	*280*

[a]Question: Has/Will the Amyvid scan result change(d) the diagnosis or treatment of this patient? /. In what way has the Amyvid scan result changed the diagnosis or management of this patient? Please mark all that apply
[b]Multiple response question

Table 54. Off-label use of the Amyvid PET scan – Per protocol Analysis

	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Total number of patient cases indicating off-label use (per protocol analysis)	33 (62.3%)	58 (60.4%)	87 (59.6%)	84 (68.3%)	262 (62.7%)
Reasons for Amyvid PET scan off-label use					
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	33 (62.3%)	57 (59.4%)	86 (58.9%)	84 (68.3%)	260 (62.2%)
Not consistent with the indicated population	4 (7.5%)	0 (0.0%)	3 (2.1%)	1 (0.8%)	8 (1.9%)
Not consistent with use of scan for AD or other cause of cognitive impairment	3 (5.7%)	2 (2.1%)	1 (0.7%)	0 (0.0%)	6 (1.4%)

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: response will be considered off-label if it does not include "As part of the evaluation of cognitive decline documented on clinical examination".

Because all of the following are uses for the purpose of monitoring or are uses not related to clinical evaluation of the patient, the following responses to Q8 would result in the case being counted as off-label, regardless of whether the scan was used as part of evaluation: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/evaluation of amyloid status in an asymptomatic individual. Responses of none/no to Q. 7a (if cognitive function tests were performed prior to the scan) and 10 (if other laboratory tests were performed prior to the scan) do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establish it.

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 (if MMSE score available) AND ADAS-Cog <=9 (if ADAS-Cog score available) AND any other reported test result considered normal after medical review (if other test performed)

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above"

Table 55. Off-label use of the Amyvid PET scan – Modified per protocol Analysis

	0-25%	26-50%	51-75%	76-100%	Total
Total number of patient cases with off-label use (modified per protocol	11 (23.4%)	26 (31.3%)	30 (26.1%)	33 (34.4%)	100 (29.3%)

	0-25%	26-50%	51-75%	76-100%	Total
analysis)					
Reasons for Amyvid PET scan off-label use					
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	9 (19.1%)	26 (31.3%)	30 (26.1%)	33 (34.4%)	98 (28.7%)
Not consistent with the indicated population	3 (6.4%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	4 (1.2%)
Not consistent with use of scan for AD or other cause of cognitive impairment	1 (2.1%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	2 (0.6%)
valid n	*47*	*83*	*115*	*96*	*341*

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: Only the following responses are off-label: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/ evaluation of amyloid status in an asymptomatic individual

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 AND ADAS-Cog <=9 AND any other reported test result considered normal after medical review AND Q9 = none AND Q11 = no

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above" AND Q8 not off-label as described above

Table 56. Summary of Inconsistent Responses related to Off-label

	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Inconsistent responses	n (%)	n (%)	n (%)	n (%)	n (%)
Q5 Reported normal cognitive status does not match cognitive test score or other responses	1 (1.9%)	0 (0.0%)	4 (2.7%)	2 (1.6%)	7 (1.7%)
Q5 cognitive normal but Q7 reports abnormal cognitive score	0 (0.0%)	0 (0.0%)	2 (1.4%)	1 (0.8%)	3 (0.7%)
Q5 cognitive normal but Q9 response indicates presence of cognitive impairment	1 (1.9%)	0 (0.0%)	4 (2.7%)	2 (1.6%)	7 (1.7%)
Q5 cognitive normal but Q11 response indicates treatment for cognitive impairment	0 (0.0%)	0 (0.0%)	4 (2.7%)	1 (0.8%)	5 (1.2%)
Q8 "asymptomatic" reasons but symptoms reported	3 (5.7%)	10 (10.4%)	20 (13.7%)	22 (17.9%)	55 (13.2%)

	0-25% (n=53)	26-50% (n=96)	51-75% (n=146)	76-100% (n=123)	Total (n=418)
Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment	3 (5.7%)	10 (10.4%)	20 (13.7%)	21 (17.1%)	54 (12.9%)
Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score	1 (1.9%)	4 (4.2%)	11 (7.5%)	15 (12.2%)	31 (7.4%)
Q8 Estimating risk of progression of MCI to dementia when the subject is already demented	2 (3.8%)	3 (3.1%)	8 (5.5%)	5 (4.1%)	18 (4.3%)
Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia	2 (3.8%)	3 (3.1%)	8 (5.5%)	5 (4.1%)	18 (4.3%)

Exclusion of case from question 5 - Reported normal cognitive status does not match cognitive test score or other responses - Q5 cognitive normal but Q7 reports abnormal cognitive score: Q5 response = "Normal Cognition" AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review; Q5 cognitive normal but Q9 response indicates presence of cognitive impairment: Q5 response = "Normal Cognition" AND Q9 includes any response except "none of the above"; Q5 cognitive normal but Q11 indicates treatment for cognitive impairment: Q5 response = "Normal Cognition" AND Q11 response = "Yes" for either medication

Exclusion of case from question 8 - "Asymptomatic" reasons were checked but symptoms reported - Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment: Q8 = see footnote* AND Q5 response NOT "Normal Cognition"; Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score: Q8 = see footnote* AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review

Exclusion of case from question 8 - Estimating risk of progression of MCI to dementia when the subject is already demented - Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia: Q8 response = "For estimating risk of MCI progression to clinical Alzheimer's disease" AND Q5 response = mild or moderate or severe dementia

*Footnote: Q8 "asymptomatic" reasons include any of the following:

- As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier
- As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)
- As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors

3. Stratification by the number of patients with cognitive complaints that the physicians have in their practices

Table 57. Patient sociodemographic information

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Sex					
Female	9 (27.3%)	29 (51.8%)	75 (51.7%)	102 (53.7%)	215 (50.7%)
Male	24 (72.7%)	26 (46.4%)	70 (48.3%)	88 (46.3%)	208 (49.1%)
Don't know/ recall		1 (1.8%)			1 (0.2%)
valid n	*33*	*56*	*145*	*190*	*424*
Age (at the time of having Amyvid PET scan)					
Mean (SD)	68.4 (8.9)	68.1 (9.1)	70.3 (13.4)	66.0 (9.9)	67.9 (11.2)
Median	68.0	68.0	71.0	65.0	68.0
(P25;P75)	(63.0; 75.0)	(60.5; 75.7)	(64.0; 78.0)	(58.0; 72.0)	(60.0; 76.0)
(Min; Max)	(52.0; 83.0)	(51.0; 90.0)	(30.0; 100.0)	(43.0; 92.0)	(30.0; 100.0)
valid n	*32*	*52*	*141*	*184*	*409*

[a]Question: What is the patient's gender? / How old was the patient at the time of having the Amyvid PET scan? Please write exact age, in years or Do Not Know.

Table 58. Time elapsed, in months, since the patient first presented to physician with the complaint/ symptom that led to physician referral for an Amyvid PET scan presented

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Mean	4.9	13.3	7.0	11.9	10.0
(SD)	(5.5)	(13.1)	(7.0)	(11.6)	(10.5)
Median	2.0	8.0	4.0	8.0	6.0
(P25;P75)	(2.0; 6.5)	(4.0; 24.0)	(3.0; 10.0)	(5.0; 15.0)	(3.0; 12.0)
(Min; Max)	(1.0; 24.0)	(0.0; 60.0)	(0.0; 48.0)	(0.0; 60.0)	(0.0; 60.0)
valid n	*20*	*46*	*117*	*158*	*341*

[a]Question: How much time (months) has elapsed since the patient first presented to you with the complaint/ symptom that led to your referral for an Amyvid scan?

Table 59. Patient's cognitive status at the time of the Amyvid PET scan

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)	Overall, as reported[b] (n=424)
Normal cognition				4 (2.1%)	4 (1.0%)	11 (2.6%)
Cognitive complaint without cognitive impairment on examination	10 (30.3%)	3 (5.5%)	17 (12.1%)	28 (14.8%)	58 (13.9%)	58 (13.7%)
Mild cognitive impairment	14 (42.4%)	24 (43.6%)	52 (37.1%)	91 (48.1%)	181 (43.4%)	181 (42.7%)
Mild dementia	4 (12.1%)	18 (32.7%)	52 (37.1%)	49 (25.9%)	123 (29.5%)	123 (29.0%)
Moderate dementia	4 (12.1%)	9 (16.4%)	15 (10.7%)	14 (7.4%)	42 (10.1%)	42 (9.9%)
Severe dementia	1 (3.0%)	1 (1.8%)	4 (2.9%)	3 (1.6%)	9 (2.2%)	9 (2.1%)
valid n	*33*	*55*	*140*	*189*	*417*	*424*

[a]Question: At the time of the Amyvid PET scan, what was the patient's cognitive status?

[b]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 70).

Table 60. Findings at the time of the Amyvid PET scan

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Impairment in activities of daily living due to cognitive impairment	17 (51.5%)	30 (53.6%)	36 (24.8%)	80 (42.1%)	163 (38.4%)
Parkinsonism	1 (3.0%)	3 (5.4%)	28 (19.3%)	11 (5.8%)	43 (10.1%)
Visual hallucinations	5 (15.2%)	6 (10.7%)	25 (17.2%)	14 (7.4%)	50 (11.8%)
Prominent fluctuations in cognitive function	11 (33.3%)	12 (21.4%)	41 (28.3%)	33 (17.4%)	97 (22.9%)
Prominent changes in personality, behavior or comportment	4 (12.1%)	24 (42.9%)	30 (20.7%)	38 (20.0%)	96 (22.6%)
Prominent language disturbance without memory loss	3 (9.1%)	6 (10.7%)	17 (11.7%)	16 (8.4%)	42 (9.9%)
Substantial concomitant cerebrovascular disease	4 (12.1%)	5 (8.9%)	11 (7.6%)	8 (4.2%)	28 (6.6%)
None of the above	9 (27.3%)	7 (12.5%)	24 (16.6%)	59 (31.1%)	99 (23.3%)

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following findings (Mark all that apply)?

