HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

18 December 2013

AMYVID 800 MBq/ml solution for injection

10 ml vial (CIP: 34009 585 065 4 3)
15 ml vial (CIP: 34009 585 066 0 4)

AMYVID 1900 MBq/ml solution for injection

10 ml vial (CIP: 34009 585 067 7 2)
15 ml vial (CIP: 34009 585 068 3 3)

Applicant: LILLY

INN	florbetapir
ATC Code (2012):	V09AX05 (other central nervous system diagnostic radiopharmaceuticals)
Reason for the request	**Inclusion**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"This medicinal product is for diagnostic use only.** **AMYVID is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. AMYVID should be used in conjunction with clinical evaluation.** **A negative PET scan indicates sparse or no amyloid plaques, which is not consistent with a diagnosis of Alzheimer's disease. For the limitations in the interpretation of a positive PET scan, see sections Warnings and precautions for use and Pharmacodynamic properties**

Actual Benefit	**Insufficient**
Improvement in Actual Benefit	**Not applicable**
Therapeutic use	**The Committee estimates that the PET imaging after administration of AMYVID (florbetapir 18F) does not have any place in the diagnostic strategy of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive impairment.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 14 January 2013 Risk Management Plan
Prescribing and dispensing conditions / special status	List I Medicinal product reserved for hospital use

ATC Classification	2012	
	V	Various
	V09	Diagnostic radiopharmaceuticals
	V09A	Central nervous system
	V09AX	Other central nervous system diagnostic radiopharmaceuticals
	V09AX05	Florbetapir

02 BACKGROUND

The company is requesting the inclusion of AMYVID solution for injection, the active substance of which is florbetapir, a medicinal product restricted to hospital use, on the list of medicines approved for hospital use.

Florbetapir ^{18}F binds itself, with high affinity and high specificity, to the β-amyloid protein. The accumulation of this protein in the aggregates known as β amyloid plaques outside the neurons represents one of the two main pathological hallmarks of Alzheimer's disease. Marking florbetapir with fluor-18 (^{18}F) allows the senile plaques to be scanned via Positron Emission Tomography (PET).

AMYVID is administered intravenously.

03 THERAPEUTIC INDICATIONS

"This medicinal product is for diagnostic use only.

AMYVID is a radiopharmaceutical indicated for Positron Emission Tomography (PET) imaging of β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive impairment. AMYVID should be used in conjunction with clinical evaluation.

A negative PET scan indicates sparse or no plaques, which is not consistent with a diagnosis of Alzheimer's disease. For the limitations in the interpretation of a positive PET scan, see sections "Warnings and precautions for use and Pharmacodynamic properties. "

04 DOSAGE

"A PET scan with florbetapir (^{18}F) should be requested by physicians skilled in the clinical management of neurodegenerative disorders.
AMYVID images should only be interpreted by nuclear medicine physicians trained in the interpretation of PET images with florbetapir (^{18}F). A recent co-registered computed tomography (CT) scan or magnetic resonance imaging (MRI) of the patient to get a fused PET-CT or PET-MRI image is recommended in cases of uncertainty about the location of grey matter and of the grey/white matter border in the PET scan.

Posology
The recommended activity for an adult weighing 70 kg is 370 MBq florbetapir (^{18}F). The volume of the injection should not be less than 1 ml and not exceed 10 ml.

Special populations
Older people
No dose adjustment is recommended based on age.

Renal and hepatic impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.Extensive dose-range and adjustment studies with the medicinal product in normal and special populations have not been performed. The pharmacokinetics of florbetapir (^{18}F) in patients with renal or hepatic impairment have not been characterised.

[…]

Method of administration
For intravenous use.
For multidose use.
The activity of florbetapir (^{18}F) has to be measured with an activimeter (dose calibrator) immediately prior to injection.
The dose is administered by intravenous bolus injection, followed by a flush of sodium chloride 9 mg/ml (0.9%) solution for injection to ensure full delivery of the dose.
Injection of AMYVID through a short intravenous catheter (approximately 4 cm or less) minimizes the potential for adsorption of the active substance to the catheter.
The injection of florbetapir (^{18}F) must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

Image acquisition
A 10 minute PET image should be acquired starting approximately 30 to 50 minutes after intravenous injection of AMYVID. Patients should be supine with the head positioned to centre the brain, including the cerebellum, in the PET scanner field of view. Reducing head movement with tape or other flexible head restraints may be employed. Reconstruction should include attenuation correction with resulting transaxial pixel sizes between 2.0 and 3.0 mm. "

05 THERAPEUTIC NEED

In 2010, in France, the number of people with Alzheimer's disease and other types of dementia was estimated, according to extrapolation of data from French and European studies, to be between 750,000 and 1,000,000, according to hypotheses, with projections between 1.29 and 1.40 million people in 2030.[1] Alzheimer's disease represents at least two thirds of dementia syndromes. The other common aetiologies are vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia and frontotemporal lobar degeneration.[2]
In more than 90% of cases, the patients are affected by late-onset or "sporadic" Alzheimer's disease which generally occurs in patients beyond the age of 65[3] and which manifests itself primarily by an amnesiac syndrome, starting up in a dominant way. In 6 to 7% of cases, we see early-onset Alzheimer's disease, starting in patients below the age of 65. This form has a strong hereditary component (10% versus less than 2% for the late-onset types).[4]

Alzheimer's disease is defined by the combination of dementia syndrome and the presence of specific cerebral lesions in the post mortem histological exam of the cerebral cortex. The two main hallmarks are the accumulation of β-amyloid peptide in aggregates known as β-amyloid plaques outside the neurons (Aβ pathology) and the formation inside the neurons, of tangles of paired helical filaments with phosphorylated tau proteins or “neurofibrillary degeneration”(tautopathy). Neurofibrillary degeneration is not specific to Alzheimer's disease and has been found in almost all brain diseases, as well as in healthy elderly subjects. However, their density and anatomical location are important parameters in the neuropathology of Alzheimer's disease.[5] The β-amyloid plaques can be classified into two groups: "diffuse" and "neuritic" (or "senile").
The hypothesis of the "amyloid cascade", according to which the accumulation of amyloid fibrils leads to dementia, is prevalent at the moment. However, this sequence of events is still controversial.
Alzheimer's disease begins long before the dementia stage through the appearance of variously associated cognitive impairment and possibly behavioural or personality disorders.Alzheimer’s disease progresses over several years with the emergence of progressive dependence that can affect many aspects of activities of daily living (such as washing, dressing, eating, moving around…) and have an impact on relatives.
Early diagnosis, before the dementia stage, aims to optimise treatment and to limit loss of autonomy. Non-drug treatments (such as psychosocial/psychoeducation intervention, training of caregivers in institutions, physical activity programmes, cognitive stimulation/training of the patient) aims to combat cognitive decline. The available medicines have a purely symptomatic effect and do not alter the disease progression.

The initial medical assessment includes an interview, a clinical examination, a functional assessment, and a standardised overall cognitive assessment using the mini-mental state examination (MMSE).
If there is a recently discovered proven cognitive impairment, a systematic cerebral MRI (or CT) is recommended. After this initial assessment, if, in spite of the mnesic complaint, the cognitive functions assessed by the MMSE and brief identification tests, the activities of daily living assessed by the IADL scale and the clinical context (absence of mood and behavioural disorders) are

[1] Institut de Veille Sanitaire (Health Monitoring Institute). Duport N. et al. Maladie d’Alzheimer et démences apparentées: taux d’ALD, de patients hospitalisés et de mortalité en France métropolitaine, 2007 et 2010. BEH 30, 10 September 2013 361-368.
[2] HAS. Practice guidelines Alzheimer’s disease and related conditions- Diagnosis and treatment. December 2011.
[3] Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. N Engl J Med 2003; 348: 1356-64.
[4] Campion D et al. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am J Hum Genet 1999; 65: 664-70.
[5] Nelson PT, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012; 71: 362-81.

normal, a comparative cognitive assessment may be given to the patients as part of a follow-up phase 6 to 12 months later.
In difficult or atypical cases, diagnostic tests can be performed by specialised teams. They include Aβ42 protein and TAU (total and phosphorylated) proteins assays in the CSF, the standard CSF analysis (cells, glucose, proteins, protein electrophoresis), SPECT imaging (even a PET scan), and the DATscan®.

As the definitive diagnosis is anatomopathological, during the lifetime of the person, the diagnosis can only be probabilistic. The "neuritic" β-amyloid plaques, more likely to be related to cognitive impairment than the "diffuse" plaques (found in the brains of the elderly with no cognitive impairment and not related to synaptic pruning[6]) are one of the diagnostic criteria of Alzheimer's disease.[5] Currently, the anatomopathological criteria of Alzheimer's disease NIA-RI criteria,[7]which gather Consortium to Establish A Registry for AD (CERAD) criteria <ph219/><pt220[8,9] (based on the density of the neuritic plaques) and Braak et Braak criteria (based on the importance of neurofibrillary tangles).[6]

The value of a new diagnostic test for Alzheimer's disease or other types of dementia is to be put into perspective with therapeutic modalities currently very limited, whether with drugs or not.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

No other medicinal product is indicated for Positron Emission Tomography (PET) imaging to estimate β-amyloid neuritic plaque density in the brains of adult patients with cognitive impairment who are being evaluated for Alzheimer’s disease and other causes of cognitive impairment.

06.2 Other health technologies

In difficult or atypical cases of suspected Alzheimer's disease or similar, some diagnostic tests may be proposed:[10]

- Total *Tubulin Associated Unit* (TAU) proteins assay in the cerebrospinal fluid (CSF), phosphorylated TAU proteins and Aß42 proteins can be performed if there is any doubt about the diagnosis and especially in young patients.

- A standard analysis of the cerebrospinal fluid (cells, glucose, proteins, protein electrophoresis) is recommended in patients with atypical and/or rapidly progressing (suspected inflammatory disorder, infectious disease, paraneoplastic syndrome or CJD) clinical presentation.

