16 February 2012
EMA/CHMP/SAWP/892998/2011
Committee for Medicinal Products for Human Use (CHMP)

Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment, for use in regulatory clinical trials in predementia Alzheimer's disease

Agreed by Scientific Advice Working Party	27 October 2011
Adoption by CHMP for release for consultation	17 November 2011
End of consultation (deadline for comments)	22 December 2011
Adoption by CHMP	16 February 2012

Keywords	*Qualification opinion, PET Biomarker, Pre-dementia Alzheimer's disease*

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Background

The European Medicines Agency's (EMA) qualification process is a new, voluntary, scientific pathway leading to either a CHMP opinion or a Scientific Advice of novel methodologies on innovative methods or drug development tools. It includes qualification of biomarkers developed by consortia, networks, public/private partnerships, learned societies or pharmaceutical industry for a specific intended use in pharmaceutical research and development.

On 23 May 2011 the applicant Bristol-Myers Squibb International Corporation requested qualification opinion for the Qualification of Alzheimer's Disease Novel Methodologies/biomarkers for PET amyloid imaging for enrichment of Predementia AD clinical trials.

Prof. Luca Pani was appointed as coordinator. The Qualification Team comprised of: Prof. Bertil Jonsson, Dr David Neil and Dr Christine Gispen-de Wied. The EMA Scientific Administrator for the procedure was Dr Maria Isaac.

The procedure started during the SAWP meeting held on 23 – 26 May 2011.

The discussion meetings with the applicant took place on 29 June 2011 and 24 October 2011.

During its meeting held on 24 – 26 October 2011, the SAWP agreed on the opinion to be given to the applicant. During its meeting held on 14 – 17 November 2011, the CHMP adopted the draft opinion to be given to the applicant.

The draft opinion was published for consultation. Following consultation, during its meeting held on 30 January – 02 February 2012, the SAWP agreed on the opinion to be given to the applicant. During its meeting held on 13 – 16 February 2012, the CHMP adopted the final opinion to be given to the applicant.

The response given by CHMP is based on the questions and supporting documentation submitted by the applicant, considered in the light of the current state-of-the-art in the relevant scientific fields.

Scope

The present opinion addresses the following scope:

Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for PET amyloid imaging (positive/negative) as a biomarker for enrichment for use in predementia AD clinical trials

The vast majority of the data used in CHMP's evaluation have been submitted by BMS, the applicant that requested the qualification. They have been supplemented by further information required by members of the qualification team.

Following the draft opinion adopted in November 2011, the EMA published a draft qualification opinion of CSF biomarkers EMA Procedure EMA/CHMP/SAWP/892998/2011. The paragraph of this qualification states:

PET biomarker signature

- Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of predementia AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population.

- However, neither the actual value of PET (+) or (-) to accurately predict rate of such progression to dementia in the referred subjects nor the relative value of other biomarkers have been reported. Thus, we recommended to follow-up these patients until clinical diagnosis of Mild AD is made.

BMS presented a document addressing a number o questions concerning the qualification of amyloid PET Biomarkers that are intimately linked to the use the Applicant intends in the development of their novel γ-secretase inhibitor. This use is the enrichment of trials populations with patients that not only fulfill the clinical criteria of predementia, which is the target of the trial but in addition have the amyloid pathology.

Background information as submitted by the applicant

In follow-up to the positive Qualification opinion on the use of cerebrospinal fluid (CSF) biomarkers in predementia AD adopted on 14-Apr- 2011 (EMA/CHMP/SAWP/102001/2011), BMS is requesting an additional qualification advice and ultimately, a qualification opinion, on an additional biomarker [amyloid positron emission tomography (PET) imaging)] for patient selection in both predementia and mild to moderately severe AD clinical studies, and to expand the positive Qualification opinion on CSF biomarkers in predementia AD for application in clinical studies of amyloid-targeted therapies in mild to moderately severe AD.

RATIONALE

AD is a serious neurodegenerative disease that begins with memory loss and progresses to severe impairment of activities of daily living, leading to death approximately 8 years on average from time of diagnosis of dementia (Brookmeyer 2002). The cause of AD is currently unknown but pathologic, genetic, and nonclinical evidence suggests that amyloid beta (Aβ) peptides and specifically, the highly amyloidogenic isoform Aβ42 (with 42 residues), are involved in the pathogenesis of AD (Artavanis-Tsakonas 1999).

Currently, clinical diagnosis of AD is probabilistic. That is, it is estimated that approximately 15% to 20% (Rinne & Någren, 2010) of patients currently enrolled in clinical trials evaluating treatments for mild to moderate AD do not have the underlying pathology, and the actual number in the clinical setting is up to 25% (Klatka 1996, Pearl 1997, Rasmusson 1996, Schneider 2010). A definitive diagnosis of AD for a demented patient requires a histopathological evaluation of the number and localization of neuritic plaques and neurofibrillary tangles upon autopsy (Consensus 1997). The most recent publication of the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria (McKhann 2011) includes the category of 'pathophysiologically proved AD dementia' that is consistent with the previous consensus. Plaques primarily consist of Aβ that are formed by a sequential proteolytic cleavage of the amyloid precursor protein (APP) first by APP-cleaving enzyme (BACE) to generate the NH-terminal domain and then by gamma (γ)-secretase to form the COOH terminal domain. Increase in the toxic species of Aβ is considered to be an early event in the disease course. Patients with mild cognitive impairment, who do not meet the criteria for dementia of AD, can already show abnormal (low) levels of Aβ in the cerebrospinal fluid (CSF) (Fagan 2007, Hansson 2006). Aβ40 is the most abundant form of Aβ synthesized (80% to 90%), while Aβ42 is most tightly linked with AD pathogenesis. In particular, mutations that lead to rare, familial forms of AD implicate Aβ42 aggregates as the primary toxic species (Wolfe 2004); current evidence suggests that oligomeric, protofibrillar and intracellular Aβ42 are essential for initiation and progression of AD (Caughey 2003, Cleary 2005, Wilson 2003). Based on the amyloid hypothesis, inhibitors of the enzymes that form

Aβ42, in particular BACE and γ-Secretase, have the potential to function as disease-modifying therapeutics for AD.

Current approved treatments are for patients who have been clinically diagnosed with mild to severe Alzheimer's dementia, and provide only modest and transient benefits. Thus, there is great interest in studying AD earlier in the disease process, and investigating whether the use of potentially disease-modifying agents can alter the long-term course of the illness and prevent the neurodegenerative cascade associated with the disease.