[b]Multiple response question; one patient can have more than one finding

Table 61. Description of the tests specially designed to measure cognitive function performed

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
No	4 (12.1%)	4 (7.1%)	2 (1.4%)	2 (1.1%)	12 (2.8%)
Yes	29 (87.9%)	52 (92.9%)	143 (98.6%)	188 (98.9%)	412 (97.2%)
Valid n	*33*	*56*	*145*	*190*	*424*
Type of test performed	n (%)	n (%)	n (%)	n (%)	n (%)
MMSE	27 (81.8%)	49 (87.5%)	120 (82.8%)	164 (86.3%)	360 (84.9%)
Mean	20.0	23.2	24.3	24.6	23.9
(SD)	(6.3)	(4.9)	(3.3)	(4.2)	(4.4)
Median	20.0	24.0	25.0	25.0	25.0
(P25;P75)	(18.0; 22.0)	(23.0; 26.0)	(22.0; 27.0)	(22.0; 28.0)	(22.0; 27.0)
(Min; Max)	(3.0; 30.0)	(7.0; 29.0)	(16.0; 30.0)	(8.0; 30.0)	(3.0; 30.0)
Valid n	25	42	101	155	323
ADAS-cog	3 (9.1%)	12 (21.4%)	33 (22.8%)	23 (12.1%)	71 (16.7%)
Mean	25.7	20.8	34.5	15.6	28.5
(SD)	(7.1)	(13.0)	(21.7)	(7.2)	(19.1)
Median	27.0	17.5	25.0	18.0	21.5
(P25;P75)	(18.0; 32.0)	(12.0; 24.0)	(16.5; 57.5)	(12.0; 20.0)	(15.0; 45.0)
(Min; Max)	(18.0; 32.0)	(9.0; 45.0)	(8.0; 66.0)	(5.0; 23.0)	(5.0; 66.0)
Valid n	*3*	*6*	*20*	*5*	*34*
Other	1 (3.5%)	15 (28.9%)	13 (9.1%)	82 (43.6%)	111 (26.9%)
ACE		2 (3.6%)	9 (6.2%)	26 (13.7%)	37 (8.7%)
Memory tests		11 (19.6%)	2 (1.4%)	17 (8.9%)	30 (7.1%)
NPS battery				13 (6.8%)	13 (3.1%)
Stroop		1 (1.8%)		10 (5.3%)	11 (2.6%)
Orientation tests		2 (3.6%)		6 (3.2%)	8 (1.9%)
Boston Naming Test				7 (3.7%)	7 (1.7%)
Other	1 (3.5%)	7 (13.5%)	3 (2.1%)	41 (21.8%)	52 (12.6%)
Valid n	*29*	*52*	*143*	*188*	*412*

[a]Question: Prior to the Amyvid PET scan, did the patient have any tests which were designed specifically to measure cognitive function? If yes, please specify below / What was the result of this test?

Table 62. Reasons for referring the patient for an Amyvid PET scan

Question[a,b]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)	Overall, as reported (n=424)[c]
As part of the evaluation of a patient with cognitive decline documented on clinical examination	16 (57.1%)	23 (50.0%)	52 (49.1%)	112 (66.3%)	203 (58.2%)	237 (55.9%)
As part of an evaluation of the severity of dementia	5 (17.9%)	5 (10.9%)	25 (23.6%)	18 (10.7%)	53 (15.2%)	72 (17.0%)
As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier				2 (1.2%)	2 (0.6%)	31 (7.3%)
For monitoring response to therapy	1 (3.6%)		11 (10.4%)	4 (2.4%)	16 (4.6%)	23 (5.4%)
As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination	6 (21.4%)	3 (6.5%)	25 (23.6%)	25 (14.8%)	59 (16.9%)	83 (19.6%)
For estimating risk of MCI progression to clinical Alzheimer's disease	6 (21.4%)	12 (26.1%)	24 (22.6%)	41 (24.3%)	83 (23.8%)	115 (27.1%)
To establish a diagnosis of Alzheimer's disease based on a positive scan result	12 (42.9%)	27 (58.7%)	36 (34.0%)	81 (47.9%)	156 (44.7%)	180 (42.5%)
As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)						13 (3.1%)
As a substitute for clinical evaluation			1 (0.9%)		1 (0.3%)	3 (0.7%)
As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors				1 (0.6%)	1 (0.3%)	22 (5.2%)
For a non-medical use (e.g., insurance coverage, legal or employment-related			1 (0.9%)	2 (1.2%)	3 (0.9%)	4 (0.9%)

Question[a,b]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)	Overall, as reported (n=424)[c]
reasons)						
Other		1 (2.2%)	1 (0.9%)	6 (3.6%)	8 (2.3%)	9 (2.1%)
Investigation		1 (2.2%)		5 (3.0%)	6 (1.7%)	7 (1.7%)
Differential diagnosis			1 (0.9%)	1 (0.6%)	2 (0.6%)	2 (0.5%)
valid n	*28*	*46*	*106*	*169*	*349*	*424*

[a]Question: When you referred the patient for an Amyvid PET scan, what was the reason for the referral? Mark all that apply.
[b]Multiple response question
[c]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 70)

Table 63. Possible diagnosis at the time of the Amyvid PET scan before receiving the scan results

Question[a,b]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Mild cognitive impairment	14 (42.4%)	20 (35.7%)	57 (39.3%)	107 (56.3%)	198 (46.7%)
Vascular dementia	11 (33.3%)	9 (16.1%)	42 (29.0%)	25 (13.2%)	87 (20.5%)
Alzheimer's disease	22 (66.7%)	35 (62.5%)	80 (55.2%)	121 (63.7%)	258 (60.8%)
Other neurodegenerative dementia , (e.g., Lewy body dementia, frontotemporal dementia)	13 (39.4%)	24 (42.9%)	38 (26.2%)	48 (25.3%)	123 (29.0%)
Dementia with unknown/uncertain diagnosis	6 (18.2%)	15 (26.8%)	28 (19.3%)	37 (19.5%)	86 (20.3%)
Other dementia diagnosis	1 (3.0%)		4 (2.8%)	14 (7.4%)	19 (4.5%)
Depressive Pseudodementia	1 (3.0%)			9 (4.7%)	10 (2.4%)
Depression			4 (2.8%)	3 (1.6%)	7 (1.7%)
Alcoholism			2 (1.4%)		2 (0.5%)
Anxiety			2 (1.4%)		2 (0.5%)
Cerebral Amyloid Angiopathy				1 (0.5%)	1 (0.2%)
Limbic encephalitis				1 (0.5%)	1 (0.2%)
None of the above		2 (3.6%)		4 (2.1%)	6 (1.4%)

[a]Question: At the time of the Amyvid PET scan, but before receiving the scan results, which of the following were included in your possible diagnosis? (Mark all that apply.)

[b]Multiple response question.

Table 64. Laboratory tests ordered prior to the Amyvid PET scan

Question[a,b]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
No	14 (42.4%)	11 (19.6%)	20 (13.8%)	15 (7.9%)	60 (14.2%)
Yes	16 (48.5%)	37 (66.1%)	118 (81.4%)	172 (90.5%)	343 (80.9%)
Don't know/ recall	3 (9.1%)	8 (14.3%)	7 (4.8%)	3 (1.6%)	21 (5.0%)
valid n	*33*	*56*	*145*	*190*	*424*
Type of Laboratory tests ordered[b]					
Clinical imaging e.g., CT, MRI	8 (50.0%)	34 (91.9%)	81 (68.6%)	163 (94.8%)	286 (83.4%)
Scan using an imaging agent, e.g., PET or SPECT scan	1 (6.2%)	18 (48.6%)	31 (26.3%)	57 (33.1%)	107 (31.2%)
Lumbar puncture	1 (6.2%)	12 (32.4%)	41 (34.7%)	32 (18.6%)	86 (25.1%)
Lab tests from blood or urine, e.g., CBC, B12, serum chemistry, etc.	15 (93.8%)	29 (78.4%)	81 (68.6%)	158 (91.9%)	283 (82.5%)
Genetic testing, e.g., ApoE or other	4 (25.0%)	7 (18.9%)	10 (8.5%)	22 (12.8%)	43 (12.5%)
Neuropsychological testing	9 (56.2%)	28 (75.7%)	51 (43.2%)	130 (75.6%)	218 (63.6%)
valid n	*16*	*37*	*118*	*172*	*343*

[a]Question: Regarding your intended management plan for this patient prior to the Amyvid scan, did you order any laboratory tests? (Y/N) If yes, please mark the tests you ordered

[b]Multiple response question.

Table 65. Medication received since they first sought treatment for cognitive impairment

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Acetylcholinesterase inhibitor [donepezil (Aricept), rivastigmine (Exelon), or galantamine (Nivalin, Lycoremine, Razadyne)]					
No	26 (78.8%)	30 (53.6%)	65 (44.8%)	138 (72.6%)	259 (61.1%)
Yes	6 (18.2%)	18 (32.1%)	76 (52.4%)	52 (27.4%)	152 (35.8%)
Don't know/ recall	1 (3.0%)	8 (14.3%)	4 (2.8%)		13 (3.1%)
Memantine (Namenda, Axura, Akatinol, Ebixa, Abixa, Memox)					
No	28 (84.8%)	43 (76.8%)	109 (75.2%)	168 (88.4%)	348 (82.1%)
Yes	2 (6.1%)	5 (8.9%)	29 (20.0%)	22 (11.6%)	58 (13.7%)
Don't know/ recall	3 (9.1%)	8 (14.3%)	7 (4.8%)		18 (4.2%)

[a]Question: Prior to the Amyvid PET scan, had the patient received any of the following medications since they first sought treatment for cognitive impairment? Indicate "Yes", "No", or "Do Not Know" for each treatment below

