16 February 2012
EMA/922/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF AB 1-42 and t-tau and/or PET-amyloid imaging (positive/negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate of Alzheimer's disease' (EMA/CHMP/SAWP/893622/2011)

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

Stakeholder no.	Name of organisation or individual
1	Janssen Pharmaceutical Companies of Johnson & Johnson, on behalf of Alzheimer's Immunotherapy Program (AIP; Janssen Alzheimer Immunotherapy and Pfizer)
2	Novartis Pharma
3	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
An agency of the European Union

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	Should the qualification be extended to the use of CSF phosphorylated tau as a biomarker for enrichment in clinical trials? The applicant makes the case (lines 92-104) that "elevated tau" is not specific to AD....elevations in phosphorylated tau is relatively unique to dementia of the AD type" and that "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".	The issue could be the subject of future application for qualification advice, but was not within the scope of this procedure.
3	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. 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 extra evidence demonstrating the link between pathology and uptake of amyloid PET tracers. 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	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)
	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 896-897	1	Comment: As the application is specifically for the qualification of CSF biomarker signature based on a low Aβ42 and a high T-tau as a biomarker for use in enrichment in mild to moderate 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 663-667) and should be deleted. Proposed change (if any): deletion of lines 896-897	The issue could be the subject of future application for qualification advice.
Line 904 – 906	1	Comment: Suggestion to change the word "highest" to "appropriate" or even "high" 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 the specific ~~highest~~ appropriate/high international standards for these measurements.	CHMP maintains that "highest" is the appropriate wording to ensure comparability of results.

Line 909-910	1	Comment: As the application is specifically for the qualification of amyloid PET imaging as a methodology/biomarker for use in enrichment in mild to moderate 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 and should be deleted. Proposed change (if any): deletion of lines 909-910	See for CSF
267 to 301	2	Comment: The use of negative predictive value and positive predictive value (PPV / NPV) is indeed probably of most relevance in answering question 1 and question 2. These values depend on the populations studied and the prevalence of the condition in these populations. As the applicant points out likelihood ratios (and sensitivity and specificity in line 273 and following) are another approach, but this approach tells more about the diagnostic test itself, rather than the test performance in the population of interest. Likelihood ratios could be used to estimate PPV / NPV under some assumptions of prevalence. Proposed change (if any): N/A	This point is understood. No change is proposed to the test of the opinion.
554 to 652	2	Comment: For question 2 it would have been good to have some PPV/NPV estimates for Amyloid PET. The use of 'concordance' (with Ab42 levels) demonstrates that a decision criterion could be defined. A correlation of Amyloid imaging with Ab42 levels will depend on the population. It could be that the correlation	The issue could be the subject of future application for qualification advice.

		of Ab42 levels with e.g. imaging SUVr is actually weak within a mild to moderate AD population that does not contradict a positive opinion on question 2. In this respect it is not necessary to show a correlation within an AD population (Table 4, line 780, ref. Grimmer 2009/Degerman 2010). Proposed change (if any): N/A	
673	2	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"	Agreed, the word 'one' is referred to the purpose.
678 et seq	2	Comment: The report describes the data and subsequent questions and answers, but lacks a scientific assessment of the data by the SAWP/CHMP to explain how they came to their conclusion. The section 'Scientific Discussion' (line 678 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.	CHMP is of the view that the merits and deficits of the data are adequately discussed.
888 to 910	2	Comment: Agree with the CHMP opinion. The qualification opinion draws on data from multiple amyloid tracers and this suggests that there is some robustness and similarity in the results from	CHMP is of the view that it is of high importance that highest international standards and standarization are applied to ensure comparability of results.

		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 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	
889	2	Comment: It is unclear if the CSF biomarkers are qualified individually or in combination, or both. Proposed change (if any): Provide clear statement if the CSF biomarkers are qualified individually or in combination, or both	They are qualified in combination.
896-7 And 909-910	2	Comment: The applicant's request was for qualification of PET & CSF biomarkers as diagnostic markers for presence of AD neuropathology and this is supported by the CHMP's draft Opinion. The context of utility of PET & CSF biomarkers is restricted to clinical trial enrichment, and does not extend to diagnosis/prognosis of individual patients. Does this mean that CHMP agrees that PET & CSF biomarkers could be used to enrich clinical trials but that they would not then become mandatory for treatment decisions in any subsequent SmPC? As stated by the applicant (lines 805-6) "biomarker testing on all patients with a clinical diagnosis to exclude a small fraction is likely to be too prescriptive and that the decision should be	Discussion of future label is outside of this scope of the opinion and no opinion is given on the matter by CHMP.

		physician and patient/caregiver driven". Proposed change (if any): A clear statement would be useful in lines 897 and 910, such as "…and would not automatically be required as a diagnostic/prognostic tool in the SmPC for a drug for which PET imaging or CSF biomarkers have been used to enrich a clinical trial population".	
912 to 934	2	Comment: We did not find the study Degerman (2010) and Grimmer (2009) in the reference list. Proposed change (if any): Update reference list to include Degerman (2010) and Grimmer (2009)	The references have been included in the list.
Line 609	3	Comment: The following information is additionally available and supports the correlation between the measurement of histopathological amyloid and PET signal. Proposed change (if any): Reference the following paper. Wolk et al (2011) studied the association of PET [18F]Flutemetamol binding in seven Normal Pressure Hydrocephalus subjects who had a previous frontal cortical biopsy. A significant relationship was observed between the presence of amyloid measured by either immunohistochemistry or thioflavin and [18F]Flutemetamol uptake. Wolk et al. Association Between In Vivo Fluorine 18–Labeled Flutemetamol Amyloid Positron Emission Tomography Imaging and In Vivo Cerebral Cortical Histopathology. Arch Neurol.	The references have not been evaluated in the context of use of this opinion.

		2011;68(11):1398-1403.	