- A single photon emission computed tomography (SPECT) scan, even a positron emission tomography (PET) scan, can be performed in the event of atypical dementia or if there is any doubt about frontotemporal degeneration or any other focal atrophy. A cerebral scintigraphy with

[6] Serrano-Pozo A, et al. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011 (September); 1: a006189.
[7] National Institute of Aging and the Reagan Institute.
[8] Mirra SS, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991; 41: 479-86.
[9] Mirra SS. The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer’s disease: A commentary. Neurobiol Aging 1997; 18: S91Y94.
[10] HAS. Practice guidelines. Alzheimer’s disease and related conditions- Diagnosis and treatment. December 2011.

ioflupane [$_{123}$I] (DATscan®) may be considered if there is any doubt about dementia with Lewy bodies.

◗ Conclusion

There is no clinically relevant drug comparator.

Various tests are recommended if there is any doubt about the diagnosis, e.g.:

- **Aβ42 and TAU proteins assay in the CSF,**
- **a standard CSF analysis (cells, glucose, proteins, protein electrophoresis),**
- **a SPECT scan, even a PET scan,**
- **a DATscan®.**

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Marketing Authorisation abroad:

Country	Marketing Authorisation	
	Date	**Indications and special condition(s)**
United States	April 2012	"AMYVID is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative AMYVID scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive AMYVID scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. AMYVID is an adjunct to other diagnostic evaluations. Limitations of Use: – A positive AMYVID scan does not establish a diagnosis of AD or other cognitive impairment. – Safety and effectiveness of AMYVID have not been established for: o Predicting development of dementia or other neurologic condition; o Monitoring responses to therapies."

Reimbursement abroad:

Country	Yes/No/Assessment in progress
United States	Decision of the CMS (Center for Medicare & Medicaid Services) dated 27 September 2013: [11]the beta-amyloid PET scan is not covered by "Section 1862 (a)(1)(A) of the Social Security Act ("The Act")". An Aβ PET scan per patient included in clinical trials meeting certain criteria specified in the decision is reimbursed within the context of "Section 1862(a)(1)(E) of the Act".
Germany	No. For reasons linked to production sites, production will not be established before 2015.
Spain	Yes (Decision of 12 December 2013): reimbursement of AMYVID 800 MBq/ml (15 ml vial) and AMYVID 1900 MBq/ml (15 ml vial) in the Marketing Authorisation indications.
Italy	Application made to IAAF in June 2013.
United Kingdom	No review by NICE planned. The NHS plans to reimburse florbetapir PET imaging.[12] Recommendations from the ARSAC:[13] "*Use in highly selected patients with cognitive impairment where i) Alzheimer's dementia (AD) is a possible diagnosis but this remains uncertain after comprehensive evaluation by a dementia expert and conventional imaging work-up and ii) where knowledge of the presence or absence of amyloid is expected to increase diagnostic certainty and influence patient management*."

[11] The Centers for Medicare & Medicaid Services (CMS). Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N). September 27, 2013.
[12] NHS OKs PET imaging to rule out Alzheimer's. December 18, 2013. by Loren Bonner , DOTmed News Online Editor. http://www.dotmed.com/news/story/22665/
[13] ARSAC Newsletter. Issue 9. October 2013.
http://www.arsac.org.uk/newsletter/documents/ARSACNewsletterOct2013.pdf

08 ANALYSIS OF AVAILABLE DATA

The evaluation of diagnostic performance (sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV)) and the correlation between the amyloid burden observed by the florbetapir PET scan and the cortical amyloid burden observed in the post-mortem is based on two phase III clinical studies:

- **An** open-label, prospective **study (A07)**[14] included 226 subjects divided into 2 cohorts: an **"autopsy" cohort** of 152 end-of-life subjects (i.e. a projected life expectancy ≤ 6 months) who consented to an autopsy, with different cognitive status (normal cognition, moderate cognition, Alzheimer's disease and other types of dementia), and a **"specificity" cohort** of 74 young subjects with no cognitive and neurological impairment and no known risk factors for Alzheimer's disease, for whom the absence of amyloid plaques was assumed. The primary efficacy analysis involved 29 patients in the "autopsy" cohort and 47 patients in the "specificity" cohort.
- An open-label study (A16),[15] **an extension of the A07 study,** allowed additional subjects who died within 12 months to be included in the "autopsy" cohort. The primary efficacy analysis involved 59 patients in the "post mortem" cohort.

In addition, the company has provided the results of supporting studies:
- A phase II (A05) study whose main objective was to generate florbetapir PET images used in different studies (A13, A11, A09 and PT01), the results of which are not presented in this opinion.
- A prospective, longitudinal, parallel-group study (A11) whose objective was to determine if the evidence of amyloid deposits in the florbetapir PET imaging could predict the progression of cognitive decline over the course of the 36 months following the scan. As the Marketing Authorisation for florbetapir does not include the prediction of the progression of cognitive decline, its results have not been taken into account for this opinion.
- **A retrospective study (A13)** on 44 cases whose objective was to evaluate the impact of florbetapir PET imaging on the diagnosis establishment for patients with mild cognitive impairment (MCI) and with Alzheimer's disease.
- **A FAIR-AD study**[16] conducted jointly on three centres in France and aimed to test the feasibility of using florbetapirPET imaging within a routine clinical context in order to differentiate patients with mild to moderate Alzheimer's disease and patients with mild cognitive impairment from healthy volunteer subjects.

The company also conducted a systematic literature review and a meta-analysis of the performance of different diagnostic tools for Alzheimer's disease.

The company dossier also included the results from three studies that are not presented in this opinion as they were low-powered and non-comparative and related to setting up of training programs for nuclear medicine physicians:
- two studies relating to an on-site training program for the reading and binary interpretation of florbetapir PET (Aβ+/Aβ-) images: the first one with 9 nuclear medicine physicians using images of 35 patients from the post-mortem cohort of the A07 study (A08 study); and the second one with 7 nuclear medicine physicians using images of 40 patients from a phase II (A05) study (25 diagnosed with "MCI" and 15 diagnosed with "Alzheimer's disease") randomly selected (A09 study);
- one study relating to an online training program for 5 nuclear medicine physicians for the reading and binary interpretation of florbetapir PET images within a clinical practice context using 151

[14] Clark CM et al. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA 2011; 305: 275-83.
[15] Clark CM et al. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid-β plaques: a prospective cohort study. Lancet Neurol 2012; 11: 669-78.
[16] Camus V et al. Using PET with 18F-AV-45 (florbetapir) to quantify brain amyloid burden in a clinical environment. Eur J Nucl Med Mol Imaging 2012; 39: 621-31.

images (images of 92 patients from the phase II (A05) study and 59 patients from the "post-mortem cohort" of the A07 study) (PT01 study).

08.1 Diagnostic efficacy

8.1.1 Open-label, prospective, phase III (A07) study

Principal study objective	- To evaluate the performance of florbetapir PET imaging for detecting β-amyloid plaques by comparing the amyloid burden assessment observed by florbetapir PET imaging and the real level of amyloid burden determined at autospy ("autopsy" cohort). - To evaluate the specificity of florbetapir PET imaging for identifying the absence of amyloid plaques in a group of young healthy volunteers (subjects with no cognitive or neurological impairment) ("specificity" cohort).
Method	Phase III, open-label, prospective study which evaluated the correlation between the florbetapir PET imaging (blind reading of all clinical information) and the presence of amyloid plaques, evaluated using immunohistochemistry at autopsy.
Main inclusion criteria	- **"Autopsy" cohort**: men and women, ≥18 years old, with a projected life expectancy of ≤6 months who have consented to the donation of their brain. An effort was made to include subjects with different cognitive states (normal cognition, moderate cognition, Alzheimer's disease and other types of dementia). - **"Specificity" cohort**: men and women aged 18 to 40 years old, with no cognitive or neurological impairment, and no known risk factors for Alzheimer's disease, including known genetic risk factors, such as the presence of an ApoE ε4 allele etc., and normal performance for their age in the "Logical Memory I & II" sub-score of the Wechsler memory scale[17] (history A).
Main non-inclusion criteria	- Cerebral tumour or other major focal cerebral abnormality. - Intensive care or palliative treatment. - Participation in an experimental study with an agent targeting the amyloid plaques and radiopharmaceutical imaging or treatment procedure within 7 days preceding the imaging session planned in the study. - Major focal structural loss of cerebral matter.
Treatment groups	A total of 226 subjects were included: - "autopsy" cohort: 152 end-of-life subjects who have consented to a post-mortem. - "Specificity" cohort: 74 subjects with no cognitive or neurological impairment. All the subjects taking part received 370 MBq (10 mCi) of florbetapir (^{18}F) by bolus IV administration.
Course of the study	
Primary efficacy endpoint	The florbetapir PET images were evaluated: - **Qualitatively** with the "specificity" cohort: a group of 3 readers who did not have any access to clinical information classified the images according to whether they were positive (Aβ+) or negative (Aβ-) for β-amyloid plaques. In order to minimise bias, the images from the "specificity" cohort were mixed randomly with 40 positive images selected in the "autopsy cohort" among those who had been noted as positive according to a semi-quantitative method (either a score of 2, 3 or 4 in the semi-quantitative evaluation). The majority result from the qualitative reading was the primary efficacy endpoint.

[17] The Wechsler scale (MEM-III – 2001), a scale for evaluating declarative memory as well as working memory consisting of 11 sub-tests, including 5 optional ones. It allows a general memory index (mnesic coefficient) to be calculated, which is an overall indicator of the mnesic functioning of a subject analogous to the intellectual coefficient (IQ). The 6 obligatory sub-tests are: *for verbal memory*: 1) logical memory I and II (I: immediate recall, II: delayed recall) which consists in freely recalling two complex stories; 2) word pairs I and II which consists in learning eight word pairs; *for visual memory*: 3) recognition of faces I and II which is a learning task then recognition of unknown faces; 4) family scenes I and II which is a visual relational memory task made up of four sketches representing members of a family engaged in different activities; *for working memory*: 5) letter-number sequencing; 6) spatial span.