Table 66. Patient's comorbidities at the time of the Amyvid PET scan

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
No	15 (45.5%)	28 (50.0%)	55 (37.9%)	112 (58.9%)	210 (49.5%)
Yes	13 (39.4%)	17 (30.4%)	83 (57.2%)	64 (33.7%)	177 (41.7%)
Don't know/ recall	5 (15.2%)	11 (19.6%)	7 (4.8%)	14 (7.4%)	37 (8.7%)
Valid n	33	56	145	190	424
Co-morbidities[b]					
Clinically meaningful cerebrovascular disease	3 (23.1%)	9 (52.9%)	14 (16.9%)	21 (32.8%)	47 (26.6%)
Renal impairment	3 (23.1%)	1 (5.9%)	36 (43.4%)	12 (18.8%)	52 (29.4%)
Hepatic impairment		3 (17.6%)	20 (24.1%)	2 (3.1%)	25 (14.1%)
Other psychiatric morbidities	9 (69.2%)	8 (47.1%)	15 (18.1%)	29 (45.3%)	61 (34.5%)
Depression	3 (33.3%)	5 (62.5%)	10 (66.7%)	26 (89.7%)	44 (72.1%)
Anxiety	1 (11.1%)		4 (26.7%)	4 (13.8%)	9 (14.8%)
Schizoaffective disorders	3 (33.3%)	1 (12.5%)	2 (13.3%)	1 (3.4%)	7 (11.5%)
Alcoholism		2 (25.0%)	3 (20.0%)		5 (8.2%)
Personality disorder	1 (11.1%)		2 (13.3%)		3 (4.9%)
Mood swings	2 (22.2%)				2 (3.3%)
Anger outburst	1 (11.1%)				1 (1.6%)
Depressive Pseudodementia	1 (11.1%)				1 (1.6%)
Insomnia	1 (11.1%)				1 (1.6%)
Irritability	1 (11.1%)				1 (1.6%)

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Valid n	*9*	*8*	*15*	*29*	*61*
Other neurological morbidities	2 (15.4%)		6 (7.2%)	9 (14.1%)	17 (9.6%)
Epilepsy				3 (33.3%)	3 (17.6%)
Parkinson disease			2 (33.3%)	1 (11.1%)	3 (17.6%)
Brain cancer				2 (22.2%)	2 (11.8%)
Dysarthria	1 (50.0%)		1 (16.7%)		2 (11.8%)
Limbic encephalitis				2 (22.2%)	2 (11.8%)
Traumatic brain injury			2 (33.3%)		2 (11.8%)
Confusion	1 (50.0%)				1 (5.9%)
Desorientation	1 (50.0%)				1 (5.9%)
Disturbance of gait	1 (50.0%)				1 (5.9%)
Post herpetic trigeminal neuralgia	1 (50.0%)				1 (5.9%)
Supranuclear palsy			1 (16.7%)		1 (5.9%)
Don't know/ recall				1 (11.1%)	1 (5.9%)
Valid n	*2*		*6*	*9*	*17*
Valid n	*13*	*17*	*83*	*64*	*177*

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following comorbidities? Please mark all that apply.

[b]Multiple response question.

Table 67. Changes on the diagnosis or treatment after Amyvid scan results

Question[a]	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Yes	22 (66.7%)	33 (58.9%)	94 (64.8%)	136 (71.6%)	285 (67.2%)
No	9 (27.3%)	14 (25.0%)	34 (23.4%)	43 (22.6%)	100 (23.6%)
Don't know/ recall	2 (6.1%)	9 (16.1%)	17 (11.7%)	11 (5.8%)	39 (9.2%)
valid n	*33*	*56*	*145*	*190*	*424*
Increased diagnostic confidence	18 (81.8%)	23 (69.7%)	63 (67.0%)	126 (92.6%)	230 (80.7%)
Decreased diagnostic confidence		1 (3.0%)	12 (12.8%)	3 (2.2%)	16 (5.6%)
Changed the medical management plan	9 (40.9%)	16 (48.5%)	36 (38.3%)	76 (55.9%)	137 (48.1%)
Changed plans for referral to other specialists	1 (4.5%)	8 (24.2%)	18 (19.1%)	24 (17.6%)	51 (17.9%)
Changed plan for counseling the patient or caregiver	1 (4.5%)	11 (33.3%)	31 (33.0%)	64 (47.1%)	107 (37.5%)
Changed planned use of other diagnostic tests	4 (18.2%)	5 (15.2%)	17 (18.1%)	27 (19.9%)	53 (18.6%)
Did not change my diagnosis or management		2 (6.1%)	3 (3.2%)		5 (1.8%)
Don't know/ recall	2 (9.1%)				2 (0.7%)
valid n	*22*	*33*	*94*	*136*	*285*

[a]Question: Has/Will the Amyvid scan result change(d) the diagnosis or treatment of this patient? /. In what way has the Amyvid scan result changed the diagnosis or management of this patient? Please mark all that apply
[b]Multiple response question

Table 68. Off-label use of the Amyvid PET scan – Per protocol Analysis

	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Total number of patient cases indicating off-label use (per protocol analysis)	22 (66.7%)	38 (67.9%)	105 (72.4%)	103 (54.2%)	268 (63.2%)
Reasons for Amyvid PET scan off-label use					
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	22 (66.7%)	37 (66.1%)	104 (71.7%)	103 (54.2%)	266 (62.7%)
Not consistent with the indicated population	0 (0.0%)	1 (1.8%)	3 (2.1%)	4 (2.1%)	8 (1.9%)
Not consistent with use of scan for AD or other cause of cognitive impairment	0 (0.0%)	2 (3.6%)	0 (0.0%)	4 (2.1%)	6 (1.4%)

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: response will be considered off-label if it does not include "As part of the evaluation of cognitive decline documented on clinical examination".

Because all of the following are uses for the purpose of monitoring or are uses not related to clinical evaluation of the patient, the following responses to Q8 would result in the case being counted as off-label, regardless of whether the scan was used as part of evaluation: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/evaluation of amyloid status in an asymptomatic individual. Responses of none/no to Q. 7a (if cognitive function tests were performed prior to the scan) and 10 (if other laboratory tests were performed prior to the scan) do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establish it.

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 (if MMSE score available) AND ADAS-Cog <=9 (if ADAS-Cog score available) AND any other reported test result considered normal after medical review (if other test performed)

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above"

Table 69. Off-label use of the Amyvid PET scan – Modified per protocol Analysis

	1-10 patients	11-50 patients	51-100 patients	>100 patients	Total
Total number of patient cases with off-label use (modified per protocol analysis)	7 (25.0%)	12 (26.7%)	33 (32.7%)	50 (29.6%)	102 (29.7%)
Reasons for Amyvid PET scan off-label use					
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	7 (25.0%)	12 (26.7%)	33 (32.7%)	48 (28.4%)	100 (29.2%)
Not consistent with the indicated population	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (2.4%)	4 (1.2%)
Not consistent with use of scan for AD or other cause of cognitive impairment	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.2%)	2 (0.6%)
valid n	*28*	*45*	*101*	*169*	*343*

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: Only the following responses are off-label: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/ evaluation of amyloid status in an asymptomatic individual

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 AND ADAS-Cog <=9 AND any other reported test result considered normal after medical review AND Q9 = none AND Q11 = no

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above" AND Q8 not off-label as described above

Table 70. Summary of Inconsistent Responses related to Off-label

	1-10 patients (n=33)	11-50 patients (n=56)	51-100 patients (n=145)	>100 patients (n=190)	Total (n=424)
Inconsistent responses	n (%)	n (%)	n (%)		n (%)
Q5 Reported normal cognitive status does not match cognitive test score or other responses	0 (0.0%)	1 (1.8%)	5 (3.4%)	1 (0.5%)	7 (1.7%)
Q5 cognitive normal but Q7 reports abnormal cognitive score	0 (0.0%)	0 (0.0%)	2 (1.4%)	1 (0.5%)	3 (0.7%)
Q5 cognitive normal but Q9 response indicates presence of cognitive impairment	0 (0.0%)	1 (1.8%)	5 (3.4%)	1 (0.5%)	7 (1.7%)
Q5 cognitive normal but Q11 response indicates treatment for cognitive impairment	0 (0.0%)	0 (0.0%)	5 (3.4%)	0 (0.0%)	5 (1.2%)
Q8 “asymptomatic” reasons but symptoms reported	4 (12.1%)	7 (12.5%)	30 (20.7%)	17 (8.9%)	58 (13.7%)
Q8 response is “asymptomatic” reason but Q5 reports cognitive impairment	4 (12.1%)	7 (12.5%)	30 (20.7%)	16 (8.4%)	57 (13.4%)
Q8 response is “asymptomatic” reason but Q7 reports abnormal cognitive score	3 (9.1%)	2 (3.6%)	19 (13.1%)	10 (5.3%)	34 (8.0%)
Q8 Estimating risk of progression of MCI to dementia when the subject is already demented	2 (6.1%)	3 (5.4%)	10 (6.9%)	5 (2.6%)	20 (4.7%)
Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia	2 (6.1%)	3 (5.4%)	10 (6.9%)	5 (2.6%)	20 (4.7%)

Exclusion of case from question 5 - Reported normal cognitive status does not match cognitive test score or other responses - Q5 cognitive normal but Q7 reports abnormal cognitive score: Q5 response = “Normal Cognition” AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review; Q5 cognitive normal but Q9 response indicates presence of cognitive impairment: Q5 response = “Normal Cognition” AND Q9 includes any response except “none of the above”; Q5 cognitive normal but Q11 indicates treatment for cognitive impairment: Q5 response = “Normal Cognition” AND Q11 response = “Yes” for either medication

Exclusion of case from question 8 - “Asymptomatic” reasons were checked but symptoms reported - Q8 response is “asymptomatic” reason but Q5 reports cognitive impairment: Q8 = see footnote* AND Q5 response

NOT “Normal Cognition”; Q8 response is “asymptomatic” reason but Q7 reports abnormal cognitive score: Q8 = see footnote* AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review

Exclusion of case from question 8 - Estimating risk of progression of MCI to dementia when the subject is already demented - Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia: Q8 response = “For estimating risk of MCI progression to clinical Alzheimer’s disease” AND Q5 response = mild or moderate or severe dementia

*Footnote: Q8 “asymptomatic” reasons include any of the following:

- As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer’s disease or known to be a ApoE4 carrier
- As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer’s disease (e.g. presenilin1, presenilin 2 or APP)
- As part of an assessment of Alzheimer’s disease in an asymptomatic individual without other risk factors

4. Stratification by the number of patients ever referred for and Amyvid PET scan

Table 71. Patient sociodemographic information

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Sex						
Female	23 (43.4%)	37 (49.3%)	58 (52.7%)	64 (57.7%)	33 (44.0%)	215 (50.7%)
Male	29 (54.7%)	38 (50.7%)	52 (47.3%)	47 (42.3%)	42 (56.0%)	208 (49.1%)
Don't know/ recall	1 (1.9%)					1 (0.2%)
valid n	*53*	*75*	*110*	*111*	*75*	*424*
Age (at the time of having Amyvid PET scan)						
Mean	64.2	63.6	68.6	71.2	68.7	67.9
(SD)	(8.2)	(9.5)	(10.8)	(13.1)	(10.2)	(11.2)
Median	64.0	64.0	68.0	73.0	70.5	68.0
(P25;P75)	(58.0; 70.0)	(56.0; 70.0)	(61.0; 75.0)	(67.0; 78.0)	(59.5; 76.5)	(60.0; 76.0)
(Min; Max)	(43.0; 83.0)	(41.0; 82.0)	(45.0; 100.0)	(30.0; 100.0)	(39.0; 92.0)	(30.0; 100.0)
valid n	*46*	*73*	*109*	*109*	*72*	*409*

[a]Question: What is the patient's gender? / How old was the patient at the time of having the Amyvid PET scan? Please write exact age, in years or Do Not Know.