Pathologic evidence obtained at post-mortem of patients with dementia of the Alzheimer's type shows several characteristic neuropathologies, including extracellular plaques, intracellular tangles, and neurodegeneration (Consensus 1997, Grundman 2004, Walsh 2004). Plaques consist primarily of amyloidogenic Aβ peptides that are formed by a stepwise proteolytic cleavage of APP, ending with cleavage by the γ-secretase complex. Aβ40 is the most abundant form of Aβ synthesized (80% to 90%), while Aβ42 is most tightly linked with AD pathogenesis. Although the most prominent form of Aβ in an AD brain is fibrillar Aβ42 accumulated in plaques, current evidence suggests that soluble Aβ, likely oligomeric Aβ42, contributes to cognitive deficits (Caughey 2003, Cleary 2005). Genetic evidence shows that mutations in the APP and components of the γ-secretase complex (the presenilin [PS]-1 and PS-2 genes) lead to rare, familial forms of AD that implicate Aβ42 aggregates as the primary toxic species (Selkoe 2001).

Nonclinical models show that APP over expression leads to plaques and cognitive deficits due to Aβ overproduction in mice (Kobayashi 2005). Studies in both transgenic and wild type animal models demonstrate that γ-secretase inhibitors can reduce brain Aβ levels (Barten 2005, Best 2005, Lanz 2006). The amount of Aβ-reduction needed for clinical benefit in AD is presently unknown. Modest decreases (15% to 30%) in Aβ synthesis by γ-secretase inhibition reversed cognitive deficits and prevented synaptic deficits in transgenic mice models (Comery 2005).

The collective evidence suggests that reducing total Aβ synthesis by inhibiting the γ-secretase complex, therefore reducing Aβ42 levels, might have the potential to intervene in the disease process of AD and thus slow down or delay the progression of the disease.

In addition to amyloid plaque deposition, the formation of neurofibrillary tangles is a central defining feature of AD pathology (Consensus 1997, Grundman 2004, Walsh 2004). Neurofibrillary tangles are intraneuronal aggregates composed of hyperphosphorylated tau protein. Tau is a microtubule-associated protein found primarily in axons. In AD, tau hyperphosphorylation has been hypothesized to elicit tau dissociation from microtubules leading to structural axonal instability and the formation of paired helical filaments, the major component of neurofibrillary tangles (Meraz-Rios 2010). Although the science around soluble tau remains incomplete, soluble forms of tau are detectable in CSF and increased levels of both tau and phosphorylated tau (p-tau) occur in AD. Interestingly, injury to neurons resulting from stroke, head injury, Creutzfedlt-Jakob (CJD) disease and other types of infectious or neurodegenerative insult will also produce increases in CSF tau (Bahl 2009, Hesse 2001, Zemlan 1999). Thus, elevated tau is not specific to AD. The lack of specificity of total tau (t-tau) is offset by the fact that within the heterogeneous class of dementia, elevations in phosphorylated tau is relatively unique to dementia of the AD type (Le Bastard 2010). Natural history studies have shown that during AD disease progression, increased brain amyloid burden (as evidenced by amyloid PET imaging or low CSF Aβ42 levels) can take place well before clinical symptoms (Aisen 2010). The appearance of elevated CSF tau, on the other hand, is often associated with clinical symptoms and dementia (Aisen 2010). As with p-tau, the combinatorial use of increased CSF tau and low CSF Aβ42 improves specificity for AD and is also useful in identifying cognitively impaired subjects at imminent

risk of progression to dementia (Blennow 2010). The coincident pathological appearance of both tau aggregates and amyloid pathology in AD has lead to multiple hypotheses that mechanistically link the two pathologies. One prevailing hypothesis poses amyloid pathology as the major driver of tau hyperphosphorylation, yet another poses that tau dendritic signaling mediates amyloid pathology and a third argues for synergistic concordance of the contributing pathologies (Ittner 2011). If amyloid and tau are indeed mechanistically linked, then it is plausible that an amyloid-modulating therapy could impact tau pathology. What remains clear is that 1) amyloid plaque and neurofibrillary tangle pathology remains a defining feature of AD, and 2) in patients at risk of progressing to AD, a pathological signature for CSF Aβ42 and tau can be detected. Recent evidence is emerging showing that in patients with a CSF AD pathological signature, increased brain amyloid burden is highly concurrent (Fagan 2006, Jagust 2010) suggesting both CSF and amyloid PET imaging are useful biomarker tools for AD clinical trials.

Question 1

PET-Amyloid Imaging: In clinical studies of amyloid targeted therapies in Predementia AD, are there sufficient data to support the use of PET-amyloid imaging as a biomarker for enrichment, by excluding patients with a clinical diagnosis of cognitive impairment who are unlikely to have underlying AD pathology?

Applicant's position

Early in the evolution of the science, the CHMP anticipated the value of studying populations in developing states of Alzheimer's disease (CPMP/EWP/553/95; Rev. 1, dated 24-Jul-2008) prior to the onset of dementia. BMS has made use of the Qualification Procedure (QP) to advance a positive opinion qualifying the use of CSF analytes to identify subjects with cognitive impairment who are highly likely to develop AD dementia and who would represent an acceptable target population for the purposes of drug development. In the published Qualification Opinion (May 2011), it is noted that "A CSF biomarker signature based on a low Aβ1-42 and a high t-tau qualifies to identify MCI patients who most nearly equate to the prodromal stage of AD (Dubois et al., 2007) and who are at risk to evolve into AD-dementia." Further, "How likely that evolution for dementia is still relatively uncertain but it is much more frequent than when the CSF biomarker profile is negative."

Within the same QP, BMS proposed that the use of PET-amyloid radiotracer imaging would also adequately identify those cognitively impaired subjects who are highly likely to develop AD dementia and focused on the data that was available on Avid's radiotracer, Florbetapir. BMS acknowledges the Qualification Team's concerns at that time that there were a limited number of publications available on this subject. While compelling data continue to accumulate in the public domain, we take this opportunity to reflect on two aspects: (1) data showing that elevated amyloid burden on PET-radiotracer imaging in patients with impairment of episodic memory are at significantly increased risk for developing AD dementia and (2) the concordance of PET and CSF criteria shows that they measure similar underlying AD pathology.

*(1) Longitudinal Performance of PET-Amyloid Imaging Biomarkers at Predicting Progression***:** In our Systematic Review, longitudinal studies of 12 months or greater that assessed the performance of PET-amyloid imaging in predicting progression from MCI to AD dementia were assessed (Study Cohort 1).

A total of 6 studies in the literature search reported the use of PET-amyloid imaging in predicting progression from MCI to AD-dementia, meeting criteria of the systematic review. These studies covered a range of geographic locations, including the United States, Europe, Australia, and Japan. Study and sample sizes varied from 15 (Koivunen 2008) to 405 (Lorenzi 2010) subjects. Mean ages ranged from 69.4 to 78.9 years. The mean duration of the studies ranged between 1.8 and 2.3 years, and in all but 1 study, the PET-amyloid ligand used was [11C]-PiB, the exception being Waragai, which used [11C]BF-227 (Waragai 2009). Results from this literature are summarized in Table 1. One report from Kiovunen et al., 2011, was not included due to publication after completion of the literature search. In this study, in subjects who progressed to AD dementia, baseline amyloid burden is higher in the lateral frontal cortex, posterior cingulate, putamen and caudate nucleus compared to those who did not progress.