<table>
<tr><td>Secondary endpoints</td><td>- Semi-quantitatively with the "post-mortem" cohort: 3 previously trained independent readers who did not have any access to clinical information noted the degree of uptake of florbetapir in the grey matter on a scale of 0 (no plaques) to 4 (high level of β-amyloid deposits) and the median score of 3 readers was used in the main correlation analysis.

- Quantitatively (semi-automated computerised analysis): the uptake of florbetapir in 6 previously defined cortical zones in the brain (precuneus, frontal cortex, anterior cingulate cortex, posterior cingulate cortex, parietal and temporal cortex) was measured quantitatively using standardised uptake values related to the cerebellum (SUV). The average cortical SUV ratios were then calculated.
The primary efficacy endpoint relating to SUVR was the median SUVR of the 6 cortical regions.

The post-mortem analysis used 2 methods:
- Immunohistochemistry for the quantitative analysis of the amyloid burden from its cerebral tissue sections prepared for each of the 6 cortical regions marked with an anti-amyloid 4G8 antibody of the β-amyloid peptide present in the diffuse senile plaques

- Density of the amyloid plaques. To perform the semi-quantitative amyloid burden assesment, the tissue sections from a batch of blocks from the same anatomical regions were coloured with silver nitrate (modified Bielschowsky). The average number of amyloid plaques was calculated for each tissue section, then for each block to obtain the density of plaques by anatomical region. Each regional count was converted into a semi-quantitative scale using the modified CERAD algorithm.
<table>
<tr><td colspan="2">Modified CERAD score with count</td></tr>
<tr><td>Average number by region</td><td>Semi-quantitative CERAD score by region</td></tr>
<tr><td><1</td><td>0 (none)</td></tr>
<tr><td>1 – 5</td><td>1</td></tr>
<tr><td>6 – 19</td><td>2</td></tr>
<tr><td>20+</td><td>3</td></tr>
</table>
</td></tr>
<tr><td>Calculation of the number of subjects required</td><td>Assuming a correlation of 0.55, a sample of 29 subjects with a florbetapirPET image then an autopsy was deemed necessary to detect a significant positive correlation between the semi quantitative amyloid burden assessment (0-4) lby the independent reading of the florbetapir PET images and the amyloid burden evaluated by quantitative immunohistochemistry at the autopsy, with a power of 90% (Spearman's Rank Order Correlation test, p>0.05, p>0).
In the case of the specificity analysis, with an expected specificity of 90%, a sample of 40 subjects was deemed necessary to obtain a 95% CI between 80% and 98%.</td></tr>
<tr><td>Statistical analysis</td><td>The main correlation analysis took account of the first 29 subjects (excluding the first 6 autopsied subjects and the test subjects) with an autopsy performed within 12 months following the florbetapir PET imaging. These analyses integrated the 6 test subjects in a second phase.
The main hypothesis was that a significantly positive correlation would be observed between the semi-quantitative reading of the florbetapir PET images (median of the 3 readers) and the quantitative amyloid burden assesment (IHC). The Spearman's Rank Correlation Coefficient was determined as well as the asymptomatic standard error (ASE) and the 95% CI using the Fisher z-transformation.
The associated test (unilateral test, p>0) was performed with an α risk=0.05 to evaluate the significant correlation.
In the case of the main specificity analysis, the population considered was the population of healthy volunteer subjects who were non-carriers of the ApoE ε4 allele (47 subjects).</td></tr>
</table>

Results:

The 226 included subjects were divided into two cohorts:
- **a "autopsy" cohort** of 152 patients with different cognitive end-of-life status (normal cognition, moderate cognition, Alzheimer's disease and other types of dementia).

- **a "specificity" cohort** of 74 young subjects with no cognitive or neurological impairment for whom the absence of amyloid plaques was presumed.

The main efficacy analysis was based on:

- 29 patients from the "autopsy" cohort (not including the first 6 test subjects analysed separately to finalise the methodology);
- 47 healthy volunteer subjects from the "specificity" cohort who are non-carriers of the ApoE ε4 allele.

Table 1: Populations of analysis (A07 study)

Populations	Autopsy cohort	Specificity cohort
Population for the safety analysis	152	74
Population for the main efficacy analysis	29	47
Population for the efficacy analysis including the test subjects / carriers of the ApoE ε4 allele	35*	74**

**Including the 6 test subjects*
***Including the carriers of the ApoE ε4 allele*

- **Characteristics of the subjects included**

Baseline characteristics of the subjects are shown in Table 2.

Table 2: Characteristics of the subjects at baseline (A07 study)

Characteristics	Autopsy cohort		Specificity cohort	
	Patients with analysable images N=152	Autopsied patients N=29	Subjects with analysable images N=74	Subjects who are non-carriers of the ApoE ε4 allele N=47
Age				
Mean ± SD	78.1 ± 13.35	80.0 ± 13.19	26.6 ± 6.50	26.3 ± 7.17
Median	81.5	85.0	25.5	24.0
Range	38 - 103	55 - 103	18 - 50	18 - 50
Gender				
Male	71 (46.7%)	15 (51.7%)	48 (64.9%)	32 (68.1%)
Female	81 (53.3%)	14 (48.3%)	26 (35.1%)	15 (31.9%)
Diagnosis				
Alzheimer's disease	56 (36.8%)	13 (44.8%)	0	0
MCI	25 (16.4%)	2 (6.9%)	0	0
Other types of dementia	21 (13.8%)	5 (17.2%)	0	0
No cognitive impairment	50 (32.9%)	9 (31.0%)	74 (100.0%)	47 (100.0%)
MMSE				
N	115	21	74	47
Mean ± SD	21.2 ± 9.34	19.9 ± 9.96	29.7 ± 0.57	29.8 ± 0.40
Median	25.0	23.0	30.0	30.0
Range	0 - 30	0 - 30	27 - 30	29 - 30
Wechsler memory scale – Immediate recall				
N	107	19	74	47
Mean ± SD	6.3 ± 5.03	5.9 ± 5.18	16.1 ± 3.34	16.3 ± 2.64
Median	6.0	6.0	16.0	16.0
Range	0 - 19	0 - 17	6 - 23	12 - 22
Wechsler memory scale – Delayed recall				
N	107	19	74	47
Mean ± SD	5.1 ± 4.82	3.8 ± 4.50	15.4 ± 3.46	15.4 ± 2.84
Median	5.0	1.0	15.0	15.0
Range	0 - 23	0 - 13	5 - 22	5 - 21
Interval between PET scan and death (months) Mean ± SD	-	3.2 ± 2.57	-	-
Interval between death and autopsy (hours) Mean ± SD	-	10.7 ± 7.95	-	-

The average age in the "autopsy cohort" was 78.1 years (38-103 years), that of the "specificity cohort" 26.6 years (18-50 years).
The 29 patients from the "autopsy" cohort included in the main efficacy analysis were divided into 4 groups: 13 patients (44.8%) with a clinical diagnosis of Alzheimer's disease, 9 patients (31.0%) with cognitive impairment or dementia, 2 patients (6.9%) with mild cognitive impairment and 5 patients (17.2%) with another type of dementia.

The "autopsy" cohort and "specificity" cohort differed particularly in terms of the:
- the average MMSE[18] score: 21.2 (0-30) vs. 29.7 (27-30);
- Wechsler clinical memory scale: the average immediate recall score: 6.3 (0-19) vs. 16.1 (6-23) and the average delayed recall score: 5.1 (0-23) vs. 15.4 (5-22).

- **Results on the primary endpoints**

- Correlation analysis ("autopsy cohort", n=29)
A significantly positive correlation was observed between the median scores obtained by the semi-quantitative reading (0-4) of the florbetapir PET images and the cortical amyloid burden evaluated by immunohistochemistry, with a statistically significant Spearman's ρ correlation coefficient of 0.78 ($p<0.0001$, 95% CI: 0.58-0.89).

- Specificity analysis ("specificity cohort", n=47)
All the 47 healthy volunteer subjects who are non-carriers of the ApoE ε4 allele were considered as Aβ- by the visual binary reading of the florbetapir PET images (95% CI: 91% - 100%), achieving the main objective of at least 90% of the florbetapir PET images of the subjects in the specificity cohort considered as Aβ- by the visual binary reading.
An exploratory analysis of all the 74 healthy volunteer subjects in the "specificity" cohort shows a similar result: 100% (74/74) (95% CI: 94% - 100%).

- **Results on the secondary endpoint:**

- Correlation analysis between the semi-quantitative reading of the blinded florbetapir PET scans and the amyloid burden assessment via IHC in the cortical regions
Statistically significant correlations were observed between the median scores obtained by the semi-quantitative reading of florbetapir PET images in the six predefined cortical regions and the cortical amyloid burden evaluated using the IHC method in these six regions: the correlation coefficients were between 0.68 and 0.77 ($p<0.0001$, 95% CI: 0.42-0.88).

- Consistency in terms of diagnosis
"autopsy" cohort (exploratory analysis)
The consistency of diagnosis between the neuropathological standard reference and semi-quantitative interpretation (0-4) of the florbetapirPET images was evaluated in the patients from the "autopsy" cohort.
For 18 of the 19 patients with pathological criteria for Alzheimer's disease (CERAD and NIA-Reagan), the florbetapir PET images were evaluated as positive, using the semi-quantitative method, thus leading to 95% sensitivity. Using the quantitative method (SUVR), the sensitivity was 100%.
The images of 16 patients with low beta-amyloid levels at autopsy and without pathological criteria for Alzheimer's disease (CERAD and NIA-Reagan) were all evaluated as negative, thus leading to 100% specificity (semi-quantitative and quantitative methods).