Table 72. Time elapsed, in months, since the patient first presented to physician with the complaint/ symptom that led to physician referral for an Amyvid PET scan presented

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Mean	11.0	11.3	10.1	8.0	11.6	10.0
(SD)	(12.3)	(11.9)	(10.5)	(8.0)	(11.6)	(10.5)
Median	8.0	6.0	6.0	6.0	8.0	6.0
(P25;P75)	(3.0; 15.0)	(3.0; 16.0)	(3.0; 12.0)	(2.0; 10.0)	(4.0; 12.0)	(3.0; 12.0)
(Min; Max)	(1.0; 60.0)	(1.0; 60.0)	(0.0; 53.0)	(0.0; 36.0)	(0.0; 60.0)	(0.0; 60.0)
valid n	*27*	*67*	*95*	*101*	*51*	*341*

[a]Question: How much time (months) has elapsed since the patient first presented to you with the complaint/ symptom that led to your referral for an Amyvid scan?

Table 73. Patient's cognitive status at the time of the Amyvid PET scan

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)	Overall, as reported[b] (n=424)
Normal cognition		3 (4.1%)	1 (0.9%)			4 (1.0%)	11 (2.6%)
Cognitive complaint without cognitive impairment on examination	8 (15.1%)	13 (17.6%)	12 (10.9%)	16 (15.1%)	9 (12.2%)	58 (13.9%)	58 (13.7%)

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)	Overall, as reported[b] (n=424)
Mild cognitive impairment	20 (37.7%)	29 (39.2%)	47 (42.7%)	46 (43.4%)	39 (52.7%)	181 (43.4%)	181 (42.7%)
Mild dementia	19 (35.8%)	23 (31.1%)	33 (30.0%)	32 (30.2%)	16 (21.6%)	123 (29.5%)	123 (29.0%)
Moderate dementia	4 (7.5%)	6 (8.1%)	15 (13.6%)	9 (8.5%)	8 (10.8%)	42 (10.1%)	42 (9.9%)
Severe dementia	2 (3.8%)		2 (1.8%)	3 (2.8%)	2 (2.7%)	9 (2.2%)	9 (2.1%)
valid n	*53*	*74*	*110*	*106*	*74*	*417*	*424*

[a]Question: At the time of the Amyvid PET scan, what was the patient's cognitive status?

[b]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 84)

Table 74. Findings at the time of the Amyvid PET scan

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Impairment in activities of daily living due to cognitive impairment	28 (52.8%)	40 (53.3%)	41 (37.3%)	27 (24.3%)	27 (36.0%)	163 (38.4%)
Parkinsonism	2 (3.8%)	3 (4.0%)	11 (10.0%)	19 (17.1%)	8 (10.7%)	43 (10.1%)
Visual hallucinations	6 (11.3%)	4 (5.3%)	17 (15.5%)	16 (14.4%)	7 (9.3%)	50 (11.8%)
Prominent fluctuations in cognitive function	11 (20.8%)	20 (26.7%)	23 (20.9%)	29 (26.1%)	14 (18.7%)	97 (22.9%)
Prominent changes in personality, behavior or comportment	16 (30.2%)	19 (25.3%)	26 (23.6%)	21 (18.9%)	14 (18.7%)	96 (22.6%)
Prominent language disturbance without memory loss	5 (9.4%)	6 (8.0%)	12 (10.9%)	11 (9.9%)	8 (10.7%)	42 (9.9%)
Substantial concomitant cerebrovascular disease	5 (9.4%)	6 (8.0%)	6 (5.5%)	5 (4.5%)	6 (8.0%)	28 (6.6%)
None of the above	13 (24.5%)	16 (21.3%)	25 (22.7%)	22 (19.8%)	23 (30.7%)	99 (23.3%)

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following findings (Mark all that apply)?

[b]Multiple response question; one patient can have more than one finding

Table 75. Description of the tests specially designed to measure cognitive function performed

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
No	5 (9.4%)		4 (3.6%)		3 (4.0%)	12 (2.8%)
Yes	48 (90.6%)	75 (100.0%)	106 (96.4%)	111 (100.0%)	72 (96.0%)	412 (97.2%)
Valid n	*53*	*75*	*110*	*111*	*75*	*424*
Type of test performed						
MMSE	41 (77.4%)	69 (92.0%)	86 (78.2%)	101 (91.0%)	63 (84.0%)	360 (84.9%)
Mean	22.5	23.0	23.7	24.9	24.6	23.9
(SD)	(7.2)	(3.9)	(4.3)	(3.6)	(4.0)	(4.4)
Median	24.0	24.0	25.0	26.0	25.0	25.0
(P25;P75)	(20.0; 28.0)	(20.0; 25.0)	(23.0; 26.0)	(22.0; 27.0)	(22.0; 28.0)	(22.0; 27.0)
(Min; Max)	(3.0; 30.0)	(12.0; 30.0)	(7.0; 30.0)	(13.0; 30.0)	(8.0; 30.0)	(3.0; 30.0)
Valid n	*30*	*63*	*82*	*88*	*60*	*323*
ADAS-cog	10 (18.9%)	8 (10.7%)	27 (24.5%)	19 (17.1%)	7 (9.3%)	71 (16.7%)
Mean	38.7	22.5	32.5	17.4		28.5
(SD)	(18.9)	(6.4)	(21.7)	(7.5)		(19.1)
Median	32.0	22.5	21.5	20.0		21.5
(P25;P75)	(24.0; 60.0)	(18.0; 27.0)	(15.0; 55.0)	(10.0; 23.0)		(15.0; 45.0)
(Min; Max)	(24.0; 60.0)	(18.0; 27.0)	(5.0; 66.0)	(8.0; 27.0)		(5.0; 66.0)
Valid n	*3*	*2*	*20*	*9*		*34*
Other	15 (31.3%)	22 (29.3%)	47 (44.3%)	11 (9.9%)	16 (22.2%)	111 (26.9%)
ACE	7 (13.2%)	13 (17.3%)	11 (10.0%)	5 (4.5%)	1 (1.3%)	37 (8.7%)
Memory tests	5 (9.4%)	7 (9.3%)	9 (8.2%)	7 (6.3%)	2 (2.7%)	30 (7.1%)
NPS battery		5 (6.7%)	7 (6.4%)		1 (1.3%)	13 (3.1%)
Stroop			3 (2.7%)	2 (1.8%)	6 (8.0%)	11 (2.6%)
Orientation tests			5 (4.5%)	2 (1.8%)	1 (1.3%)	8 (1.9%)
Boston Naming Test					7 (9.3%)	7 (1.7%)
Other	5 (10.4%)	6 (8.0%)	29 (27.4%)		12 (16.7%)	52 (12.6%)
Valid n	*48*	*75*	*106*	*111*	*72*	*412*

[a]Question: Prior to the Amyvid PET scan, did the patient have any tests which were designed specifically to measure cognitive function? If yes, please specify below / What was the result of this test?

Table 76. Reasons for referring the patient for an Amyvid PET scan

Question[a,b]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)	Overall, as reported (n=424)[c]
As part of the evaluation of a patient with cognitive decline documented on clinical examination	25 (52.1%)	43 (68.3%)	48 (53.3%)	49 (57.0%)	38 (61.3%)	203 (58.2%)	237 (55.9%)
As part of an evaluation of the severity of dementia	6 (12.5%)	4 (6.3%)	14 (15.6%)	19 (22.1%)	10 (16.1%)	53 (15.2%)	72 (17.0%)
As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier		1 (1.6%)	1 (1.1%)			2 (0.6%)	31 (7.3%)
For monitoring response to therapy	2 (4.2%)		3 (3.3%)	7 (8.1%)	4 (6.5%)	16 (4.6%)	23 (5.4%)
As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination	12 (25.0%)	17 (27.0%)	8 (8.9%)	10 (11.6%)	12 (19.4%)	59 (16.9%)	83 (19.6%)
For estimating risk of MCI progression to clinical Alzheimer's disease	9 (18.8%)	11 (17.5%)	17 (18.9%)	20 (23.3%)	26 (41.9%)	83 (23.8%)	115 (27.1%)
To establish a diagnosis of Alzheimer's disease based on a positive scan result	22 (45.8%)	29 (46.0%)	48 (53.3%)	23 (26.7%)	34 (54.8%)	156 (44.7%)	180 (42.5%)
As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)							13 (3.1%)
As a substitute for clinical evaluation	1 (2.1%)					1 (0.3%)	3 (0.7%)

Question[a,b]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)	Overall, as reported (n=424)[c]
As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors		1 (1.6%)				1 (0.3%)	22 (5.2%)
For a non-medical use (e.g., insurance coverage, legal or employment-related reasons)	1 (2.1%)	1 (1.6%)			1 (1.6%)	3 (0.9%)	4 (0.9%)
Other	2 (4.2%)		1 (1.1%)	5 (5.8%)		8 (2.3%)	9 (2.1%)
Investigation	1 (2.1%)			5 (5.8%)		6 (1.7%)	7 (1.7%)
Differential diagnosis	1 (2.1%)		1 (1.1%)			2 (0.6%)	2 (0.5%)
valid n	*48*	*63*	*90*	*86*	*62*	*349*	*424*