These data indicate that elevated amyloid burden as determined by PET-amyloid imaging is a strong indicator of an increased risk of progression from MCI to AD-dementia. In the six studies cited, 12-24 month progression rates for PET-positive subjects ranged from 38-100%; whereas, PET-negative group demonstrated progression rates that ranged from 0 to 28% (3 studies reported no progressions to AD-dementia among the PET-negative subjects).

Table 1: Performance of PET-Amyloid Imaging in Predicting Progression from MCI to AD-dementia

Author, Year	Country	Study Population	Follow-up Duration (Range)	PET Biomarker (cut-off)	Progression Rate		Conclusion and Comments
					PET Positive	PET Negative	
Koivunen, 2008	Finland	15 aMCI; Mean age: 71.1 (SD=7.2)	2 years	PiB	7/11 64%	0/10 0%	All MCI converters had increased [11 C]PIB uptake ratios in the posterior cingulate and in the frontal cortex, or increased neocortical [11 C]PIB scores at the MCI stage.
Lorenzi, 2010	Multi-national	405 MCI (64 with PET) Mean age: 74.5 (SD=7.5)	2 years	PiB	16/32 50%	3/32 9%	Using data-derived cutpoint for screening out amyloid-positive patients as part of an enrichment strategy, 16 of 19 converters (84%) were PET positive.
Okello, 2009	UK, Finland	31 MCI Mean age:69.4 (SD=7.9)	2.7 years (range,1-3 years)	PiB	14/17 82%	1/14 7%	14 of the 15 converters were PIB-positive at baseline, conversion rate in the PIB-positive subgroup 82% (14 out of 17).
Villemagne, 2011	Australia	65 MCI Mean age 73.4 (SD=8.5)	1.8 years	PiB	30/45 67%	1/20 5%	Progression to DAT occurred in 67% of MCI with high PiB versus 5% of those with low PiB, but 20% of the low PiB MCI subjects progressed to other dementias. In high PiB healthy controls, 16% developed MCI or DAT by 20 months and 25% by 3 years.

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Author, Year	Country	Study Population	Follow-up Duration (Range)	PET Biomarker (cut-off)	Progression Rate		Conclusion and Comments
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Wolk, 2009	US	26 MCI Mean age: 70.2 (SD=8.8)	1.8 years	PiB	5/13 38%	0/10 0%	Using cutoffs established from a control cohort, 14 (54%) had elevated levels of PiB retention and were considered "amyloid-positive."
Waragai, 2009	Japan	13 aMCI Mean age: 78.9 (SD=3.6)	2.3 years	[^{11}C]BF-227 (>1.11)	6/6 100%	2/7 28%	A significant elevation of BF-227 SUVR was observed in the frontal, temporal and parietal cortices of MCI converters compared with the control subjects. The average neocortical SUVR was significantly higher in MCI converters than in MCI non-converters. A significant inter-group difference between MCI converters and nonconverters was observed in the frontal and the average neocortical SUVR assayed by BF-227–PET

In addition to the systematic review, a search of ongoing studies reveals other data that address the relationship between elevated amyloid burden as assessed by PET-amyloid imaging and clinical worsening in populations without AD-dementia:

- 18F Florbetapir: An ongoing study with florbetapir is following 60 subjects diagnosed with MCI who had baseline PET-radiotracer scans. Preliminary data presented at the International Conference on Alzheimer's Disease (ICAD; Sperling 2010 abstract) showed that after 12 months of follow-up, 22% (4 of 18) of subjects with elevated PET-amyloid binding at baseline progressed to dementia; whereas, only 3% (1 of 29) without elevated amyloid binding progressed.
- 11C PiB: A study by Morris et al. (2009) followed 159 elderly patients with normal cognition (Clinical Dementia Rating [CDR] = 0) for up to 2 years. Of the 159 participants (average age 71.5 years), 23 had progressed to a score of 0.5 on the CDR (mild impairment) and 9 were diagnosed with AD. Elevated PiB at baseline resulted in a hazard ratio of 4.85 (CI 1.22-19.01, p = 0.02) for progression to CDR 0.5 or greater. This study demonstrates that subjects with normal cognition who have elevated amyloid burden are at an increased risk of developing cognitive impairment.

These additional, ongoing studies provide strong support for the ability of PET-amyloid imaging to identify subjects that are at significantly increased risk of progression to AD-dementia from an MCI stage. An additional ongoing study of 18F Florbetaben that is fully-recruited, is assessing the ability of baseline Florbeteben scans in 45 subjects with MCI to predict progression to dementia (NCT01138111), with year 2 visits due to be completed by March 2012. A similar study with Flutematemol (18F PiB) is currently being conducted in 225 subjects with amnestic MCI (NCT01028053), with an estimated study completion date of January 2013.

(2) Consistency between PET-amyloid imaging and CSF Biomarkers: there is strong agreement on the information obtained via PET-amyloid imaging and CSF analyte profile (e.g., low Aβ42, high t-tau) in broad populations with a range of severity of AD (i.e., predementia through mild-to-moderate AD). In this section, we detail the agreement between PET-amyloid imaging and CSF profile in patients with mild cognitive impairment (i.e., Predementia AD as well as impairment unrelated to AD pathology). These relevant studies are assessed in Study Cohort 2 of our Systematic Review and comprised a total of 7 studies that are summarized in Table 2, along with additional reports. The studies that specifically pertain to predementia populations include the following:

- Internal BMS data supporting high concordance has been shown in the ongoing BMS study CN156018 (Phase 2 study in predementia AD). In this study a subset of patients with cognitive impairment underwent both ante-mortem lumbar puncture and PET-amyloid imaging (using Florbetapir) prior to randomization. Among the 64 patients, concordance between PET-florbetapir scanning (qualitative read) and pathologic CSF profile (either Aβ42 < 200 pg/ml or t-tau:Aβ42 ratio ≥ 0.39) was 89%, with an observed agreement statistic Kappa of 0.73 (95% confidence interval of 0.55 - 0.92). Sixty-six percent and 23% of subjects were either positive or negative on both biomarkers, respectively. Five subjects were positive only on PET-amyloid radiotracer imaging while two subjects were positive only on CSF biomarkers. [BMS Preliminary Data].
- Forsberg et al. (2008) reported on 21 subjects with MCI who underwent PET-amyloid imaging (11C PiB) and ante-mortem CSF profile assessment. Correlation between CSF Aβ42

concentrations and PiB retention was statistically significant in frontal, parietal, temporal and posterior cingulate regions (coefficients ranging from -0.64 to -0.74). CSF t-tau concentrations correlated significantly with PiB retention in the frontal and parietal cortex (0.61 - 0.64). Categorization as normal or abnormal was fully concordant for assessment with PiB vs CSF Aβ42. (Of note, an extended cohort including subjects with AD-dementia was reported in Forsberg 2010 and included in Table 2). Jagust et al. (2009) reported on accumulating data from the ADNI cohort. The observed pattern of CSF Aβ42 and t-tau concentrations were impressionably similar between AD-dementia and MCI groups. Accounting for clinical diagnosis, the relationship for PiB retention and CSF Aβ42 was significant; whereas, it was not for CSF t-tau concentrations.