[18] The Mini Mental State Examination (MMSE or MMS) is an assessment tool for cognitive functions developed for rapid screening of cognitive decline. The MMSE comprises a series of questions gathered together in seven sub-tests and designed in such a way that the normal subjects can easily respond to each question. The questions focus on: time orientation (5 points), space orientation (5 points), immediate recall in three words (3 points), concentration (5 points), delayed recall in three words (3 points), language (8 points) and constructive praxis (1 point). The maximum score is therefore 30 points.

Overall, the results of the reading of the florbetapir PET images, achieved blinded, were in accordance with the final results of the autopsiess in 34 cases out of 35 (97% accuracy). **The negative predictive value (NPV) was 94% and the positive predictive value (PPV) was 100%.**

The SUVR analysis showed a 100% consistency with the autopsies results.

"Specificity" cohort: All the healthy volunteer subjects (n=47/47) were considered as having Aβ- status in the florbetapir PET imaging (main analysis).
A secondary analysis including all the subjects from the specificity cohort (including those carriers of the ApoE ε4 allele) showed similar results.

Overall, 95% (38/40) of the positive images (from the "autopsy cohort" and noted at 2 to 4 weeks according to the semi quantitative method) were considered as positive by three different readers (Table 3). The SUVR analysis (quantitative method) showed similar results.

Table 3: Consistency in terms of diagnosis (A07 study – "Specificity cohort")

		Standard reference		
Results of the florbetapir PET imaging		**Presumed amyloid status**		
		Positive (autopsy cohort) N=40*	**Negative (young SC) N=47**	
Qualitative visual method	**Positive (Aβ+)**	38	0	PPV = 100%
	Negative (Aβ-)	2	47	NPV = 96%
		Sensitivity = 95%	Specificity = 100%	Accuracy = 98%

*Positive images mixed with the negative images of the "specificity cohort" so as to minimise the bias.

Consistency of reading

- In terms of diagnosis

The results of the consistency of reading between the different readers in the "autopsy" and "specificity" cohorts are presented in Table 4.

Table 4: Consistency of reading (A07 study)

	N	Observed consistency	Kappa
"Autopsy cohort"			
Reader 1 vs. Reader 2	29	91%	0.72
Reader 1 vs. Reader 3	29	95%	0.84
Reader 2 vs. Reader 3	29	91%	0.68
"Specificity cohort"			
Reader 4 vs. Reader 5	114	94%	0.86
Reader 4 vs. Reader 6	114	99%	0.98
Reader 5 vs. Reader 6	114	93%	0.84

- Performance in terms of individual reading

The correlation between the semi-quantitative reading of the florbetapir PET images and the amyloid burden assessment using the quantitative IHC method ("autopsy cohort") was shown for the three readers (Table 5).

Table 5: Performance in terms of individual reading (A07 study – "Autospy cohort")

	N	Correlation between the semi-quantitative reading and the IHC Spearman's ρ (95% CI)	p
Reader 1	29	0.73 (0.49 - 0.86)	<0.0001
Reader 2	29	0.81 (0.64 - 0.91)	<0.0001
Reader 3	29	0.65 (0.37 - 0.82)	<0.0001

Each reader achieved the set objective of a specificity of at least 90% ("specificity cohort") (Table 6).

Table 6: Performance in terms of individual reading (A07 study – "Specificity cohort")

	N	Specificity % (95% CI)
Reader 4	47	100 (90.6 - 100)
Reader 5	47	97.9 (87.3 - 99.9)
Reader 6	47	100 (90.6 - 100)

Comparison with the clinical diagnosis (exploratory analysis)

The clinical diagnosis was compared with the neuropathological diagnosis made during the post-mortem.
Among the 23 patients in the "autospy cohort" with a clinical diagnosis of dementia (Alzheimer's disease and other types of dementia), 3 patients (13%) presented a clinical diagnosis which was not consistent with the neuropathological diagnosis:
- a patient with a probable clinical diagnosis of Alzheimer's disease proved to be negative for Alzheimer's disease at the autospy;
- two patients with a clinical diagnosis of other dementia disorders (Parkinson's disease and dementia with Lewy bodies) for whom the neuropathological diagnosis concluded on Alzheimer's disease.

8.1.2 A16 study extension of the A07 study

Principal study objective	To test the link between the amyloid burden assessment observed using florbetapir PET imaging and the amyloid burden assessment evaluated using histopathology.
Method	- To determine the diagnostic performance (sensitivity and specificity) of an independent and blinded, binary visual evaluation of the florbetapir PET imaging (Aβ+ or Aβ-) versus the final neuropathological diagnosis made at autopsy (CERAD diagnosis – probable or definitive Alzheimer's disease); - To reassess (with a higher number of cases) the correlation between the amyloid burden observed using the florbetapir PET imaging measured using a semi-quantitative visual method and the cortical amyloid burden observed at autopsy measured using quantitative immunohistochemistry.
Main inclusion criteria	The subjects included met the inclusion criteria of the A07 study.
Primary efficacy endpoint	a) Evaluation of the florbetapir PET images: - qualitatively (5 readers trained in routine binary reading); - semi-quantitatively (3 readers); - quantitatively (SUVR – semi-automated computerised analysis). The analysis of the images was centralised in one single laboratory. b) Post-mortem procedures and analyses according to 2 types of evaluation: - Neuropathological diagnosis (standard reference for the sensitivity and specificity analysis) The neuropathology expert used the tissue sections in the frontal cortex, the temporal cortex, and the parietal cortex to make a diagnosis using the density of neocortical neuritic plaques on the basis of recommendations from the CERAD.

<table>
<tr><td></td><td>The CERAD algorithm was used for the semi-quantitative evaluation of the density of neuritic plaques from the sections, as well as for the neuropathological diagnosis.
<table>
<tr><td colspan="4">Modified CERAD score</td></tr>
<tr><td>Average number by region</td><td>Semi-quantitative CERAD score by region</td><td>Modified CERAD diagnosis</td><td>Binary neuropathological diagnosis</td></tr>
<tr><td><1</td><td>0 (none)</td><td>No AD</td><td rowspan="2">Negative</td></tr>
<tr><td>1 – 5</td><td>1 (rare)</td><td>Possible AD</td></tr>
<tr><td>6 – 19</td><td>2 (moderate)</td><td>Probable AD</td><td rowspan="2">Positive</td></tr>
<tr><td>20+</td><td>3 (frequent)</td><td>Confirmed AD</td></tr>
</table>
- Overall evaluation of the amyloid burden
The overall density of cortical β-amyloid plaques measured using the quantitative IHC method was the primary endpoint used for the correlation analysis. The average result by region was produced to obtain an overall score.</td></tr>
<tr><td>Calculation of the number of subjects required</td><td>On the basis of a hypothesis of a sensitivity ≥ 80%, and an estimation of 50 autopsied, 50% of them would have a positive amyloid profile. The 95% CI would be between 64% and 96%, for an 80% sensitivity.</td></tr>
<tr><td>Statistical analysis</td><td>The diagnostic measurements (sensitivity, specificity) were provided with bilateral confidence intervals 95%.CI
All correlation analyses used a unilateral statistical test with a α risk=0.05.
Two main analysis were performed:
- The sensitivity and specificity of the quantitative reading of the florbetapir PET images (majority score among the 5 readers) were measured in all subjects for whom an autopsy was performed within 24 months following the florbetapir PET imaging. Two hypotheses were tested:
- Hypothesis A: The observed sensitivity of the florbetapir PET imaging is ≥ 80%. Assuming a total of 50 subjects for whom autopsies were performed and would have considered that 50% of them as Aβ+ (N=25 for the sensitivity analysis), the 95% CI for an observed sensitivity of 80% would be between 64% and 96%.
- Hypothesis B: The specificity of the florbetapir PET imaging is ≥ 80%. Assuming a total of 50 subjects for whom autopsies were performed and would have considered that 50% of them as Aβ- (N=25 for the specificity analysis), the 95% CI for an observed specificity of 80% would be between 64% and 96%.
- The correlation between the amyloid burden assessment via the florbetapir PET imaging and the levels actually observed at autopsy was measured and the main hypothesis of the A07 study was re-tested in this study and also included the subjects from the A07 study.</td></tr>
</table>

Results

At the end of the A07 study, autopsies of 35 deceased patients were available out of a total of 152 included patients. Among the patients followed for 12 months more, 24 were autopsied. Thus, the sample for the main analysis in the A16 study was 59 patients.

A secondary analysis was performed on all patients for whom an autopsy was available within 12 months following florbetapir PET imaging procedure, i.e. 46 patients.

Table 7: Baseline characteristics of the subjects (A16 study)

	Autospy cohort	
Characteristics	**Population for the secondary analysis (≤ 12 months) N=46**	**Population for the main analysis (≤ 24 months) N=59**
Age		
Mean ± SD	79.0 ± 12.38	79.4 ± 12.64
Median	82.5	83.0
Range	47 - 103	47 - 103
Gender		
Male	25 (54.3%)	29 (49.2%)
Female	21 (45.7%)	30 (50.8%)
Diagnosis		
Alzheimer's disease	20 (43.5%)	29 (49.2%)
MCI	4 (8.7%)	5 (8.5%)
Other types of dementia	11 (23.9%)	13 (22.0%)
No cognitive impairment	11 (23.9%)	12 (20.3%)
MMSE		
N	30	36
Mean ± SD	17.2 ± 10.18	17.3 ± 9.71
Median	18.5	17.5
Range	0 - 30	0 - 30
Wechsler clinical memory scale – Immediate recall		
N	27	31
Mean ± SD	5.0 ± 5.16	5.0 ± 4.88
Median	5.0	5.0
Range	0 - 17	0 - 17
Wechsler clinical memory scale – Delayed recall		
N	27	31
Mean ± SD	3.6 ± 4.58	3.6 ± 4.35
Median	0	1.0
Range	0 - 14	0 - 14
Interval between PET imaging and death (months)		
Mean ± SD	3.8 ± 3.03	6.6 ± 5.99
Median	3.5	4.0
Range	0 - 11	0 - 22
Interval between death and autopsy (hours)		
Mean ± SD	10.6 ± 7.4	10.1 ± 7.0

Sensitivity and specificity of the florbetapir PET imaging evaluated using a qualitative visual method compared with the modified CERAD diagnosis provided by a neuropathologist

Among the 59 patients, 30 (51%) had a definitive diagnosis of Alzheimer's disease, 9 (15%) probable Alzheimer's disease, 5 (8%) possible Alzheimer's disease and 15 (25%) no Alzheimer's disease, according to the CERAD diagnosis.