[a]Question: When you referred the patient for an Amyvid PET scan, what was the reason for the referral? Mark all that apply.
[b]Multiple response question
[c]The column 'Overall, as reported' reports the original data. The other columns report the data after removing inconsistent reponses (see Table 84)

Table 77. Possible diagnosis at the time of the Amyvid PET scan before receiving the scan results

Question[a,b]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Mild cognitive impairment	22 (41.5%)	35 (46.7%)	52 (47.3%)	44 (39.6%)	45 (60.0%)	198 (46.7%)
Vascular dementia	12 (22.6%)	13 (17.3%)	11 (10.0%)	30 (27.0%)	21 (28.0%)	87 (20.5%)
Alzheimer's disease	29 (54.7%)	49 (65.3%)	75 (68.2%)	63 (56.8%)	42 (56.0%)	258 (60.8%)
Other neurodegenerative dementia , (e.g., Lewy body dementia, frontotemporal dementia)	18 (34.0%)	31 (41.3%)	37 (33.6%)	16 (14.4%)	21 (28.0%)	123 (29.0%)
Dementia with unknown/uncertain diagnosis	12 (22.6%)	20 (26.7%)	20 (18.2%)	14 (12.6%)	20 (26.7%)	86 (20.3%)
Other dementia diagnosis	4 (7.5%)	6 (8.0%)	1 (0.9%)	4 (3.6%)	4 (5.3%)	19 (4.5%)
Depressive Pseudodementia	1 (1.9%)	2 (2.7%)	1 (0.9%)	4 (3.6%)	2 (2.7%)	10 (2.4%)
Depression	2 (3.8%)	4 (5.3%)			1 (1.3%)	7 (1.7%)

Question[a,b]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Alcoholism		2 (2.7%)				2 (0.5%)
Anxiety		2 (2.7%)				2 (0.5%)
Cerebral Amyloid Angiopathy	1 (1.9%)					1 (0.2%)
Limbic encephalitis					1 (1.3%)	1 (0.2%)
None of the above	1 (1.9%)	3 (4.0%)	2 (1.8%)			6 (1.4%)

[a]Question: At the time of the Amyvid PET scan, but before receiving the scan results, which of the following were included in your possible diagnosis? (Mark all that apply.)
[b]Multiple response question.

Table 78. Laboratory tests ordered prior to the Amyvid PET scan

Question[a,b]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
No	13 (24.5%)	8 (10.7%)	13 (11.8%)	20 (18.0%)	6 (8.0%)	60 (14.2%)
Yes	33 (62.3%)	63 (84.0%)	91 (82.7%)	88 (79.3%)	68 (90.7%)	343 (80.9%)
Don't know/ recall	7 (13.2%)	4 (5.3%)	6 (5.5%)	3 (2.7%)	1 (1.3%)	21 (5.0%)
valid n	*53*	*75*	*110*	*111*	*75*	*424*
Type of Laboratory tests ordered[b]						
Clinical imaging e.g., CT, MRI	30 (90.9%)	51 (81.0%)	83 (91.2%)	60 (68.2%)	62 (91.2%)	286 (83.4%)
Scan using an imaging agent, e.g., PET or SPECT scan	2 (6.1%)	20 (31.7%)	22 (24.2%)	36 (40.9%)	27 (39.7%)	107 (31.2%)
Lumbar puncture	3 (9.1%)	18 (28.6%)	23 (25.3%)	22 (25.0%)	20 (29.4%)	86 (25.1%)
Lab tests from blood or urine, e.g., CBC, B12, serum chemistry, etc.	30 (90.9%)	62 (98.4%)	78 (85.7%)	50 (56.8%)	63 (92.6%)	283 (82.5%)
Genetic testing, e.g., ApoE or other	2 (6.1%)	13 (20.6%)	13 (14.3%)	8 (9.1%)	7 (10.3%)	43 (12.5%)
Neuropsychological testing	20 (60.6%)	48 (76.2%)	60 (65.9%)	36 (40.9%)	54 (79.4%)	218 (63.6%)
valid n	*33*	*63*	*91*	*88*	*68*	*343*

[a]Question: Regarding your intended management plan for this patient prior to the Amyvid scan, did you order any laboratory tests? (Y/N) If yes, please mark the tests you ordered
[b]Multiple response question.

Table 79. Medication received since they first sought treatment for cognitive impairment

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Acetylcholinesterase inhibitor [donepezil (Aricept), rivastigmine (Exelon), or galantamine (Nivalin, Lycoremine, Razadyne)]						
No	34 (64.2%)	61 (81.3%)	69 (62.7%)	40 (36.0%)	55 (73.3%)	259 (61.1%)
Yes	14 (26.4%)	11 (14.7%)	39 (35.5%)	69 (62.2%)	19 (25.3%)	152 (35.8%)
Don't know/ recall	5 (9.4%)	3 (4.0%)	2 (1.8%)	2 (1.8%)	1 (1.3%)	13 (3.1%)
Memantine (Namenda, Axura, Akatinol, Ebixa, Abixa, Memox)						
No	43 (81.1%)	72 (96.0%)	98 (89.1%)	76 (68.5%)	59 (78.7%)	348 (82.1%)
Yes	4 (7.5%)		9 (8.2%)	30 (27.0%)	15 (20.0%)	58 (13.7%)
Don't know/ recall	6 (11.3%)	3 (4.0%)	3 (2.7%)	5 (4.5%)	1 (1.3%)	18 (4.2%)

[a]Question: Prior to the Amyvid PET scan, had the patient received any of the following medications since they first sought treatment for cognitive impairment? Indicate "Yes", "No", or "Do Not Know" for each treatment below

Table 80. Patient's comorbidities at the time of the Amyvid PET scan

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
No	26 (49.1%)	40 (53.3%)	70 (63.6%)	39 (35.1%)	35 (46.7%)	210 (49.5%)
Yes	19 (35.8%)	29 (38.7%)	33 (30.0%)	67 (60.4%)	29 (38.7%)	177 (41.7%)
Don't know/ recall	8 (15.1%)	6 (8.0%)	7 (6.4%)	5 (4.5%)	11 (14.7%)	37 (8.7%)
Valid n	53	75	110	111	75	424
Co-morbidities[b]						
Clinically meaningful cerebrovascular disease	5 (26.3%)	7 (24.1%)	14 (42.4%)	12 (17.9%)	9 (31%)	47 (26.6%)
Renal impairment	3 (15.8%)		7 (21.2%)	35 (52.2%)	7 (24.1%)	52 (29.4%)
Hepatic impairment	1 (5.3%)		4 (12.1%)	17 (25.4%)	3 (10.3%)	25 (14.1%)
Other psychiatric morbidities	12 (63.2%)	19 (65.5%)	9 (27.3%)	10 (14.9%)	11 (37.9%)	61 (34.5%)
Depression	7 (58.3%)	13 (68.4%)	7 (77.8%)	8 (80.0%)	9 (81.8%)	44 (72.1%)
Anxiety	2 (16.7%)	4 (21.1%)			3 (27.3%)	9 (14.8%)
Schizoaffective disorders	2 (16.7%)	2 (10.5%)	1 (11.1%)	2 (20.0%)		7 (11.5%)
Alcoholism	2 (16.7%)	2 (10.5%)			1 (9.1%)	5 (8.2%)
Personality disorder	1 (8.3%)		1 (11.1%)	1 (10.0%)		3 (4.9%)
Mood swings	1 (8.3%)	1 (5.3%)				2 (3.3%)
Anger outburst		1 (5.3%)				1 (1.6%)
Depressive Pseudodementia		1 (5.3%)				1 (1.6%)

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Insomnia		1 (5.3%)				1 (1.6%)
Irritability		1 (5.3%)				1 (1.6%)
Valid n	12	19	9	10	11	61
Other neurological morbidities	5 (26.3%)	3 (10.3%)	2 (6.1%)	2 (3%)	5 (17.2%)	17 (9.6%)
Epilepsy	1 (20.0%)		1 (50.0%)		1 (20.0%)	3 (17.6%)
Parkinson disease	1 (20.0%)				2 (40.0%)	3 (17.6%)
Brain cancer				1 (50.0%)	1 (20.0%)	2 (11.8%)
Dysarthria	1 (20.0%)	1 (33.3%)				2 (11.8%)
Limbic encephalitis				1 (50.0%)	1 (20.0%)	2 (11.8%)
Traumatic brain injury		2 (66.7%)				2 (11.8%)
Confusion	1 (20.0%)					1 (5.9%)
Desorientation	1 (20.0%)					1 (5.9%)
Disturbance of gait	1 (20.0%)					1 (5.9%)
Post herpetic trigeminal neuralgia	1 (20.0%)					1 (5.9%)
Supranuclear palsy			1 (50.0%)			1 (5.9%)
Don't know/ recall	1 (20.0%)					1 (5.9%)
Valid n	5	3	2	2	5	17
Valid n	19	29	33	67	29	177

[a]Question: At the time of the Amyvid PET scan, did the patient have any of the following comorbidities? Please mark all that apply.
[b]Multiple response question.