- Koivunen et al (2008) reported on the concordance of PiB retention with CSF Aβ42 concentrations in subjects with amnestic MCI and control subjects. Thirteen of 15 subjects with MCI (87%) had elevated amyloid burden as assessed by PiB retention. More than half of the subjects with elevated amyloid burden (N=7, 54%) had abnormally low Aβ42 concentrations. Furthermore, N= 9 subjects had abnormal t-tau (69%) and N=8 subjects had abnormal Aβ42: p-tau ratios (67%).
- Tolboom et al. (2009a), in a population comprised of AD-dementia, MCI, and healthy controls, showed robust correlation of PiB retention with CSF concentrations of Aβ42 and t-tau. Data for the MCI cohort alone was not reported separately.

Table 2: Summary of Literature Review of Studies on PET-PiB Imaging in Patients with AD dementia, Healthy Elderly Controls (HC), Mild Cognitive Impairment (MCI) and Other Dementias

Study	Year	N	PET	CSF	Correlation	Concordance	Comment
Fagan	2006	24 (AD 4; HC 18; non-AD 2)	PiB	Aß42	n/a	100%	Correlations were not reported for any measure. Among a population of healthy controls, and mild AD patients, those with positive PIB binding had the lowest CSF Aβ42 level and those with negative PIB binding had the highest CSF Aβ42 level. Data suggest that a specific plaque-associated alteration in Aβ42 metabolism is involved in the PiB/CSF Aβ42 association, and suggest that in vivo amyloid imaging, as well as CSF Aβ42 measures may have utility as antemortem AD biomarkers.
Koivunen	2008	37 (15 MCI; 22 HC)	PiB	Aβ42	ns	54%	54% of PIB-positive subjects showed AD-type (<450 pg/ml) Aβ42 values. The corresponding figures showed 69% for t-tau, 63% for p-tau and 67% for the Aβ42:p-tau ratio, indicating a moderate to strong correlation between amyloid binding and CSF analytes. Correlations of PiB to CSF Aβ42 concentrations were not significant. It is worth noting that in a later report by this group (Koivunen 2011) using similar PET methods, a higher definition of abnormal cortex-to-cerebellum ration (1.5) was offered. Optimized cut-points would have suggested concordance in 11 of 15 subjects (Aβ42 <450 pg/ml) and cortex-to-cerebellum ration > ~1.45).
Jagust	2009	55 (AD 10; HC 11; MCI 34)	PiB	Aß42	-0.73	91%	Dichotomous categorization showed substantial agreement between PIB-PET and CSF Aβ1-42 measures (91% agreement, k=0.74), modest agreement between PIB-PET and p-tau (76% agreement, k=0.5). Regression models showed that PIB-PET was significantly correlated with Aβ42, t-tau, and p-tau181p.
			PiB	t-tau	0.42	55%	
Tolboom	2009a	37 (AD 15; 10 HC; 12 MCI)	PiB	Aß42	-0.72	n/a	For global 11C-PiB binding, significant correlations with CSF levels of Aβ42 and tau were found across groups. Linear regression analyses showed that, adjusted for regional volume, age, sex, and diagnosis, global 11C-PiB uptake had an inverse association with Aβ42 CSF levels.
			PiB	t-tau	0.58	n/a	
Grimmer	2009	30 (AD)	PiB	Aβ42	-0.48	est 87%	All patients showed a positive [11C]PiB scan demonstrating amyloid deposition. Linear regression analysis revealed a significant inverse

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Study	Year	N	PET	CSF	Correlation	Concordance	Comment
							correlation between the overall [11C]PiB uptake and CSF Aβ42 levels. Voxel-based regression and regional correlation analyses did not attain statistical significance after correction for multiple comparisons. Numerically, correlation coefficients were higher in brain regions adjacent to CSF spaces. Only 5 patients had CSF Aβ42 concentrations in the normal range and only 2 patients had normal 11C-PiB binding -- with graphs suggesting these latter two patients overlapping with the former (hence estimated 87% agreement).
Forsberg	2010	58 (AD 37; 21 MCI)	PiB	Aß42	-0.46	n/a	Significant correlations between PiB and Aβ42, t-tau and p-tau were observed in most brain regions when including full cohort. No significant correlations were observed between 11CPIB retention and the CSF biomarkers when the AD patients were analyzed separately (p>0.05). Among MCI subjects (Forsberg 2008), PiB correlations to Aβ42 (r, 0.64 - 0.74) were greater than to t-tau (0.51 - 0.64) -- both with significant nominal p-values.
Galvin	2010	31(HC, AD, unspecified dementia)	PiB	Aβ42	n/a	n/a	Among 10 subjects with clinical AD, CSF and PiB showed 70% agreement. Similar agreement among entire sample.
Degerman Gunnarsson	2010	10 (AD)	PiB	Aβ42	n/a	100%	PiB binding strongly inversely related to low CSF Aβ42 (p = 0.01). CSF and PiB assessment of pathologic amyloid burden agreed in all patients (6 pathologic;4 non-pathologic). Correlations between PiB and CSF Aβ42 were significant (although values were not reported). Similar correlations with t-tau and p-tau were reported as not significant.
Fagan	2011	103 (14 AD; 89 HC)	PiB	Aß42	-0.71	n/a	ROC curves demonstrate higher AUC for t-tau:Aβ42 ratio (0.94 - 0.96) than for Aβ42 concentrations alone (0.89 - 0.93)
				Aß42: t-tau ratio	0.73	n/a	
FOLLOWING DATA NOT INCLUDED IN SYSTEMATIC REVIEW -- UNPUBLISHED OR PUBLISHED AFTER CUT-OFF							

Table 2: Summary of Literature Review of Studies on PET-PiB Imaging in Patients with AD dementia, Healthy Elderly Controls (HC), Mild Cognitive Impairment (MCI) and Other Dementias

