16 February 2012
EMA/991202/2011
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on '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' (EMA/CHMP/SAWP/892998/2011)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	F. Hoffmann La-Roche Ltd
2	Janssen Pharmaceutical Companies of Johnson & Johnson, on behalf of Alzheimer's Immunotherapy Program (AIP; Janssen Alzheimer Immunotherapy and Pfizer)
3	Novartis Pharma
4	GE Healthcare

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	This assessment was based on a total of 6 studies using PET-amyloid imaging to follow progression from MCI to AD-dementia. The ligand used was [11C]-PiB in all but one study. In the CHMP's conclusion, would they consider PET "positivity" equivalently across various ligands. Could one conceivably combine datasets (or patients) who were tested amyloid "positive" using PiB, Florbetapir, Florbetaben? This may be relevant if anyone were ever to use amyloid positivity to enrich a pivotal trial; for example, if a registration-enabling trial for an amyloid therapy were enriched with PiB, but later Florbetapir and Florbetaben became commercially available, could the ultimate label apply to patients who were amyloid positive regardless of the tracer used?	The issue could be the subject of future application for qualification advice.
2	While the application is for the use of amyloid PET imaging (positive/negative) as a biomarker for enrichment for use in predementia AD clinical trials, the majority of evidence comes from studies using one imaging agent, 11C-PIB and applicability of other amyloid imaging agents for this specific use needs empirical evidence. Amyloid PET imaging is the tool/method for detecting brain amyloid burden, which is the biomarker for use in patient selection. Only one of the many references cited seems to have been provided. The others should be listed in the final document.	The reference list has been updated to include all relevant references.
4	GE Healthcare welcomes the opportunity to comment on the draft Qualification Opinion for additional biomarkers for patient selection in both predementia and mild to moderately severe AD clinical studies.	The issue could be the subject of future application for qualification advice, but was not within the scope of this procedure.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	This Qualification Opinion is an important development in enabling use of amyloid PET imaging as a biomarker to enrich subject selection in clinical trials which target amyloid in predementia and mild to moderately severe AD populations. The Opinion gives an adequate description of the field and the questions, positions and conclusions are relevant. However, we offer some additional information on the follow up of MCI subjects that further supports the use of amyloid imaging in predicting the increased risk of progression to AD – see specific comments. For PET standardization, GE Healthcare recognises that it is important to have consistent inclusion criteria, not only within each trial, but also across trials. If quantification is used to measure brain amyloid, consistent methods for computation of cut-offs should be used (e.g. use of specific reference region, how are the thresholds between normality and abnormality computed etc.). GE Healthcare endorses the approach of providing individual training materials for PET amyloid naïve nuclear medicine physicians.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 498-500	2	Suggestion to change the word “highest” to “appropriate” standards since dictating “highest” could ultimately be an unreasonable and burdensome expectation as technologies continue to evolve. Proposed change (if any): Collection, handling and measurements of all PET signals should be performed according to Good Clinical Practice and to ~~highest~~ appropriate international standards for these measurements.	CHMP maintains that “highest” is the appropriate wording to ensure comparability of results.
Line 479-486	2	Comment: The potential for subjects to meet inclusion criteria based on an atypical scan, especially a scan with a single positive abnormal region, should be minimized by the common practice of using an integrated measure of multiple regions of interest known to accumulate amyloid as the basis for determination of amyloid positivity. This approach could apply to both quantitative (Standard Uptake Value Ratio-based) methods and qualitative (visual rating-based) methods for positivity determination.	The issue could be the subject of future application for qualification advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 503-504	2	Comment: As the application is specifically for the qualification of amyloid PET imaging as a methodology/biomarker for use in enrichment in predementia AD clinical trials and no evidence are provided for its use as a diagnostic tool or as an outcome or longitudinal measure, we feel that this opinion is outside the scope of the application (see lines 245-249) and should be deleted. Proposed change (if any): deletion of lines 503-504	
187 to 452	3	Comment: Referring to lines 295 and following: A correlation of Amyloid imaging with Ab42 levels will depend on the population. It could be that the correlation of Ab42 levels with e.g. imaging SUVr is actually weak within a pre-dementia or mild to moderate AD population. That does not contradict a positive opinion on question 1. In this respect, the consistency between PET-amyloid and CSF biomarkers (lines 187 and following) is interesting across healthy AND pathological populations, but is not necessary within the pathological population. Indeed (lines 427 and following) changes within some pathological groups are likely only to be small over time. Proposed change (if any): N/A	The issue could be the subject of future application for qualification advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
254	3	In the statement “the one contemplated in this procedure” it is unclear to what the word ‘one’ refers. Proposed change (if any): “the purpose contemplated in this procedure…”	
263 et seq	3	Comment: The report describes the data and subsequent questions and answers, but lacks a detailed scientific assessment of the data by the SAWP/CHMP to explain how they came to their conclusion. The section ‘Scientific Discussion’ (line 263 et seq) is rather superficial and does not discuss the merits or deficits of the data in any detail. Proposed change (if any): Provide a more detailed description of the Scientific Assessment by the SAWP/CHMP. It would be logical to place this at line 488 in order to discuss all the information provided by the applicant.	CHMP is of the view that the merits and deficits of the data are adequately discussed.