Table 81. Changes on the diagnosis or treatment after Amyvid scan results

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Yes	29 (54.7%)	50 (66.7%)	67 (60.9%)	75 (67.6%)	64 (85.3%)	285 (67.2%)
No	15 (28.3%)	15 (20.0%)	31 (28.2%)	32 (28.8%)	7 (9.3%)	100 (23.6%)
Don't know/ recall	9 (17.0%)	10 (13.3%)	12 (10.9)	4 (3.6%)	4 (5.3%)	39 (9.2%)
valid n	*53*	*75*	*110*	*111*	*75*	*424*
Increased diagnostic confidence	22 (75.9%)	46 (92.0%)	52 (77.6%)	50 (66.7%)	60 (93.8%)	230 (80.7%)
Decreased diagnostic confidence		1 (2.0%)	2 (3.0%)	13 (17.3%)		16 (5.6%)
Changed the medical management plan	14 (48.3%)	25 (50.0%)	37 (55.2%)	28 (37.3%)	33 (51.6%)	137 (48.1%)
Changed plans for referral to other specialists	2 (6.9%)	12 (24.0%)	14 (20.9%)	7 (9.3%)	16 (25.0%)	51 (17.9%)
Changed plan for counseling the patient or caregiver	9 (31.0%)	20 (40.0%)	33 (49.3%)	15 (20.0%)	30 (46.9%)	107 (37.5%)

Question[a]	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Changed planned use of other diagnostic tests	3 (10.3%)	13 (26.0%)	14 (20.9%)	7 (9.3%)	16 (25.0%)	53 (18.6%)
Did not change my diagnosis or management	1 (3.4%)		3 (4.5%)		1 (1.6%)	5 (1.8%)
Don't know/ recall	2 (6.9%)					2 (0.7%)
valid n	*29*	*50*	*67*	*75*	*64*	*285*

[a]Question: Has/Will the Amyvid scan result change(d) the diagnosis or treatment of this patient? /. In what way has the Amyvid scan result changed the diagnosis or management of this patient? Please mark all that apply
[b]Multiple response question

Table 82. Off-label use of the Amyvid PET scan – Per protocol Analysis

	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Total number of patient cases indicating off-label use (per protocol analysis)	36 (67.9%)	42 (56.0%)	68 (61.8%)	73 (65.8%)	49 (65.3%)	268 (63.2%)
Reasons for Amyvid PET scan off-label use						
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	35 (66.0%)	42 (56.0%)	68 (61.8%)	72 (64.9%)	49 (65.3%)	266 (62.7%)
Not consistent with the indicated population	0 (0.0%)	4 (5.3%)	1 (0.9%)	3 (2.7%)	0 (0.0%)	8 (1.9%)
Not consistent with use of scan for AD or other cause of cognitive impairment	1 (1.9%)	3 (4.0%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	6 (1.4%)

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: response will be considered off-label if it does not include "As part of the evaluation of cognitive decline documented on clinical examination".

Because all of the following are uses for the purpose of monitoring or are uses not related to clinical evaluation of the patient, the following responses to Q8 would result in the case being counted as off-label, regardless of whether the scan was used as part of evaluation: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/evaluation of amyloid status in an asymptomatic individual. Responses of none/no to Q. 7a (if cognitive function tests were performed prior to the scan) and 10 (if other laboratory tests were performed prior to the scan) do not establish off-label use. Responses of yes to any item would suggest that an evaluation is ongoing, supporting an on-label classification, but not independently establish it.

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 (if MMSE score available) AND ADAS-Cog <=9 (if ADAS-Cog score available) AND any other reported test result considered normal after medical review (if other test performed)

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above"

Table 83. Off-label use of the Amyvid PET scan – Modified per protocol Analysis

	1-2 patients	3-5 patients	6-10 patients	11-20 patients	>20 patients	Total
Total number of patient cases with off-label use (modified per protocol analysis)	13 (27.1%)	15 (24.2%)	21 (23.3%)	23 (28.4%)	30 (48.4%)	102 (29.7%)
Reasons for Amyvid PET scan off-label use						
Not consistent with use of scan as part of a clinical evaluation for cognitive impairment	13 (27.1%)	13 (21.0%)	21 (23.3%)	23 (28.4%)	30 (48.4%)	100 (29.2%)
Not consistent with the indicated population	0 (0.0%)	3 (4.8%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	4 (1.2%)
Not consistent with use of scan for AD or other cause of cognitive impairment	0 (0.0%)	1 (1.6%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.6%)
valid n	*48*	*62*	*90*	*81*	*62*	*343*

Not consistent with use of scan as part of a clinical evaluation for cognitive impairment: Q8: Only the following responses are off-label: monitoring response to therapy/ estimating risk of MCI progression/ substitute for genetic testing/ substitute for clinical evaluation/ nonmedical use/ evaluation of amyloid status in an asymptomatic individual

Not consistent with the indicated population: Q2 age <= 18 years old OR Q5 = "Normal cognition" AND Q7a/b MMSE >=27 AND ADAS-Cog <=9 AND any other reported test result considered normal after medical review AND Q9 = none AND Q11 = no

Not consistent with use of scan for AD or other cause of cognitive impairment: Q9 = "none of the above" AND Q8 not off-label as described above

Table 84. Summary of Inconsistent Responses related to Off-label

	1-2 patients (n=53)	3-5 patients (n=75)	6-10 patients (n=110)	11-20 patients (n=111)	>20 patients (n=75)	Total (n=424)
Inconsistent responses	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Q5 Reported normal cognitive status does not match cognitive test score or other responses	0 (0.0%)	1 (1.3%)	0 (0.0%)	5 (4.5%)	1 (1.3%)	7 (1.7%)
Q5 cognitive normal but Q7 reports abnormal cognitive score	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	1 (1.3%)	3 (0.7%)
Q5 cognitive normal but Q9 response indicates presence of cognitive impairment	0 (0.0%)	1 (1.3%)	0 (0.0%)	5 (4.5%)	1 (1.3%)	7 (1.7%)
Q5 cognitive normal but Q11 response indicates treatment for cognitive impairment	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.5%)	0 (0.0%)	5 (1.2%)
Q8 “asymptomatic” reasons but symptoms reported	5 (9.4%)	7 (9.3%)	16 (14.5%)	20 (18.0%)	10 (13.3%)	58 (13.7%)
Q8 response is “asymptomatic” reason but Q5 reports cognitive impairment	5 (9.4%)	7 (9.3%)	16 (14.5%)	20 (18.0%)	9 (12.0%)	57 (13.4%)
Q8 response is “asymptomatic” reason but Q7 reports abnormal cognitive score	2 (3.8%)	5 (6.7%)	12 (10.9%)	9 (8.1%)	6 (8.0%)	34 (8.0%)
Q8 Estimating risk of progression of MCI to dementia when the subject is already demented	0 (0.0%)	6 (8.0%)	4 (3.6%)	6 (5.4%)	4 (5.3%)	20 (4.7%)
Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia	0 (0.0%)	6 (8.0%)	4 (3.6%)	6 (5.4%)	4 (5.3%)	20 (4.7%)

Exclusion of case from question 5 - Reported normal cognitive status does not match cognitive test score or other responses - Q5 cognitive normal but Q7 reports abnormal cognitive score: Q5 response = “Normal Cognition” AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review; Q5 cognitive normal but Q9 response indicates presence of cognitive impairment: Q5 response = “Normal Cognition” AND Q9 includes any response except “none of the above”; Q5 cognitive normal but Q11

indicates treatment for cognitive impairment: Q5 response = "Normal Cognition" AND Q11 response = "Yes" for either medication

Exclusion of case from question 8 - "Asymptomatic" reasons were checked but symptoms reported - Q8 response is "asymptomatic" reason but Q5 reports cognitive impairment: Q8 = see footnote* AND Q5 response NOT "Normal Cognition"; Q8 response is "asymptomatic" reason but Q7 reports abnormal cognitive score: Q8 = see footnote* AND Q7 reports MMSE <27 or ADAS-Cog >9 or any other reported test result considered abnormal after medical review

Exclusion of case from question 8 - Estimating risk of progression of MCI to dementia when the subject is already demented - Q8 response is using scan to predict progression to dementia but Q5 response indicates presence of dementia: Q8 response = "For estimating risk of MCI progression to clinical Alzheimer's disease" AND Q5 response = mild or moderate or severe dementia

*Footnote: Q8 "asymptomatic" reasons include any of the following:

- As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier
- As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP)
- As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors

5. Listing of patient cases considered off-label use for no clinical evaluation per protocol with evidence of ongoing evaluation from detailed analysis

Listing 1. Patient Cases Considered Off-label Use For No Clinical Evaluation Per Protocol with Evidence of Ongoing Evaluation from Detailed Analysis