Study	Year	N	PET	CSF	Correlation	Concordance	Comment
CN156018 (ongoing)	2011	64 (all MCI)	Florbeta pir	Aß42 & t-tau	n/a	89.1%	In this interim analysis on baseline data from an ongoing study a subset of patients with cognitive impairment underwent both spinal taps and PET amyloid scanning prior to randomization. Concordance between PET florbetapir scanning (qualitative read) and pathologic CSF (either Aβ42<200 or t tau:Aβ42 ratio ≥ 0.39) was 89.1%, with an observed agreement statistic Kappa of 0.73 (95% confidence interval of 0.55 - 0.92). Sixty-six percent and 23% of subjects were either positive or negative on both biomarkers, respectively. Five subjects were positive only on PET radiotracer imaging while 2 subjects were positive only on CSF biomarkers. [Preliminary data]
Weigand (ADNI)	2011	41 (10 AD; 22 MCI; 9 HC)	PiB	Aβ42	0.77 (R^2)		Regression model of log-transformed PiB binding and CSF Aβ42 concentrations (with ApoE status as covariate) yielded R^2 of 0.77. ADNI sample with CSF Aβ42 alone shown to have similar modeled distributions (e.g., probability density) as PiB-studied population with measured amyloid burden.
BMS ADNI Analysis		9 mild AD	PiB	Aβ42 t-tau		100%	Pathologic 11C PiB binding (i.e., SUVr > 1.5) was concordant with pathologic CSF (i.e., either Aβ42 < 200 or t-tau:Aβ42 ratio $\geq$ 0.39) in all 9 mild AD patients for whom data could be analyzed

Abbreviations: AD, Alzheimers Disease dementia; MCI, mild cognitive impairment; HC, Healthy Controls; n/a, not assessed

Taken together, the literature of both longitudinal progression from MCI to AD-dementia and cross-sectional correlation with CSF biomarkers, suggests that elevated PET amyloid binding is useful for enriching clinical studies in both predementia and mild to moderate AD populations.

Given the evidence presented herein, BMS is requesting Qualification advice, and ultimately a Qualification opinion on amyloid- PET imaging as a biomarker for patient selection in studies of predementia AD.

Based on the coordinator's and Qualification team report the CHMP gave the following Qualification Opinion:

PET amyloid imaging for enrichment of predementia AD clinical trials

Summary

The purpose of this "qualification" procedure is to assess whether PET-amyloid imaging, as a dichotomized variable (positive or not), can be considered a marker (a risk/ prognostic factor) of progression to dementia in subjects with cognitive deficit compatible with early Alzheimer's disease.

The potential value of the proposed marker in other settings (e.g. in subjects without cognitive deficit or unlikely to have early AD for other reasons) or for other purposes (e.g. as a criterion for the diagnosis of a condition/disease -namely Alzheimer's disease- in a particular subject or the usefulness of repeated measurements to assess the effect of therapeutic interventions -as a marker of efficacy-) are not considered here.

The one contemplated in this procedure is to "enrich" recruitment into clinical trials aimed at studying drugs potentially slowing the progress/conversion to (AD) dementia of the included patients. Enrolling "non-enriched" samples (basing inclusion only on the cognitive deficit) could mean that few subjects would convert during the duration of the trial. Impractically large numbers of subjects and/or duration of follow-up would be required and the trials would be unfeasible or inefficient. Other biomarkers to "enrich" recruitment into this type of clinical trials are known (e.g. some CSF analytes, low hippocampal volume, have been already been qualified).

Scientific discussion

The issue at stake in the decision to QUALIFY the PET amyloid imaging (positive/negative) is to decide if there is sufficiently good accuracy (sensitivity and specificity) to discriminate patients that are at risk of developing AD, *i.e.* will the use of these biomarkers be sufficiently accurate to correctly predict that a given individual who is suffering from predementia AD (Dubois 2007) will evolve to develop a full blown dementia status of Alzheimer's type in a relative short time window of up to 2 years, and that the methodology is sufficiently reliable to be generalizabled.

Accepting the value of the biomarker to "enrich" recruitment is arguably less demanding than on assessing its value in other potential uses. This is because less accuracy of the prediction is required than, to include a particular individual in a diagnostic category. Ultimately, the rate of patients spontaneously converting in the control arm of the trial (whether accurately predicted or not) will be known at the end of the trial. This means the consequences of some out of target predictions would not be as crucial as the same inaccuracy would be to establish the relevant diagnosis in an individual.

The methodology requirement for qualified biomarkers in the pre-dementia stage of AD has been described in previous qualification opinions by the CHMP. Including a positive CSF biomarker profile is considered predictive of the evaluation of the AD-Dementia type (EMA/CHMP/SAWP/102001/2011). However, although high CSF tau and low CSF AB42 are predictive of AD, the criterion, "positive CSF tau/AB42 ratio" is not well defined (Isaac, M., et al 2011).

Low hippocampal volume, as measured by MRI and considered as a dichotomized variable (low volume or not), appears to help enriching recruitment into clinical trials aimed at studying drugs that potentially slow the progress of or conversion to AD dementia of the participants. Low hippocampal volume might be a marker of progression to dementia in subjects with cognitive deficit compatible with pre-dementia stage of AD (Dubois 2007). However, neither the actual value of low hippocampal volume to predict accurately the rate of such progression to dementia in the referred subjects nor the relative value of other biomarkers have been reported (EMA/CHMP/SAWP/809208/2011).

The data on which the Sponsor base their request for the biomarker to be accepted as qualified derive from a systematic review they have conducted after searching the literature for longitudinal studies evaluating PET imaging in predicting conversion to AD dementia from a baseline memory impaired state.

The conclusions are mainly obtained with a "voting" procedure ('the majority of studies report that…'); but although it can be accepted that a true meta analysis might have been unfeasible, given the heterogeneity of the studies, further attempts to obtain global estimates are probably justified.

However, some discussion with the Sponsor was needed, both to clarify some aspects of the systematic review and its internal and external validity and to explore whether a deeper analysis of the retrieved data could justify a more precise statement than simply accepting the vague view that using CSF or PET as a biomarker would "somewhat" enrich recruitment into clinical trials within the considered context. If the review is finally considered valid, this is the type of statement that would be supported by the current analyses.

Based on the co-ordinator's report, the Scientific Advice Working Party concluded that before opinion can be provided the applicant should discuss the following points:

SAWP/CHMP question

Please provide, if available, data to clarify the association of PET amyloid being stronger with Aβ42 than with Tau.