The results for the detection of probable or definitive Alzheimer's disease in this population show (Table 8):
- 92% sensitivity (95% CI: 78 - 98%),
- 100% specificity (95% CI: 80 - 100%),
- 95% accuracy (95% CI: 85% - 99%),
- an NPV of 87% (95% CI: 65 - 97%) and a PPV of 100% (95% CI: 88 - 100%).

Table 8: Results of diagnostic performance (A16)

Results of the florbetapir PET imaging		CERAD diagnosis	
		Positive (probable AD, definitive AD) N=39	Negative (no AD, possible AD) N=20
Qualitative visual method	Positive Aβ+	36 (92.3%)	0
	Negative Aβ-	3 (7.7%)	20 (100.0%)

The secondary analysis in 46 autopsied patients within 12 months following the florbetapir PET imaging procedure imaging showed:
- 96% sensitivity (95% CI: 80% - 100%),
- 100% specificity (95% CI: 78% - 100%),
- 98% test accuracy (95% CI: 87% - 100%),
- an NPV of 100% and a PPV of 95%.

Correlation analysis between the amyloid burden assessment evaluated using the semi-quantitative reading of the florbetapir PET images and the amyloid burden assessment using immunohistochemistry

The correlation analysis showed a statistically significant correlation, with a Spearman's ρ correlation coefficient of 0.76 (95% CI: 0.62 - 0.85; p<0.0001).
The secondary analysis in 46 patients with a post-mortem performed within 12 months following the florbetapir PET imaging procedure showed a positive correlation, with a Spearman's ρ coefficient correlation of 0.79 (95% CI: 0.65 - 0.88; p<0.0001).

- Analysis of the reader performance

A total of 295 (5 readers x 59 images) evaluations (qualitative method) of florbetapir PET images were compared with the autopsies results. The grouped sensitivity was 87% (95% CI: 82%-91%), the grouped specificity 95% (95% CI: 88%-98%) and the accuracy of the test 90% (95% CI: 86%-93%).

Table 9: Analysis of the reader performance (A16 study)

Results of the florbetapir PET imaging		CERAD diagnosis (neuropathologist)		
		Positive (probable Alzheimer's disease, definitive Alzheimer's disease) Read images = 195	Negative (no Alzheimer's disease, possible Alzheimer's disease) Read images = 100	
Qualitative visual method Overall amyloid burden	**Positive Aβ+**	170 (87%)	5 (5%)	
	Negative Aβ-	25 (13%)	95 (95%)	
		Sensitivity = 87%	Specificity = 95%	Accuracy = 90%

The Fleiss Kappa coefficient was 0.75 (65% CI: 0.67-0.83) for the analysis of consistency between the five readers (p<0.0001).

- Performance in terms of individual reading

The correlation between the semi-quantitative reading of the florbetapir PET images and the amyloid burden assessment using the quantitative IHC method ("autopsy cohort") was shown for the 3 readers (Table 10).

Table 10: Performance in terms of individual reading (A16 study)

	All the autopsied subjects N=59		Autopsied subjects within 12 months following florbetapir PET imaging procedure N=46	
	Spearman's ρ correlation (95% CI)	p	Spearman's ρ correlation (95% CI)	p
Reader 1	0.75 (0.61 - 0.84)	<0.0001	0.77 (0.61 - 0.86)	<0.0001
Reader 2	0.69 (0.52 - 0.80)	<0.0001	0.71 (0.52 - 0.83)	<0.0001
Reader 3	0.62 (0.44 - 0.76)	<0.0001	0.71 (0.52 - 0.83)	<0.0001

- Comparison of the neuropathological diagnosis made during the autopsy (exploratory analysis)

Among the 42 patients in the "autopsy" cohort with a diagnosis of dementia (Alzheimer's disease and other types of dementia), 1 patient had a probable clinical diagnosis of Alzheimer's disease which was not confirmed at autopsyand one of the 12 patients considered as clinically normal at baseline had a definitive diagnosis of Alzheimer's disease at autopsy.

8.1.3 Retrospective study (A13)

Principal study objective	To determine if the information obtained using the florbetapir PET imaging alters the diagnostic reasoning adopted by the physician
Method	Retrospective, non-comparative study
Study population	44 patients (from the phase II (A05) study) with florbetapir PET imaging, selected randomly among 90 patients by controlling the age and the MMSE score at the study site.
Main inclusion criteria	The patients considered as suffering from Alzheimer's disease met the NINCDS criteria of probable Alzheimer's disease and had MMSE scores of ≤24. The patients considered as having MCI complained of memory problems or cognitive impairment corroborated by a caregiver; they were over 50 years of age, had a CDR (Clinical Dementia Rating) of 0.5 and a MMSE score of >24. This was the first evaluation of their cognitive state where the patients had to have been diagnosed with MCI for at least one year.
Course of the study	For each of these patients, the Avid companies developed a narrative report in 2 parts (blinded for the florbetapir PET imaging results) which did not specify the initial diagnosis of the clinician at baseline in the A05 study. In parallel, a nuclear medicine physician who is an expert in readingflorbetapir PET images and unaware of the clinical information relating to the patients, reviewed the images for the 44 patients. In the 44 cases, he delivered the same verdict as the majority of experts from the A05 study in terms of the positive or negative nature of the PET images. The nuclear medicine physician issued a clinical report so as to categorise the result of the Aβ+ et Aβ- PET imaging. An electronic report (eCRF) including clinical information (with no diagnosis) and the result of the florbetapir PET imaging was established for each patient. The 44 eCFR were presented to 3 experts in a random and different order for 3 of each. Each expert provided, independently for each case, an initial diagnosis from the review of clinical and blinded characteristics of the imaging results. In a second phase, the result of the imaging was presented to the clinicians; they therefore issued a final diagnosis for each case. Each expert blindly reviewed the clinical characteristics of the patient from the result of the florbetapir PET imaging and made a diagnosis among 7 categories. In addition, the clinician provided the confidence level that he gave to his diagnosis (continuous scale from 0-100 with the high numbers signalling great certainty). Finally, each clinician indicated the components which had to be included, in his opinion, in the patient treatment plan, choosing one or more components among a list of 6. Having submitted the diagnosis based on the patient's clinical record, the confidence level associated with the diagnosis and the patient treatment plan, the clinicians had access to the report including the result of the florbetapir PET imaging. No revision or alteration of their diagnosis or prior response was permitted. The expert therefore replied to the same questions as before (diagnosis category, confidence level and patient treatment plan).
Primary efficacy endpoint	Proportion of cases where the clinicians have changed their initial diagnosis so as to make it consistent with the result of the florbetapir PET imaging, after being aware of the result.

<table>
<tr><td>Secondary endpoints</td><td>The secondary exploratory analyses aimed to evaluate the change in the confidence level of the clinicians in their diagnosis and the change in their recommendations for the treatment of patients after reviewing the results of the florbetapir PET imaging.</td></tr>
<tr><td>Calculation of the number of subjects required</td><td>Taking into account:
- the possibility of changing the diagnosis in 60% of cases;
- diagnosis switch rate more than 20%;
- an intra-cluster correlation of 0.3;
a sample of 44 cases and 3 observations by experts per case ensured a power higher than 90% to detect a significantly different level of 0% with α=5%.</td></tr>
<tr><td>Statistical analysis</td><td>The main analysis was done on the cohort from the efficacy analysis that is in the cases where the pre-imaging diagnosis was not consistent with the imaging result. The pre-imaging diagnostic classification was considered as inconsistent with the results of the florbetapir PET imaging in the cases marked with an X in the table below.
<table>
<tr><th rowspan="2">Pre-PET imaging clinical diagnosis from the doctor</th><th colspan="2">Result of the florbetapir PET imaging</th></tr>
<tr><th>Aβ+</th><th>Aβ-</th></tr>
<tr><td>Normal cognitive function</td><td>X</td><td></td></tr>
<tr><td>MCI with unknown aetiology</td><td>X</td><td>X</td></tr>
<tr><td>MCI due to Alzheimer's disease / early symptoms implying Alzheimer's disease</td><td></td><td>X</td></tr>
<tr><td>MCI probably not due to Alzheimer's disease</td><td>X</td><td></td></tr>
<tr><td>Dementia with unknown aetiology</td><td>X</td><td>X</td></tr>
<tr><td>Dementia due to Alzheimer's disease</td><td></td><td>X</td></tr>
<tr><td>Dementia probably not due to Alzheimer's disease</td><td>X</td><td></td></tr>
</table>
A binary variable (yes/no) indicated whether the clinician had altered his pre-imaging diagnosis so as to be consistent with the imaging result in the event of prior inconsistency between them . The results were reported for each alone clinician and for the 3 clinicians together in terms of the diagnosis switch rate ("yes") with a unilateral confidence interval of 95%. The zero hypothesis of the main objective was tested by comparing the percentage of cases where the diagnosis changed with the percentage where the diagnosis was not altered using a Chi² test. A difference was considered as statistically significant when p<0.05.</td></tr>
</table>

Results

➢ Patient characteristics

The characteristics of included patients are shown in table 11.