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild cognitive impairment	05			06|07	Yes	01|03|04|06
		Mild cognitive impairment	01|06|07|08	27		07	Yes	01|02|04|05|06
		Mild dementia	01	21		07	Yes	01|04|06
		Mild dementia	01	24		07	Yes	01|04|06
		Mild cognitive impairment	09			07	Don't know/ recall	
		Mild cognitive impairment	01	28		06|07	Yes	01|02|06
		Mild dementia	01|10	27		07	Yes	01|02|04|06
		Cognitive complaint without cognitive impairment on examination	01	29		05	Yes	01|04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Moderate dementia	01	24		07	Yes	01|02|06
		Mild dementia	01|10	25		07	Yes	01|02|04|06
		Cognitive complaint without cognitive impairment on examination	01	30		03|05	No	
		Mild cognitive impairment	01|11	28		06	Yes	01|04|06
		Mild cognitive impairment	01	28		06|07	Yes	01|06
		Mild cognitive impairment	01	29		06|07	Yes	01|03|04|06
		Mild cognitive impairment	01|14|15|16|17|18	28		06	Yes	01|02|04|06
		Mild cognitive impairment	01	26		07	Yes	01|04|06
		Moderate dementia	01|06|07|08	18		07	Yes	01|02
		Mild cognitive impairment	01|02	NR	NR	05|06|07	Don't know/ recall	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Cognitive complaint without cognitive impairment on examination	01|19	30		05	Yes	01|04|06
		Mild cognitive impairment	02		NR	02	Yes	04|06
		Mild cognitive impairment	01	27		03|05	Yes	02|04
		Mild cognitive impairment	01|02	27	27	05	Yes	01
		Cognitive complaint without cognitive impairment on examination	01	28		06	Yes	03
		Mild cognitive impairment	01|10	26		06|07	Yes	01|02|03|04|06
		Cognitive complaint without cognitive impairment on examination	01	29		03|05	Yes	04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild dementia	01	NR		07	Don't know/ recall	
		Moderate dementia	01	22		07	Yes	01|06
		Moderate dementia	01	16		07	Yes	01|04|06
		Mild dementia	01|02	19	NR	02|07	Yes	01|03|04|05|06
		Mild cognitive impairment	01	24		06	Yes	01|02|04|06
		Cognitive complaint without cognitive impairment on examination	01|02	NR	NR	05	Yes	01|02|04|06
		Cognitive complaint without cognitive impairment on examination	01	27		05|06	Yes	01|04|06
		Mild cognitive impairment	01	26		06	Yes	01|02|03|04|05|06
		Mild dementia	01	NR		07	Don't know/ recall	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Cognitive complaint without cognitive impairment on examination	01|02	26	NR	05	Yes	01|02|04|06
		Mild cognitive impairment	01|10	29		06	Yes	01|03|04|06
		Mild cognitive impairment	01	21		05|06	Yes	01|04|06
		Mild cognitive impairment	01|19	24		06	Yes	01|04
		Moderate dementia	01|07	17		05|07	Yes	01|02|03|04|06
		Normal cognition	01	24		06	No	
		Mild cognitive impairment	01	25		05	Yes	01|02|03|04|06
		Moderate dementia	01	8		07	No	
		Mild cognitive impairment	01|21|14|15|17|22|23	28		06	Yes	01|02|04|06
		Mild cognitive impairment	02		NR	05	Yes	01|02|04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Cognitive complaint without cognitive impairment on examination	01	28		05|06	Yes	01|04
		Mild dementia	12			07	Yes	01|04
		Mild cognitive impairment	01|07|15|24	25		06	Yes	01|02|03|04|05|06
		Mild cognitive impairment	01	24		05	Yes	01|03|04|06
		Mild cognitive impairment	01	24		05|07	Yes	01|03|04
		Cognitive complaint without cognitive impairment on examination	01	28		06	Yes	01|04|06
		Cognitive complaint without cognitive impairment on examination	12			05|06	Yes	04|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Cognitive complaint without cognitive impairment on examination	01|07	29		05|07|10	Yes	01|03|04|06
		Cognitive complaint without cognitive impairment on examination	01	30		11	Yes	01|04|06
		Mild cognitive impairment	01|02|25	27	NR	07	Yes	01|02|04|05|06
		Mild cognitive impairment	01	18		06	Yes	01|04|06
		Cognitive complaint without cognitive impairment on examination	01|12|07	30		05|07	Yes	01|04|06
		Mild cognitive impairment	01	22		03|04|05|06	Yes	01|04|06
		Cognitive complaint without cognitive	01	30		05|11	Yes	01|02|04|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		impairment on examination						
PPD		Mild cognitive impairment	01	28		05|06|07	Yes	01|02|04
		Mild cognitive impairment	01|02	28	60	05|06|10	Yes	01|04
		Mild cognitive impairment	01	18		07	Yes	03|04|06
		Mild cognitive impairment	01	27		10	Don't know/ recall	
		Mild dementia	12			07	Yes	01|04|06
		Mild dementia	12			07	Yes	01|04|06
		Mild cognitive impairment	01|02	24	NR	05	Yes	01|03|04|06
		Mild cognitive impairment	01|21|14| 15|17|22| 23	25		06	Yes	01|02|04|06
		Mild cognitive impairment	01	29		06	Yes	01|04|06
		Mild cognitive impairment	01|12	28		05	Yes	01|04|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild cognitive impairment	01	NR		02	Yes	01|03
		Mild dementia	01	23		02|06|10	Yes	01|04|06
		Cognitive complaint without cognitive impairment on examination	12			03|05|06|07|08	Yes	01|02|04|06
		Mild dementia	02		NR	02	Yes	04
		Mild cognitive impairment	01|14|15|17|22|23|29	29		06	Yes	01|02|04|06
		Cognitive complaint without cognitive impairment on examination	01	29		05	Yes	01|04|06
		Mild dementia	12			07	Yes	01|04|06
		Normal cognition	01	28		03	Yes	01|06
		Mild cognitive impairment	01|07	27		05|06	Yes	01|02|04|06
		Mild	01|12	27		06	Yes	01|03|04|05|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		cognitive impairment						
PPD		Cognitive complaint without cognitive impairment on examination	01	30		05	No	
		Mild cognitive impairment	01	25		07	Yes	01|04
		Mild dementia	01	23		05|10	Yes	04|06
		Cognitive complaint without cognitive impairment on examination	01	30		05	Yes	01|04
		Mild cognitive impairment	01|02	22	NR	06|07	Yes	01|04|06
		Moderate dementia	01|19	19		07	Yes	01|04
		Mild cognitive impairment	01	25		06|07	No	
		Moderate dementia	01	23		05|06|07	No	
		Mild	01|02	NR	NR	07	Yes	01|04|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		dementia						
PPD		Mild cognitive impairment	01	27		07	Yes	01|04|06
		Mild cognitive impairment	12			05	Yes	01|02
		Mild cognitive impairment	01	24		07	No	
		Cognitive complaint without cognitive impairment on examination	01	28		05	No	
		Moderate dementia	01|10	9		07|13	Yes	01|02|03|04|06
		Mild dementia	01	21		02|04|07	Yes	01|03|04|06
		Cognitive complaint without cognitive impairment on examination	01	18		05	Yes	03|04|06
		Cognitive complaint without cognitive impairment	01	28		05|06	Yes	04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		on examination						
PPD		Mild cognitive impairment	01|07|15|26	22		07	Yes	01|04|06
		Moderate dementia	01	24		07	Yes	01|04|06
		Mild cognitive impairment	02		NR	07	Yes	01|04|06
		Mild dementia	01	25		07	Yes	01|02|04|06
		Moderate dementia	01	27		03	Yes	01
		Mild dementia	01	26		07	Yes	03|04|06
		Mild dementia	01|07	24		14	Yes	01|04|06
		Mild dementia	01|06|07|18	28		07	Don't know/ recall	
		Cognitive complaint without cognitive impairment on examination	01	20		06	Yes	04|05
		Mild cognitive impairment	01	22		07	No	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Normal cognition	01	29		05	Yes	01|04|06
		Mild dementia	01	20		04|08	Yes	01|02|03
		Mild cognitive impairment	12			02|05|06|07	Yes	01|04|06
		Cognitive complaint without cognitive impairment on examination	01	27		03	Yes	01
		Mild cognitive impairment	01|27	26		07	Yes	01|04|06
		Mild cognitive impairment	01|26|08	28		06|07	Yes	01|02|04|06
		Mild cognitive impairment	01	25		02	Yes	03
		Mild cognitive impairment	01|02	27	NR	07	Yes	01|04|06
		Mild dementia	01|12	24		07	Yes	01|04|06
		Moderate dementia	01|02	17	8	02|04|06	Yes	01|04|06
		Moderate	01	NR		02	Don't	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		dementia					know/ recall	
PPD		Moderate dementia	01|02	NR	NR	02|04|07	Yes	01|02|03|04|05|06
		Cognitive complaint without cognitive impairment on examination	01	28		05	Yes	01|04
		Cognitive complaint without cognitive impairment on examination	01	29		05	Yes	01|04
		Severe dementia	01	8		05|07	Yes	01|04
		Moderate dementia	01	16		02|05|07|10	Yes	01|04
		Cognitive complaint without cognitive impairment on examination	01|02	27	5	05	Yes	01|04|06
		Cognitive complaint without cognitive	01	27		06	Yes	02

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		impairment on examination						
PPD		Mild cognitive impairment	01|02	27	63	05|06	Yes	01|04
		Mild dementia	02		NR	02|04|05|06|07	Yes	02|03|04
		Cognitive complaint without cognitive impairment on examination	01	28		05	Yes	01|03|04|06
		Mild dementia	01			13	No	
		Mild dementia	01|12	27		06|14	Yes	01|03|04|06
		Cognitive complaint without cognitive impairment on examination	01	24		10	Yes	04|06
		Moderate dementia	01	NR		02|07	No	
		Mild cognitive impairment	01	26		02	Yes	03
		Moderate	01	24		03	No	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		dementia						
PPD		Mild cognitive impairment	01	NR		04|05|06|07	Yes	01|03|04|05
		Mild dementia	01	NR		02|03|04|07	Yes	02|03|04
		Mild cognitive impairment	01	26		06|07	Yes	01|04
		Cognitive complaint without cognitive impairment on examination	01	19		10	Yes	04|05
		Moderate dementia	01	19		02|06|07|11	Yes	01|04|06
		Normal cognition	01	29		05|07	Yes	01|04|06
		Normal cognition	01	30		03	Yes	01|03|04|05|06
		Normal cognition	01	30		10	Yes	01|04|05|06
		Mild cognitive impairment	01	25		03|06	Yes	01
		Mild cognitive impairment	01	26		03	No	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild dementia	01	27		02	Yes	01
		Mild dementia	01	27		02	Yes	02
		Mild dementia	01	26		04	Yes	02
		Mild dementia	01	27		04	Yes	01
		Moderate dementia	01	24		07	Yes	03|06
		Mild dementia	02		18	08	No	
		Mild dementia	01	27		08	Yes	05
		Mild dementia	01	NR		06	Yes	01|03|04
		Cognitive complaint without cognitive impairment on examination	01|19	26		03|05	Yes	01|02|04
		Severe dementia	01	27		08	No	
		Mild cognitive impairment	01	25		06	No	
		Mild dementia	01	28		08	Yes	01