Applicant's response and SAWP discussion

During the June 29 clarification meeting with the Scientific Advice Working Party (SAWP), BMS was asked to provide data to clarify whether the association of PET amyloid was stronger with CSF Aβ42 than with CSF T-Tau. The studies were summarized in the context of concordance, but a direct comparison in terms of characterizing CSF sensitivity and specificity based on a definition of amyloid brain burden was not conducted. In addition, the description of the relationship between amyloid PET and each individual biomarker was not described. Recent data from Washington University described more directly the relationship between amyloid PET using Pittsburg Compound B PIB and each of the CSF biomarkers as well as combined use of both CSF Aβ42 and T-Tau. The results are summarized in Figure 3-1. In brief, correlations between PET amyloid CSF Aβ42 and T-Tau were high in data provided from the Washington University cohort, with disease stages ranging from normal to mild-moderate AD. Interestingly, the association was the highest with tau/Aβ42, suggesting good concordance of the CSF Aβ42 and T-Tau biomarkers with amyloid PET imaging.

Figure 1: Relationship Between CSF Biomarker Data And Amyloid Pet Imaging

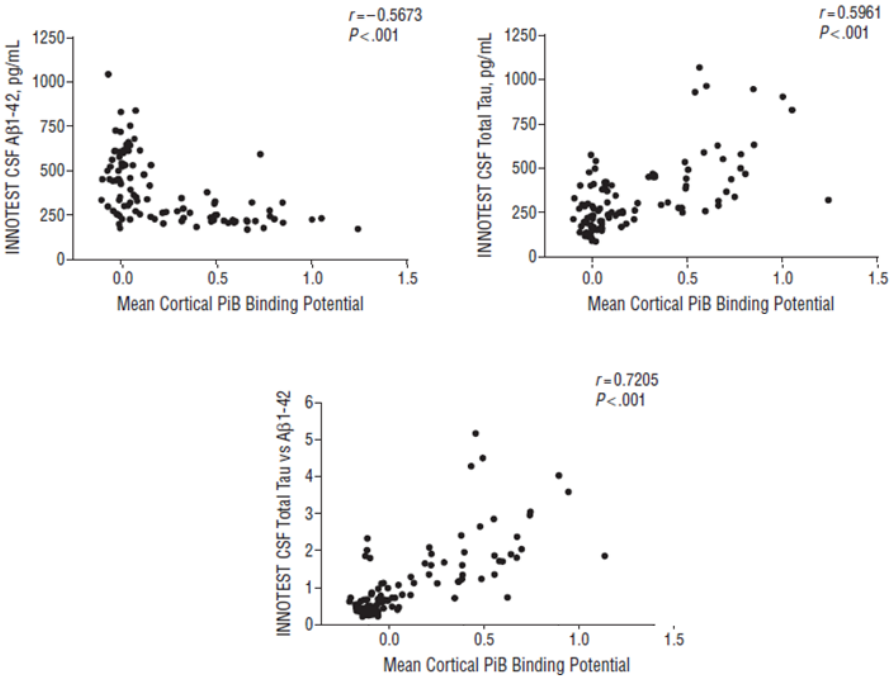
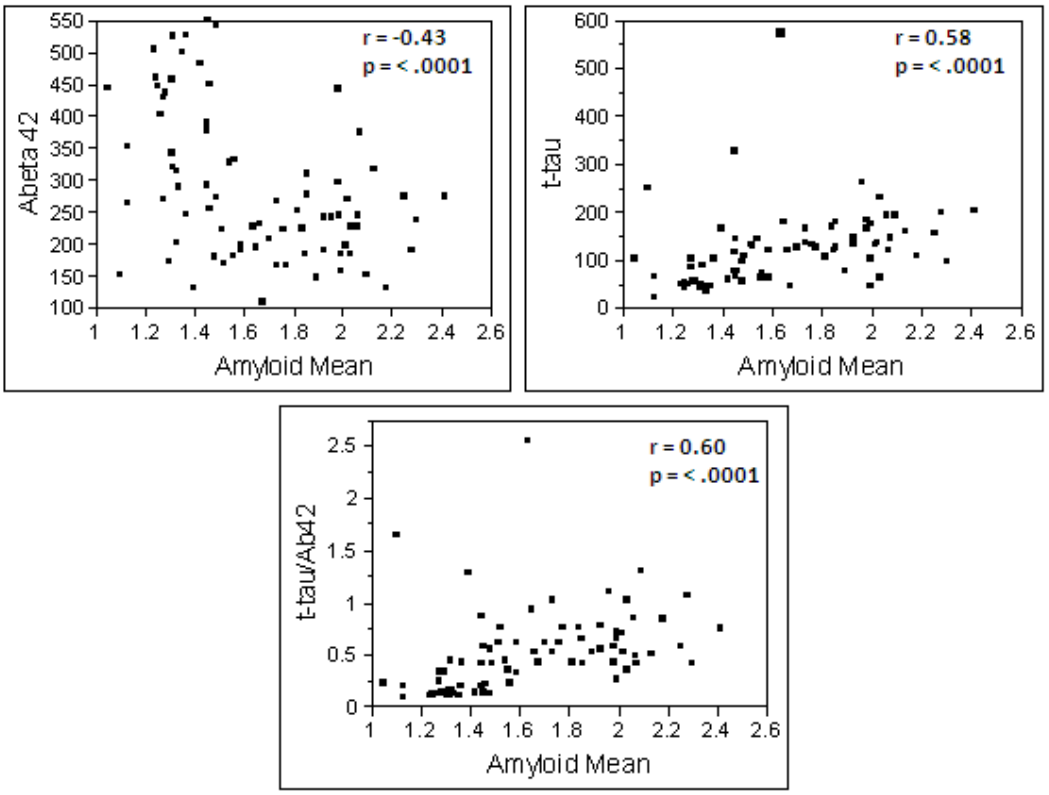


Figure 1 is excerpted from Fagan et al., 2011. 103 patients were examined. There were 89 with a CDR of 0, 11 with a CDR of 0.5 and 3 with a CDR > to 1.

Similar data were also obtained from a blinded ongoing Phase 2 safety study in pre-dementia AD with the BMS compound BMS-708163 and from the ADNI cohort. Figure 3-2 illustrates the Spearman's correlation between CSF biomarkers using the Alzbio3 kits and Florbetapir (AV-45) amyloid PET imaging. There were significant correlations between CSF Aβ42, T-Tau and tau/Aβ42 ratios compared to amyloid brain imaging using the mean standard uptake value ratio (SUVR) data. In both the Washington University and the BMS datasets, the best correlations occur when comparing tau/Aβ42 ratios vs. amyloid PET data.