489 to 504	3	Comment: The qualification opinion draws on data from multiple amyloid tracers and this suggests that there is some robustness and similarity in the results from those various sources. Further the data used depends on differing acquisition and analysis strategies, yet results seem to be robust to these differences. That is	This point is understood. No change is proposed to the test of the opinion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		encouraging and shows that the general principle is founded in the pathophysiology and is not strongly dependent on complicated measurement standardization. Proposed change (if any): N/A	
492	3	Comment: The applicant's request was for qualification of PET as a prognostic marker for risk of progression to dementia (lines 241-243), and this is what they based their literature review on (Table 1). The applicant should have computed PPV for amyloid imaging, but we think the studies do show that PET imaging is predictive of progression. SAWP/CHMP asked mainly for information on association between PET and soluble CSF biomarkers, as well as some methodological topics. CHMP then concluded that PET is qualified as a marker for risk of underlying AD neuropathology (line 492). The CHMP conclusion thus does not match the applicant's original proposal yet no reason is given for rejection of the original proposal. Alternatively, we wonder if a typing error has possibly been made, because of the mis-match between the	CHMP is of the view that the merits and deficits of the data are adequately discussed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Opinion (line 492) and the applicant's original proposal, and because the second Opinion (line 494) mentions 'such progression to dementia' (i.e. as if referring to a preceding statement on progression to dementia). (NB the Opinion text in line 492 is also identical to that in the other draft Opinion; EMA/CHMP/SAWP/893622/2011, lines 890-1). It could be that the CHMP Opinions should have stated that PET is qualified to identify patients at increased risk of progression to dementia, but not "to accurately predict rate of such progression to dementia" (lines 494-5). Proposed change (if any): **Either:** A CHMP rationale should be given explaining why the applicant's original biomarker proposal (risk of progression to dementia) was rejected, and why the altered biomarker purpose (risk of underlying AD neuropathology) is supported. **Or:** If the text in line 492 (on 'underlying AD neuropathology') is incorrectly written, it should be corrected (eg to 'increased risk of progression to dementia').	
493	3	Comment: The context of utility of PET is restricted to clinical trial enrichment, and does not extend to	Discussion of future label is outside of this scope of the opinion and no opinion is given on the matter by CHMP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		diagnosis/prognosis of individual patients. Does this mean that CHMP agrees that PET could be used to enrich clinical trials but that it would not then become mandatory for treatment decisions in any subsequent SmPC? Proposed change (if any): A clear statement would be useful in line 504, such as "…and would not automatically be required as a diagnostic/prognostic tool in the SmPC for a drug for which PET imaging has been used to enrich a clinical trial population".	
494 to 497	3	Comment: Agree with the CHMP opinion (line 494) and it might have been useful to give a PPV in reference to question 1, based on the data in table 1. In the heading of table 1 it mentions a 'cut-off', but this is only given for the reference Waragai 2009, yet the other publications did classify PET+ or PET-. Proposed change (if any): N/A	This point is understood. No change is proposed to the test of the opinion.
Line 162	4	1) Comment: There are additional data available which demonstrate the value of a PET amyloid scan in examining the relationship between amyloid burden and cognitive status. A two year follow up of the 19/20 mild cognitive impairment (MCI) subjects reported by Vandenberghe et al (2010) in the Annals of	These references have not been evaluated in the context of use of this opinion.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Neurology indicated that 7/9 of the [18F]Flutemetamol amyloid positive subjects progressed to Alzheimer's Disease whereas only 2/10 [18F]Flutemetamol amyloid negative subjects showed any progression. This data was presented at ICAD 2011 by Professor Vandenberghe and at EANM 2011 by Professor Van Laere, both from Leuven University Hospital, Belgium. Vandenberghe et al. 18F-Flutemetamol Amyloid Imaging in Alzheimer Disease and Mild Cognitive Impairment A Phase 2 Trial Ann Neurol 2010;68:319–329.	