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild dementia	01	19		07	Yes	01|02|03|06
		Mild dementia	01	26		04	Yes	02
		Severe dementia	02		23	08	Don't know/ recall	
		Severe dementia	01	30		08	No	
		Severe dementia	01	30		08	Yes	06
		Moderate dementia	01	20		03|05|06	Yes	01|04|06
		Cognitive complaint without cognitive impairment on examination	01|19	21		05|07	Yes	01|04
		Cognitive complaint without cognitive impairment on examination	01	21		03	Yes	04|05
		Mild cognitive impairment	01	NR		02|06	Yes	01|02|04|06
		Moderate dementia	01	25		07	Yes	01|04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Normal cognition	01	30		02	Yes	01
		Moderate dementia	01	21		02|08	Don't know/ recall	
		Mild dementia	01	25		05	Yes	03
		Mild dementia	01	27		06	Yes	01
		Cognitive complaint without cognitive impairment on examination	01	27		07	Yes	03
		Cognitive complaint without cognitive impairment on examination	19			02	Yes	01
		Mild cognitive impairment	02		20	02	Yes	01
		Mild dementia	02		20	06	Yes	02
		Mild cognitive impairment	01	25		02	Yes	01
		Mild	01	20		02|07	Yes	02|04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		dementia						
PPD		Mild dementia	01	26		07	Don't know/ recall	
		Severe dementia	01	26		08	Don't know/ recall	
		Mild dementia	01	27		04|05|06|07	Yes	02
		Severe dementia	01	29		02|04	Yes	01|04|06
		Mild dementia	01	27		04	Yes	02
		Mild cognitive impairment	02		15	04	No	
		Mild dementia	01	25		02	No	
		Moderate dementia	02		24	02	No	
		Mild dementia	02		15	01|03	No	
		Mild dementia	01|02	NR	NR	01|03	Yes	04
		Mild cognitive impairment	01|02	NR	NR	01|03|05	Don't know/ recall	
		Mild cognitive impairment	01|12|19	22		01|06	Yes	01|04|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Normal cognition	01	22		01|02|05|06|07|10	Yes	01|04|06
		Mild dementia	01|12	24		01|06	No	
		Moderate dementia	01|02	27	26	01|03	Yes	02|05
		Cognitive complaint without cognitive impairment on examination	01	27		01|03	Yes	01|03
		Mild cognitive impairment	01|02	27	62	01|06	Yes	01|02|04|05|06
		Mild dementia	01|07	24		01|11	Yes	01|03|04|05|06
		Normal cognition	01	27		01|04	Yes	03|04
		Mild cognitive impairment	01|12	22		01|06|07	Yes	01|04|06
		Cognitive complaint without cognitive impairment on examination	01	21		01|05|06|07	Yes	01|04|06
		Mild cognitive	01	21		01|05|06|07|10	Yes	01|04|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		impairment						
PPD		Moderate dementia	01|02	13	12	01|05|06	Yes	01|03|04|06
		Mild cognitive impairment	01|02	26	60	01|06	Yes	01|04|06
		Mild cognitive impairment	12			01|03|06|07	Yes	04|06
		Mild cognitive impairment	01	27		01|03|06	Yes	01|02|04|05|06
		Mild dementia	01|02	22	NR	01|06	Yes	01|02|04|06
		Mild cognitive impairment	01	26		01|06|07	Yes	01|03|04|06
		Mild cognitive impairment	01	22		01|06	Yes	01|04
		Mild cognitive impairment	01|07	25		01|06|07	Yes	01|02|03|04|06
		Mild dementia	01	NR		01|06|07	Yes	01|03|04|06
		Mild cognitive impairment	10			01|06|07	Yes	01|03|06
		Severe dementia	01	15		01|04|07	No	

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild cognitive impairment	18|13|32			01|06|07	Yes	01|02|03|04|06
		Cognitive complaint without cognitive impairment on examination	01|02	20	27	01|06|07	No	
		Mild cognitive impairment	01	29		01|05|06|07	Yes	01|04
		Mild cognitive impairment	01|12|07|19	24		01|06	Yes	01|04|06
		Mild cognitive impairment	01|07	25		01|03|06|07	Yes	01|02|03|04|05|06
		Mild dementia	01	21		01|02|03|10	Yes	04|06
		Mild cognitive impairment	01|02	14	15	01|02|03	Yes	01|03|04|06
		Mild dementia	01|12|20	21		01|02|06|07	No	
		Mild cognitive impairment	01|06|07	28		01|06	Yes	01|02|04|06
		Mild dementia	01	24		01|06|07	Yes	01|03|04|05|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild cognitive impairment	01|12	23		01|06	Yes	01|04|06
		Mild cognitive impairment	02		24	01|03	Yes	01|04
		Mild dementia	01	22		01|02|03|10	Yes	04
		Cognitive complaint without cognitive impairment on examination	02		66	01|06	Yes	01
		Mild cognitive impairment	01	5		01|05|06	Yes	01|04|06
		Mild cognitive impairment	01	19		01|02|03|06|07|08|10	Yes	01|03|04|05
		Mild cognitive impairment	01|12|10	26		01|06|07	Yes	01|02|04|06
		Mild dementia	01	21		01|09	Yes	01|03|04|06
		Mild dementia	01	NR		01|03|07	Yes	01|03|04|05|06
		Mild cognitive impairment	01|19	24		01|06	Yes	01|04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Moderate dementia	12			01|02|04|07	Yes	01|04|06
		Mild cognitive impairment	01|12	29		01|06	Yes	01|04|06
		Mild cognitive impairment	01	26		01|06|07	Yes	01|02|03|04
		Mild cognitive impairment	01	18		01|05|06	Yes	01|04|06
		Mild cognitive impairment	01	22		01|06|07	Yes	01|04
		Mild cognitive impairment	01|28|21|18|32|04|33|30|31	20		01|06	Yes	01|02|03|04|06
		Mild cognitive impairment	01	26		01|06	Yes	01|03|04|06
		Cognitive complaint without cognitive impairment on examination	02		NR	01|04|05|06|07	Yes	02|03|04
		Mild cognitive impairment	01	25		01|06|07	Yes	01|02|04|06
		Cognitive complaint	01	28		01|05|09|10	Yes	01|04

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
		without cognitive impairment on examination						
PPD		Mild dementia	02		NR	01|02|05|06|07|08|09	Yes	02|03|06
		Mild cognitive impairment	01|19	24		01|06	Yes	04
		Cognitive complaint without cognitive impairment on examination	01	28		01|04|06	Yes	01|02|03|04
		Mild cognitive impairment	01	29		01|05|06	Yes	01|04
		Cognitive complaint without cognitive impairment on examination	01|02	18	8	01|02|04|05|06|07|10	Yes	01|04|05|06
		Mild cognitive impairment	01	24		01|02|05|06|07	Yes	01|02|03|04|06
		Mild dementia	01	20		01|03	Yes	01|02|03

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild cognitive impairment	01|12|07	25		01|06	Yes	01|02|04|06
		Mild cognitive impairment	03			01|06|07	Yes	01|04
		Mild cognitive impairment	01|10|13	28		01|06|07	Yes	01|03|04|06
		Mild cognitive impairment	19			01|04	Yes	01|02
		Mild cognitive impairment	01|07	25		01|06	Yes	01|02|04|06
		Moderate dementia	01	19		01|02|06|07	Yes	01|04
		Mild dementia	01	25		01|06|07	No	
		Severe dementia	02		32	01|04	No	
		Mild cognitive impairment	01	25		01|06|07	Yes	01|02|04
		Mild cognitive impairment	01|26	25		01|06|07	Yes	01|04|06
		Mild cognitive impairment	01	27		01|06	Yes	01|02|04|05|06

RESPID	Q2_ Age	Q5_ Cognitive_ status	Q7a_ Cognitive function tests[a]	Q7b_ Results MMSE	Q7b_ Results ADAS-cog	Q8_ Reasons for Amyvid PET scan referral[b]	Q10_ Laboratory tests ordered	Q10a_ Type of Laboratory tests ordered[c]
PPD		Mild cognitive impairment	01	28		01|06	Yes	01|03|04|05|06
		Mild cognitive impairment	01|07	24		01|06	Yes	01|04|06
		Mild cognitive impairment	01	29		01|06	Yes	01|02|04
		Mild cognitive impairment	01	29		01|06|10	Yes	01|02|04|06
		Mild cognitive impairment	01	27		01|06	Yes	01|02|04|06

NR = Not reported

[a]01: MMSE; 02: ADAS-cog; 03: No ("none"); 04: Poppelreuter overlapping figure test; 05: CAMDEX; 06: Frontal Assessment Battery (FAB); 07: Memory tests, 08: Seashore Rhythm Test (SRT); 09: Glucose PET scan; 10: NPS battery; 11: NBACE; 12: ACE; 13: T@M;14: CERAD; 15: Stroop; 16: Boston Anomia; 17: Wechsler Adult Intelligence Scale; 18: TMT; 19: Montreal Cognitive Assessment (MoCA); 20: Rivermead Behavioural Memory test (RBMT); 21: Boston Naming Test; 22: 18-A; 23: 18-B; 24: Fluency tests; 25: Clinical Dementia Rate (CDR); 26: Orientation tests; 27: Clock's test; 28 :Praxia batteries;;29 :Boston test; 30: Luria series test; 31: Digit span test; 32: Photo test; 33: Go/ no Go test

[b]01: As part of the evaluation of a patient with cognitive decline documented on clinical examination; 02: As part of an evaluation of the severity of dementia; 03: As part of an evaluation of amyloid status in an asymptomatic individual with either a family history of Alzheimer's disease or known to be a ApoE4 carrier; 04: For monitoring response to therapy; 05: As part of an evaluation of a cognitive complaint that was unconfirmed on clinical examination; 06: For estimating risk of mild cognitive impairment (MCI) progression to clinical Alzheimer's disease; 07: To establish a diagnosis of Alzheimer's disease based on a positive scan result; 08: As a substitute for genetic testing in an asymptomatic person with a family history of a genetic mutation known to cause Alzheimer's disease (e.g. presenilin1, presenilin 2 or APP); 09: As a substitute for clinical evaluation; 10: As part of an assessment of Alzheimer's disease in an asymptomatic individual without other risk factors; 11: For a non-medical

use (e.g., insurance coverage, legal or employment-related reasons); 12: Other, please specify; 13: Differential diagnosis; 14: Investigation

[c]01: Clinical imaging e.g., CT, MRI; 02: Scan using an imaging agent, e.g., PET or SPECT scan; 03: Lumbar puncture; 04: Lab tests from blood or urine, e.g., CBC, B12, serum chemistry, etc.; 05: Genetic testing, e.g., ApoE or other; 06: Neuropsychological testing

Annex 2. List of standalone documents

No.	Date	Title
1.	8th July 2017	Protocol
2.	4th July 2014	Enrolment grid
3.	9th June 2017	Statistical Analysis Plan (SAP)
4.		Summary of Product Characteristics (SmPC)