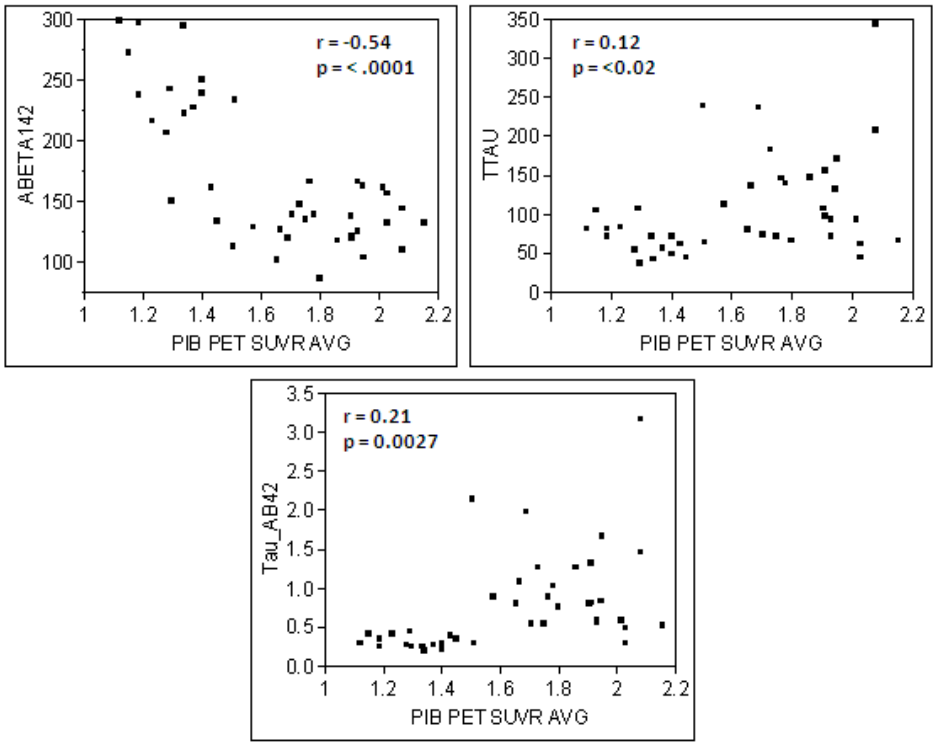
Figure 2: Correlation between CSF Biomarker Data and Florbetapir Amyloid PET Imaging Data from CN156018, Phase 2 Predementia Safety Study with BMS-708163



Total N = 77.

An analysis was also conducted with the ADNI cohort. However, caution must be applied as the N was small and the distribution across disease groups was relatively uneven (Total N = 36, 2 Controls, 26 MCI and 8 AD based upon baseline classification). Figure 3 depicts Spearman's correlation analysis of the CSF biomarkers vs. amyloid PET imaging with the PIB ligand. In brief, there were significant correlations between CSF Aβ42, T-tau and the ratio of tau/Aβ42 vs. averaged SUVR data. The correlation was greatest for CSF Aβ42 and amyloid PIB PET imaging rather than Tau or tau/Aβ42. The underlying reasons for the difference in correlations between the ADNI datasets and the other two datasets are not readily apparent, but may be attributed to differences in assay performance or in cognitive selection criteria.

Figure 3: Correlation of CSF AB42, T-tau and Tau/AB42 vs. Amyloid PIB PET SUVR Averages in the ADNI Cohort



Total N = 36.

Finally, a request from BMS to the Washington University group was made to provide sensitivity and specificity data based upon a classification of amyloid positive vs. amyloid negative. The NPV values range between 90-96% suggesting that when a subject tests negative on the CSF biomarker test the probability that they are truly amyloid positive is very low (or in other words, the probability that they are amyloid negative is very high). Again, caution needs to be taken as the true prevalence of brain amyloid pathology in a typical clinical trial population is unknown. A similar analysis was conducted with the BMS Phase 2 safety data and the ADNI datasets.

In summary, existing data support a significant correlation between low Aβ42 and high T-tau vs. amyloid PET imaging, irrespective of assay or ligand used. Although significant correlations were noted between CSF biomarkers and amyloid PET imaging across all 3 datasets, the degree of the correlation varied across datasets. Additional sub-analysis within the context of prospective studies using validated and approvable CSF assays and amyloid ligands would likely be required to confirm concordance.

SAWP/CHMP question

The applicant should present the studies in which the Dubois's criteria is been used for the inclusion.

Applicant's response and SAWP discussion

In order to address this issue, the applicant presented published research in predementia AD where PET amyloid imaging has been used in studies in the context of the Dubois criteria and ongoing clinical trials and observational research studies evaluating the Dubois criteria and PET amyloid as an enrichment for predementia AD. An overview of PET amyloid data from BMS CN156-018 study was also presented focusing on the strong correlation and concordance between qualitative PET amyloid and CSF biomarker signature.

Following the applicant's presentation, the SAWP asked whether any differences in correlation were found in the BMS CN156-018 study when looking at individual brain regions.

- The applicant clarified that correlations of CSF biomarker signature with PET amyloid positivity for individual regions show no improvement over correlations of the composite measure with CSF.

The SAWP enquired about the use of the CSF Aβ42/tau ratio rather than Aβ42 alone in the studies showing correlation between PET amyloid and CSF biomarkers.

- The applicant stated that both the CSF ratio and CSF Aβ42 alone performed well and that the data had been analyzed using individual values in addition to ratio-quotients. The applicant acknowledged that a single analyte or individual cut points for each of the analytes is preferable. The applicant adopted the use of the tau/Aβ42 ratio in the Phase 2 studies to manage technical challenges with the research use only assays. The technical issues are being addressed by the next generation of assays and the optimal criteria will be applied.

The SAWP asked if there was data to show if one or the other biomarker is preferable (CSF or PET).

- The applicant indicated that there is no clear advantage of one biomarker over the other and data was cited from both ADNI and Washington University studies to support the position.

The SAWP raised the concern of the generalizability of the either/or biomarker approach noting that it is a good approach for proof of concept but more difficult for pivotal trials with regard to the eventual ability to generalize the results of the study to patients who do not have biomarker testing.

- The applicant acknowledged the concern that heterogeneity of response may exist between those enrolled based on CSF or those eligible based on PET amyloid and noted that the large sample sizes in the Phase 3 studies may allow for assessments that may address this question. To further inform this, the applicant plans to include a subset of patients in the Phase 3 studies who will have both biomarkers tested. Of note, available studies showing high concordance between CSF and PET amyloid support the notion that either biomarker largely selects a very similar population.

The SAWP asked if there was a way to achieve proof of concept with amyloid lowering therapies without the need for a large clinical trial.

- The applicant recognised that this is an unsolved problem in the field but not related to the purpose of the current qualification procedure.

SAWP/CHMP question

The applicant should explain the reliability of the regional PET up-take data, and if they have any cross-over test-retest study with acceptable results. If that exist, these results might support this request, the period of 2-4 weeks between the two scans would not suffice for the question.

Applicant's response and SAWP discussion

Data confirming that measurement of cerebral amyloid retention shows good test-retest reliability over periods of weeks to years was presented by the applicant. No comments were raised on this topic.