Table 11: Patient characteristics (A13 study)

Characteristics	Main analysis (N=44)
Age (years)	
Mean (SD)	74.5 (9.8)
Minimum	51
Median	76.5
Maximum	88
Gender	
Female	18 (41%)
Male	26 (59%)
MMSE score	
Mean (SD)	24.6 (4.0)
Minimum	13
Median	24.5
Maximum	30
Alzheimer's disease and florbetapir+ PET image	11 (25%)
Alzheimer's disease and florbetapir- PET image	11 (25%)
MCI and florbetapir+ PET image	11 (25%)
MCI and florbetapir- PET image	11 (25%)

- **Primary endpoint**

A total of 132 images were analysed (3 readers X 44 images). On average, the clinicians made an initial diagnosis that was not consistent with the result of the florbetapir PET imaging in 59% of cases (N=78).

Table 12: Proportion of alteration in initial diagnosis after reviewing the florbetapir PET imaging results(A13 study)

Clinician	Number of cases evaluated	Number of cases where the initial diagnosis was not consistent with the PET result, N (%)	Number of cases where the diagnosis changed after the PET result, N (%)[1]*	Percentage of cases where the initial diagnosis changed after the PET[1]** result (95% CI***)	p
1	44	27 (61%)	25 (57%)	93% (84% - 100%)	<0.0001
2	44	22 (50%)	22 (50%)	100%	-
3	44	29 (66%)	19 (43%)	66% (51% - 100%)	<0.0001
Total	**132**	**78 (59%)**	**66 (50%)**	**85% (80% - 100%)**	**<0.0001**

[1]Cohort for the efficacy analysis
*The percentage was calculated with respect to all cases
**The percentage was calculated with respect to the number of cases where the initial diagnosis was not consistent with the result of the florbetapir PET imaging
***Unilateral confidence interval of 95%

Among these 78 cases, the clinicians changed their diagnosis after reviewing the imaging results in 85% of cases (N=66; p<0.0001; 95% CI: 80%-100%).

The final diagnosis (after reviewing imaging results and changing the initial diagnosis in the event of inconsistency with the imaging results) was consistent with the result of the florbetapir PET imaging in 87% of cases (95% CI:82%-92%) (Table 13), i.e. a level which is lower than the expected result of consistency between the final diagnosis and the florbetapir PET imaging results of at least 90%. One of the explanations for this assessment is the fact that for one of the three clinicians, the level of consistency between the final diagnosis and the the florbetapir PET imaging results was 68% (95% CI: 53%-80%); these inconsistencies were mainly due to the fact that the clinician classified the MCI patients with a negative image in the category "MCI with unknown aetiology" and not in the category "MCI probably not due to Alzheimer's disease".

Table 13: Consistency between the final diagnosis and the florbetapir PET imaging results (A13 study)

Clinician	Number of cases reviewed	Number of cases where the post-imaging diagnosis was consistent with the PET result, N (%)	95% CI[1]	Number of cases where the post-imaging result was not consistent with the PET result, N (%)
1	44	42 (95%)	85% - 99%[2]	2 (5%)
2	44	43 (98%)	88% - 100%[2]	1 (2%)
3	44	30 (68%)	53% - 80%[2]	14 (32%)
Total	**132**	**115 (87%)**	**82% - 92%[3]**	**17 (13%)**

[1]The bilateral confidence interval associated with the proportion of cases where the final diagnosis was consistent with the result of the florbetapir PET imaging
[2]The confidence interval for each expert was calculated using the Wilson method
[3]The estimation of the confidence interval took into account the intra-individual correlation

Across the 44 cases, the clinicians significantly changed the patient treatment plan, after learning the imaging results, in 80% of cases reviewed (75% to 84% of 44 cases depending on the expert; p>0.0001).

8.1.4 FAIR-AD study

A FAIR-AD study conducted jointly at three centres (Tours, Caen and Toulouse) aimed to test the feasibility of using florbetapir PET imaging within a routine clinical context so as to differentiate the patients with mild to moderate Alzheimer's disease and patients with MCI from the healthy volunteer subjects.

Overall, 46 subjects were included in this study (from the memory consultations at previously cited centres), including:
- 13 patients with Alzheimer's disease (NINCDS-ADRDA criteria for probable Alzheimer's disease and DSM-IV criteria for dementia of the Alzheimer type),
- 12 patients with MCI (diagnostic criteria for amnesiac MCI),
- 21 healthy volunteer subjects.

Their florbetapir PET images were blindly (from the clinical and diagnostic informations) visually evaluated by two nuclear medicine physicians, using a binary scale (0-1) and having been previously trained for half a day by the Avid company. Furthermore, the images were also quantitatively evaluated via the SUVR calculation in the specific regions of interest.

Results
The consistency analysis between the two nuclear medicine physicians showed a κ value of 0.71 (95% CI: 0.50-0.93).
In comparison with the initial clinical diagnosis, the visual analysis of the florbetapir PET images classed 11 out of 13 patients with Alzheimer's disease (85%) and 13 out of 21 healthy volunteer subjects (60%) as positive (Aβ+). A calculation of the sensitivity and visual specificity compared with the clinical diagnosis showed respective values of 84.6% (95% CI 0.55-0.98) and 38.1% (95% CI: 0.18-0.62). The quantitative analysis showed sensitivity of 92.3% and specificity of 90.5%.
The authors of this trial justified the inconsistency between the visual and semi-quantitative analyses by citing the following reasons: the parameters of the cameras of two sites were adapted according to those of the camera of the 3rd site which had the weakest spatial resolution. This is liable to have caused errors in reading. At least one healthy volunteer subject had a family history of Alzheimer's disease, high SUVR values, and was a carrier of the ApoE ε4 allele.

Among the 12 patients with MCI, 6 were considered as positive (Aβ+) and 6 as negative (Aβ-). The patients with MCI showed a more significant uptake of florbetapir in the posterior cingulate cortex in comparison with the healthy volunteer subjects.
The average SUVR values were more significant in the patients with Alzheimer's disease than in healthy volunteer subjects in the cortex generally and in all the cortical (precuneus, anterior and posterior cingulates, median frontal, temporal, parietal and occipital cortex) regions.
The authors of this preliminary study conclude on the necessity of implementing other studies so as to document the accuracy of the florbetapir PET imaging in the diagnosis of Alzheimer's disease and to compare florbetapir PET imaging with other currently available tests.

8.1.5 Systematic literature review and meta-analysis of the performance of different diagnostic tools for Alzheimer's disease

The objective of this literature review was to identify the scientific publications that report the diagnostic performance results, in terms of sensitivity and specificity, of the following imaging procedures: MRI, PET (with different agents), SPECT (with different agents), CT scan and CSF biomarkers (T-tau, P-tau, $A\beta_{42}$). The systematic literature review identified 123 studies, 20 of whom met the inclusion criteria (particularly post-mortems). The objective of the studies was to differentiate patients suffering from Alzheimer's disease from healthy subjects or patients with other forms of dementia.
The results show:

- 86.8% sensitivity (95% CI: 81.9 - 91.7%) and 78.7% specificity (95% CI: 70.3 - 87.1%) for the imaging tests (17 studies with 20 results),
- 81.7% sensitivity (95% CI: 72.4 - 91.6%) and 74.8% specificity (95% CI: 59.6-90.0%) for the CSF biomarkers (3 studies with 7 results).

According to this meta-analysis, the diagnostic tests based on the imaging seem to have better performance values than the CSF biomarkers.

However, one of the difficulties in comparing the different studies which evaluated the performance of diagnostic tests for Alzheimer's disease was linked to the heterogeneity between the studies. Furthermore, the low number of studies (n=20) that used the autopsy as reference diagnostic criteria constituted an obstacle in implementing a more detailed analysis for each diagnostic test.

08.2 Safety/Adverse effects

8.2.1 Safety data for the clinical studies

The adverse events recorded in the clinical studies focus on 555 subjects, including 286 with cognitive decline and 269 with normal cognitive functions. Table 14 presents the list of adverse events, all combined, that were reported during the clinical trials, whether or not they were linked to florbetapir in the investigator's opinion, in 496 subjects included in the database of the safety of florbetapir for submission of the registration dossier.

Table 14: List of adverse events reported during the completed clinical studies

Adverse event (whatever the causal link with the study product)	N (%) Total (N=496)
Number of patients with at least 1 AE	47 (9.5)
Headaches	**8 (1.6)**
Musculoskeletal pain	4 (0.8)
Fatigue	3 (0.6)
Nausea	**3 (0.6)**
Anxiety	2 (0.4)
Dorsal pain	2 (0.4)
Claustrophobia	2 (0.4)
Hypertension	2 (0.4)
Insomnia	2 (0.4)
Neck pain	2 (0.4)
Abdominal distension	1 (0.2)
High blood pressure	1 (0.2)
Chest pain	1 (0.2)
Shivers	1 (0.2)
Constipation	1 (0.2)
Diarrhoea	1 (0.2)
Dizziness	1 (0.2)
Dysgeusia	**1 (0.2)**
Cold sensation	1 (0.2)
Flatulence	1 (0.2)
Hot flushes	**1 (0.2)**
Haematuria	1 (0.2)
Extravasation at infusion site	1 (0.2)
Rash at the injection site	**1 (0.2)**
Bleeding at the infusion site	1 (0.2)
Irritation at the infusion site	1 (0.2)
Haematoma at the injection site	1 (0.2)
Musculoskeletal stiffness	1 (0.2)
Peripheral oedema	1 (0.2)
Pain	1 (0.2)
Palpitations	1 (0.2)
Parosmia	1 (0.2)
Generalised pruritus	**1 (0.2)**
Respiratory failure	1 (0.2)
Sinus pain	1 (0.2)
Supraventricular extrasystoles	1 (0.2)
Upper limb fracture	1 (0.2)
Urine discoloration	1 (0.2)
Urticaria	**1 (0.2)**
Ventricular extrasystoles	1 (0.2)
Vomiting	1 (0.2)
High number of white blood cells	1 (0.2)
Total adverse events	**62**

Only non-serious, common (1 to 10%) and uncommon (1 to 0.1%) adverse advents that have been linked to florbetapir and occurred during the completed clinical trials were identified. The size of the source database was not sufficient enough to allow the identification of rare effects.
The adverse events - linked - or adverse effects most commonly reported during the completed clinical trials were:
- headaches (1 to 10%),
- nausea (0.1 to 1%),
- dysgeusia (0.1 to 1%),
- pruritus, urticaria (0.1 to 1%),
- erythema at the injection site (0.1 to 1%),
- flushing (0.1 to 1%).