SAWP/CHMP question

The applicant would need, even if only in a limited number of subjects, to demonstrate that after one year the PET finding in the brain regions of one individual is reproducible.

Applicant's response and SAWP discussion

The applicant presented data showing that there is demonstrated reproducibility of PET findings in predementia AD over 1 year and recognised that while there are some changes over time, they do not result in change in PET amyloid classification.

The SAWP expressed some potential interest in the longitudinal utility of PET amyloid, particularly as it may be applied in Health Technology Assessment.

- The applicant acknowledged this interest but noted that this qualification procedure is intended for clinical trial enrichment and cross-sectional use of the biomarker only.

SAWP/CHMP question

The applicant should discuss whether an increase in the up-take after one year could happen, but no decrease is expected.

Applicant's response and SAWP discussion

Available data was presented by the applicant to substantiate that amyloid retention in AD and aMCI may increase or remain stable but does not typically decrease over time.

The SAWP noted that in the recent therapeutic trials, there appears to be only small changes in PET amyloid retention in longitudinal studies and questioned if this raised concerns for the applicant.

- The applicant acknowledged this point but reminded the SAWP that the applicant's intention at this stage is to use the biomarkers for enrichment of clinical trials as opposed to longitudinal assessment.

Further comment was made by the SAWP around the timing of the development of amyloid pathology in AD and therefore for the timing of therapeutic interventions.

- The applicant recognised that the amyloid deposition occurs early in the disease, which justifies the applicant's emphasis on predementia AD in its development plan.

The SAWP noted that PET amyloid is acceptable for trial enrichment but there is concern down the line that it may be used to exclude patients from receiving treatment and therefore some patients that might benefit would be excluded, particularly early in the disease.

- The applicant acknowledged the concern and reiterated that the purpose of the qualification procedure was to address the enrichment of clinical trials and not to make a diagnosis or to define the patient population suitable for treatment. The applicant noted that PET amyloid imaging is appropriate for enrichment since it is a sensitive and specific measure for determining amyloid positivity but using PET amyloid to monitor patient response to a treatment is a different matter as there is still much to be learned.

SAWP/CHMP question

Can the applicant give standardization suggestions for PET Biomarkers?

Applicant's response and SAWP discussion

The main points presented by the applicant to address this issue are summarised below:

1. *PET amyloid imaging standardization:*

    - PET amyloid standardization issues related to image acquisition and analysis are well defined.

- Best practices are being developed by the manufacturers, academic community and sponsors of clinical studies, and will be applied.
- There is an important role for the core imaging laboratory to address issues of quality control, rater training and analytical standardization. This will address consistency and reliability in the PET measures.

The SAWP asked whether the applicant was envisaging the core imaging laboratory doing the rating of all the images or doing only QC rating, and whether the data to be presented in an MAA will therefore come only from the core imaging laboratory or also from all the sites.

- The applicant clarified that the data from all sites will be transmitted to the core imaging laboratory, which will do the rating of all the scans so that, in the end, all the study data will come from the core laboratory.
- Nevertheless, the applicant cited a very recent study sponsored by Avid Radiopharmaceuticals showing that an on-line training of previously PET amyloid imaging-naive nuclear medicine physicians can successfully ensure appropriate rating at the individual sites.

The SAWP asked if there are conditions that could be associated with a scan which was atypical for PET amyloid, notably a scan with a single positive region or other distribution pattern atypical for AD.

- The applicant responded that single areas or atypical distribution patterns do occur, although infrequently, and subjects with such patterns could still meet the criteria for study inclusion as demonstrating amyloid positivity. (The applicant further noted that all patients would have previously received a clinical assessment and diagnosis and that the PET scan was being used for clinical trial enrichment). Analysis could be undertaken with individuals having such atypical patterns.

CHMP Qualification opinion

PET biomarker

- Amyloid related positive/negative PET signal qualifies to identify patients with clinical diagnosis of predementia AD who are at increased risk to have an underlying AD neuropathology, for the purposes of enriching a clinical trial population.
- However, neither the actual value of PET (+) or (-) to accurately predict rate of such progression to dementia in the referred subjects nor the relative value of other biomarkers have been reported. Thus, we recommended to follow-up these patients until clinical diagnosis of Mild AD is made.
- Collection, handling and measurements of all PET signals should be performed according to Good Clinical Practice and to the specific highest international standards for these measurements.
- The concurrent assessment of recently qualified biomarkers in the predementia stage of AD would be highly desirable and of greatest value.
- Amyloid related positive/negative PET is not qualified as diagnostic tool or outcome or longitudinal measure.

List of abbreviations

Aβ	β-Amyloid
ADL	Activities of Daily Living
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging
ANCOVA	Analysis of Covariance
APP	Amyloid precursor protein
BACE	Beta-site APP-Cleaving Enzyme
BIRC3	Baculoviral IAP repeat-containing protein 3
BMS	Bristol-Myers Squibb
CBD	Corticobasal Degenerative
CDR-sb	Clinical Dementia Rating (sum of boxes)
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHMP	Committee for Medicinal Products for Human Use
CJD	Creutzfedlt-Jakob disease
CRO	Clinical Research Organization
CSF	Cerebrospinal Fluid
DESCRIPA	Development of Screening Guidelines and Diagnostic Criteria for Predementia Alzheimer's Disease
DLB	Dementia with Lewy Body
DSM-IV-TR	Diagnostic and Statistical Manual, 4th version)
DVR	Distribution Volume Ratio
EC_{50}	Concentration required for 50% of maximal activity
ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
FAQ	Functional Assessment Questionnaire
FCSRT	Free and Cued Selective Reminding Test
FDA	US Food and Drug Administration
FTD	Frontotemporal Dementia
γ-Secretase	Gamma-Secretase
GI	Gastrointestinal
HC	Healthy Controls
HES-1	Hairy enhancer of split gene-1
IC_{50}	Concentration at which 50% inhibition observed
ITT	Intention to Treat
LOCF	Last Observation Carried Forward
MAA	Marketing Authorization Application
MAD	Multiple ascending dose
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Exam
MMRM	Mixed Model Repeated Measures
NINCDS-ADRDA	National Institute for Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association
NPH	Normal Pressure Hydrocephalus
NPV	Negative Predictive Value
OD	Other Dementia
p-tau	Phosphorylated Tau

PET	Positron Emissions Topography
PiB	Pittsburgh Compound B
PPV	Positive predictive values
PS	Presenilin
PSP	Progressive Supranuclear Palsy
QP	Qualification Procedure
SA	Scientific Advice
SAD	Single ascending dose
SUVr	Standard Update Volume Ratio
t-tau	Total Tau
TFF	Trefoil Family Factor 3
vMRI	Volumetric Magnetic Resonance Imaging
VaD	Vascular Dementia
VUMC	VU Medical Center cohort

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