No adverse event with a frequency higher than 10% was observed in exposed subjects.
Taking account of all the completed clinical trials as well as the clinical trials under way on 15 April 2012, 2578 patients were exposed to florbetapir. In these clinical trials, seven serious adverse

events were reported, including three deaths. No serious adverse event linked, in the investigator's opinion, to the administration of AMYVID was reported, including the three cases of fatal progression.

8.2.2 PSUR safety data

The marketing of AMYVID around the world started in the United States in June 2012. The 1st updated periodic benefit risk evaluation report (PSUR/PBRER) is to come.

8.2.3 Risk Management Plan

This proprietary medicinal product is subject to a risk management plan and includes monitoring of the "significant" risks:
- potential: hypersensitivity reactions, carcinogenicity and hereditary effects, risk of errors in the interpretation of PET imaging.

- missing information: safety in patient with hepatic failure, safety of patients suffering from significant cerebrovascular disease.

Apart from the potential risk of carcinogenicity or hereditary effects inherent in using any radiopharmaceutical product, the RMP endeavours to measure and minimise the potential risk of errors in the interpretation of the florbetapir (^{18}F) PET imaging in real conditions of use. Two post-authorisation studies will mainly focus on the efficacy of the nuclear medicine physician training programme as well as the real conditions of use in the diagnostic approach to Alzheimer's disease and other causes of cognitive decline.

8.2.4 SPC safety data

The adverse events mentioned in the AMYVID SPC are:

	Uncommon (≥ 1/1000, <1/100)	**Common (≥ 1/100, < 1/10)**
Nervous system disorders	Dysgeusia	Headaches
Vascular disorders	Flushing	
Gastrointestinal disorders	Nausea	
Skin and subcutaneous tissue disorders	Pruritus, urticaria	
General disorders and administration site conditions	Erythema at the injection site	

08.3 Summary & discussion

An open, prospective **study (A07)** evaluated the diagnostic performances of florbetapir PET imaging on the basis of an efficacy analysis focusing on:
- an "autopsy" cohort of 29 patients aged 55 to103 (average of 80 years old), at the end of life (life expectancy ≤ 6 months because of different diseases: cancer, heart failure, dementia etc.) who had consented to an autopsy. Among them, 13 (44.8%) had a diagnosis of Alzheimer's disease, 5 (17.2%) had another type of dementia, 2 (6.9%) had mild cognitive impairment (MCI) and 9 (31.0%) had no cognitive impairment or dementia.
- a "specificity" cohort of 47 young subjects aged 18 to 50 (average of 26.3 years old) with no cognitive or neurological impairment and with no known risk factors for Alzheimer's disease, therefore for whom the absence of amyloid plaques (Aβ-) was presumed.
In the cohort of 29 patients who had an autopsy, a significantly positive correlation was observed between the median scores obtained by the semi-quantitative reading (0-4) of the florbetapir PET images and the cortical amyloid burden evaluated using immunohistochemistry: Spearman's ρ correlation coefficient (primary endpoint) = 0.78 (p>0.0001, 95% CI: [0.58 - 0.89]).

All 47 (100%) witness subjects who were non-carriers of the ApoE ε4 allele were considered as Aβ- by the binary visual reading[19] (primary endpoint) (95% CI: [91 - 100]).

In the cohort of 29 patients who had a post-mortem, the median scores obtained by the semi-quantitative reading of the florbetapir PET images in the six predefined cortical regions was correlated to the cortical amyloid burden evaluated using the immunohistochemistry method in these six regions; the correlation coefficients were between 0.68 and 0.77 (p<0.0001, 95% CI: 0.42-0.88) (secondary endpoint).

An extension A07 study was able to include in the "autopsy" cohort additional subjects who died within 12 months. A total of 59 patients were thus included in the "autopsy" cohort, 30 (51%) of whom had a diagnosis of definitive Alzheimer's disease, 9 (15%) probable Alzheimer's disease, 5 (8%) possible Alzheimer's disease and 15 (25%) no Alzheimer's disease according to the CERAD diagnosis. The analysis of 59 patients in the "autopsy" cohort showed evidence for the detection of probable or definitive Alzheimer's disease:
- 92% sensitivity (95% CI: 78 - 98%) (96% when the autopsy was performed less than one year after the diagnostic test);
- 100% specificity (95% CI: [80 - 100]);
- 95% accuracy (95% CI: [85 - 99]);
- a negative predictive value (NPV) of 87% (95% CI: [65 - 97]) and a positive predictive value (PPV) of 100% (95% CI: [88 - 100]).

It should be noted that:

- the specificity of AMYVID was studied with regard to a "specificity" cohort (n=47) comprised of young adults with no cognitive impairment for whom the absence of amyloid plaques was presumed (A07 study) and a cohort of elderly patients (n=59) that only included 12 patients with no cognitive impairment (A16 study). However, the hypothesis of specificity in the A16 study was based on a total of 50 subjects who underwent an autopsy, half of whom were considered as Aβ- (i.e. n=25 for the specificity analysis).
- the population of the "autopsy" cohort corresponding to the end-of-life patients who are carriers of various serious diseases raises the question of the relevance of the clinical diagnosis chosen for dementia, the possibility of non-neurodegenerative origin and, as a result, the transferability, in daily practice, of observed results.
- 152 patients in the "autopsy" cohort received florbetapir PET imaging (safety population). 39% (59/152) of these patients underwent an autopsy.

A statistically significant correlation was established between the amyloid burden evaluated by the semi-quantitative reading of the florbetapir PET images and that evaluated by immunohistochemistry with a Spearman's ρ correlation coefficient of 0.76 (95% CI: [0.62-0.85], p<0.0001).

For the 295 (5 readers x 59 images) evaluations (qualitative method) of florbetapir PET imaging compared with the post-mortem results, the grouped sensitivity was 87%, the grouped specificity 95% and the accuracy of the test 90%. The Fleiss Kappa coefficient for the analysis of consistency between the five readers trained in the routine binary reading was 0.75 (p<0.0001).

No correlation was sought between the florbetapir PET imaging and the biomarkers assayed in the CSF (Aβ42, TAU proteins, phosphorylated TAU proteins) currently recommended in the event of the diagnosis being doubted, particularly for young patients.

A retrospective study (A13) focusing on 44 cases from a phase II study that aimed to evaluate the impact of the florbetapir PET imaging on the diagnosis of patients with mild cognitive

[19] A group of three readers who did not have access to clinical information classified the images according to whether they were positive (Aβ+) or negative (Aβ-) for β-amyloid plaques.

impairment (MCI) or suffering from Alzheimer's disease. A total of 132 images were analysed (3 readers X 44 images). On average, the clinicians made an initial diagnosis that was not consistent with the result of the florbetapir PET imaging in 59% of cases (N=78). Of these 78 cases, the clinicians altered their diagnosis after reviewing the imaging results in 85% of cases (N=66; p<0.0001; 95% CI: [80 - 100]). This high percentage calls to mind and raises the question of excessive confidence in the florbetapir PET imaging. The retrospective, non-comparative methodology gives an exploratory character to this study results. Thus, this study does not provide the proof that the clinicians had reason to revise the diagnosis to the extent that the diagnosis currently considered as definitive is anatomopathological.

The FAIR-AD study, whose objective was to test the feasibility of using routine florbetapir PET imaging so as to differentiate patients with mild to moderate Alzheimer's disease and patients with MCI from healthy volunteer subjects, is a preliminary study.

In so far as no high evidence level study able to estimate the risk of progression of mild cognitive impairment (MCI) towards clinical Alzheimer's disease has been performed, the florbetapir PET imaging is not able to predict the conversion of MCI patients to Alzheimer's disease.

A total of 47 adverse events were notified out of 496 subjects included in the database for florbetapir safety on submission of the registration dossier. Only non-serious, common (1 to 10%) and uncommon (1 to 0.1%) adverse advents that have been linked to florbetapir and occurred during the completed clinical trials were identified, the size of the source database was not sufficient enough to allow the identification of rare effects.
The most commonly reported adverse events during the completed clinical trials were: headaches (1 to 10%), nausea (0.1 to 1%), dysgeusia (0.1 to 1%), pruritus, urticaria (0.1 to 1%), erythema at the injection site (0.1 to 1%), and flushing (0.1 to 1%).

Taking into account all the completed clinical trials and those under way on 15 April 2012, 2578 patients were exposed to florbetapir. In these studies, seven serious adverse events were reported, including three deaths. No serious adverse event linked, in the investigator's opinion, to the administration of AMYVID was reported, including the three cases of fatal progression.

08.4 Planned studies

The protocol of two post-Marketing Authorisation safety studies was submitted to the ANSM [French National Agency of Medicine and Health Products Safety] on 28 March 2013. Their objectives are:
- to evaluate the efficacy of the training program, particularly the use according to the indication and frequency of reading errors (study 1),
- to evaluate the usage patterns of AMYVID and identify its possible off-label use (study 2).

AMYVID is currently used in France in different clinical studies conducted by universities. Two clinical studies are currently under way:

- The MAPT randomised, parallel-group, placebo-controlled study evaluates the efficacy of isolated omega-3 fatty acid supplementation, isolated multi-domain intervention (nutrition, physical exercise, cognitive stimulation etc.), or their combination in terms of progression of cognitive functions in fragile elderly people over 70 years of age. Florbetapir is used in one of the ancillary studies of the MAPT study (MAPT-AV45) whose objective is to determine the prevalence of amyloid lesions in a population of fragile elderly people.

- The MEMENTO cohort was implemented within the context of Measure 29 of the National Alzheimer Plan 2008-2012 whose objective was to constitute a cohort of French patients who have clinical signs that could be suggestive of an incipient form of Alzheimer's disease or a similar disease. The main objective is to study the progression of early signs (memory complaints, cognitive decline etc.) that could be suggestive of Alzheimer's disease or a similar disease and to evaluate the prognostic value of a series of markers on the progression of these early signs towards clinical dementia then towards death. The protocol provides a complete clinical examination, neuropsychological and psychiatric evaluations, a structural MRI, biological samples and the establishment of a biobank. A lumbar puncture and PET imaging will also be suggested to all the participants. Physiciansplan to use florbetapir. The study lasts 6 and a half years, with an inclusion period of 18 months and a participation period per patient of 5 years. This study concerns the majority of French CMRR and the estimated size of the cohort is 2300 patients. The florbetapir PET imaging concerns 400 patients.

Clinical research work on the diagnostic efficacy of AMYVID in appropriate populations, ensuring their transferability to real conditions of use, is needed.

09 DIAGNOSTIC USE

The objective of the treatment of Alzheimer's disease is to treat the disease symptoms, to improve the patients' quality of life, to delay admission to an institution, to reduce morbidity and mortality and to assist the caregivers[20]. An early diagnosis (relating to the onset of the first clinical signs) is essential to optimise this treatment and limit the loss of autonomy.

The initial assessment conducted by the general practitioner treating the patients includes an interview, a clinical examination, a functional, and a standardised overall cognitive assessment using the mini-mental state examination (MMSE).

If there is a proven cognitive impairment, guiding the diagnostic tests in accordance with the aetiological hypothesis is recommended.

[20] HAS. Practice guidelines. Alzheimer's disease and related conditions- Diagnosis and treatment. December 2011.

Systematic cerebral imaging is recommended for any recently discovered proven cognitive impairment. This test is nuclear magnetic resonance imaging (MRI) with T1, T2, T2* and FLAIR (Fluid Attenuated Inversion Recovery) sequences and coronal cuts which allows the hippocampus to be visualised. Failing that, a CT brain scan is performed.

After this initial assessment, if, in spite of the mnesic complaint, the cognitive functions assessed by the MMSE and brief identification tests, the activities of daily living assessed by the IADL scale and the clinical context (absence of mood and behavioural disorders) are normal, a comparative cognitive assessment may be proposed to the patients as part of a follow-up phase 6 to 12 months later.
If this initial assessment rules in favour of a cognitive decline, the general practitioner is advised to ask for an expert opinion, and to implement emergency or daily assistance measures if necessary.

Suspicion of Alzheimer's disease or a similar disease
To achieve an aetiological diagnosis and define the development of the treatment and assistance plan, the approach should be based on:
- an interview with the patient with, if he agrees, an identified companion able to give reliable information;
- a clinical examination;
- an in-depth functional assessment;
- a psychic and behavioural assessment;
- a neuropsychological assessment;
- specialised diagnostic examinations.

In difficult or atypical cases, some paraclinical examinations can be proposed by specialised teams. These examinations include in particular:

- Functional imaging

Systematic performance of single photon emission computed tomography (SPECT), a brain scintigraphy with ioflupane [^{123}I] (DATscan®) or positron emission tomography (PET) is not recommended for providing a positive diagnosis of Alzheimer's disease.
A SPECT, or even a PET scan may be performed in the event of atypical dementia, or if there is any doubt about frontotemporal degeneration or other focal atrophy. A DATscan® may be considered if there is any doubt about dementia with Lewy bodies (DLB).

- CSF analysis

A standard CSF analysis (cells, glucose, proteins, protein electrophoresis) is recommended for patients with an atypical and/or rapidly progressing (suspected inflammatory disorder, infectious disease, paraneoplastic syndrome or CJD) clinical presentation. The biomarker assay in the CSF is sometimes difficult to perform in elderly subjects. Some patients may present a contraindication to the performance of a lumbar puncture. This is an indirect measure for amyloid deposits in the brain.

The assay in the CSF of total *Tubulin Associated Unit* (TAU) proteins, phosphorylated TAU and Aß42 may be performed if there is any diagnostic doubt and in particular in young patients.

- **Role of AMYVID in the diagnostic strategy:**

To the extent that:

- the florbetapir PET imaging shall in no case confirm a diagnosis alone, as its interpretation has to take into consideration the clinical and neuropsychological data and other diagnostic tests. The florbetapir PET imaging does not exempt other diagnostic tests (CSF biomarkers, DAT scan etc.) as it does not particularly make a distinction between Alzheimer's disease and a disease with Lewy

bodies. The morphological imaging remains mandatory in the diagnostic approach to limit errors of interpretation.

- sparse or no cortical amyloid plaques is not consistent with Alzheimer's disease and corresponds with a negative florbetapir scan. However, we already have diagnostic means to exclude Alzheimer's disease. Indeed, if the three CSF biomarkers are all normal (beta-amyloid, Tau, PTau proteins), which indirectly measure amyloid deposits, the diagnosis of Alzheimer's is therefore very unlikely at the time of testing. In the absence of a comparison between florbetapir PET imaging and CSF markers, the correlation between these two types of results cannot be established, which is unfortunate because florbetapir PET imaging is easier to perform, especially for elderly patients, and would be more acceptable than lumbar puncture. In this context, there is concern that the florbetapir PET imaging, although it does not demonstrate the same level of diagnosis, replaces the CSF biomarker assay, including the patients who have no contraindication to lumbar puncture.

- β-amyloid senile plaques can be present in the grey matter of patients with other neurodegenerative types of dementia (dementia with Lewy bodies, Parkinson's disease dementia) as well as in asymptomatic elderly people. In so far as the determination of the specificity of florbetapir PET imaging is established on a "specificity" cohort comprising young asymptomatic subjects (n=47) and an "autopsy" cohort of elderly patients (n=59, 79 years on average) that only included 12 elderly patients without cognitive impairment, and not based on a "specificity" cohort comprising a sufficiently large number of elderly subjects without cognitive impairment, the specificity of AMYVID, established at 100% in the pivotal studies, is not transferable in real practice. A moderate to significant density of amyloid plaques corresponds with a positive florbetapir PET scan that does not allow a diagnosis of Alzheimer's or other instances of cognitive decline to be established individually. The question about the amyloid plaques density threshold able to guide the diagnosis towards Alzheimer's disease is not resolved by florbetapir PET imaging, just like that of the differential diagnosis, bearing in mind that a positive test is possible in patients with other neurodegenerative conditions, even in asymptomatic elderly subjects.

- there is no treatment altering the natural progression of Alzheimer's disease or other types of dementia. Indeed, the only treatments are symptomatic, and have at best a modest effect size and debatable clinical relevance. Any potential benefit they have is insufficiently documented beyond 6 months and not established on major clinical criteria, such as the delay of institutionalisation. Thus, if AMYVID allowed the diagnosis of Alzheimer's disease to be established, which is not the case at the moment, there are no therapeutic means allowing the course of its progression to be altered.

- AMYVID does not allow neither the disease progression of Alzheimer's disease to be predicted in the case of patients with mild cognitive impairment, nor the response to treatment implemented to be assessed.

The Committee estimates that PET imaging after administration of AMYVID (florbetapir ^{18}F) does not have any place in the diagnostic strategy of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive impairment.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Alzheimer's disease is a severe and incapacitating, degenerative, neurological disease of the central nervous system, with significant impact on social and family life.

◗ These medicinal products are a radiopharmaceutical drug for diagnostic purposes.

◗ Given the available data, the diagnostic efficacy/adverse effects ratio of these medicinal products is poorly established to contribute to the diagnostic strategy of Alzheimer's disease or other types of dementia.

◗ There is no alternative drug treatment. Various tests are recommended if there is any doubt as to diagnosis, such as CSF assay of Aβ42 and TAU proteins, a standard CSF analysis (cells, glucose, proteins, protein electrophoresis), SPECT imaging, even PET imaging, and a DATscan®.

◗ The Committee estimates that PET imaging after administration of AMYVID (florbetapir ^{18}F) does not have any place in the diagnostic strategy of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive impairment.

◗ Public health benefit:
The burden represented by Alzheimer's disease and other causes of cognitive decline is major considering the high prevalence and incidence and increase in Alzheimer's disease, its impact on loss of autonomy and on the mortality of patients and its effect on caregivers.
The improvement in the diagnosis and treatment of patients presenting with Alzheimer's disease or a similar disease is a public health need, registered especially in the Alzheimer Plan 2008-2012.
AMYVID allows the diagnosis of Alzheimer's disease to be ruled out in the event of a negative result (high negative predictive value). However, it is not the only test that allows an exclusion diagnosis. This may also be achieved by the assay of three CSF biomarkers (β-amyloid, Tau, PTau proteins). AMYVID does not allow any distinction to be made between Alzheimer's disease and other causes of the onset of senile plaques and its efficacy is not established to be able to predict the disease progression of Alzheimer's disease or to assess the response to treatment.
Therefore, AMYVID is not expected to have any effect on the morbidity and mortality and the quality of life of patients with Alzheimer's disease. Because of the possibility with AMYVID to exclude Alzheimer's disease, an impact on the organisation of care might be expected, linked with a reduction in "diagnostic delay" for some patients presenting a moderate to severe cognitive impairment. However, this impact has not been demonstrated.
Overall, in the current state of knowledge and limitations presented, it is not expected that AMYVID will benefit public health in this indication.

Consequently and in the current state of available data, the Committee considers that the actual benefit of AMYVID to estimate ß-amyloid neuritic plaque density in the brain of adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive impairment within the framework of Positron Emission Tomography (PET) with clinical evaluation, is insufficient to justify reimbursement by National Health Insurance.

The Committee does not recommend inclusion of AMYVID on the list of medicines approved for hospital use for Positron Emission Tomography (PET) imaging to estimate ß-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease and other causes of cognitive impairment, with clinical evaluation and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

Not applicable.

010.3 Target population

Not applicable.