14 April 2011
EMA/252172/2011
Committee for Medicinal Products for Human Use (CHMP)

# Overview of comments received on 'Qualification Opinion of Alzheimer's Disease Novel Methodologies/biomarkers for BMS-708163' (EMA/CHMP/SAWP/102001/2011)

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

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | EFPIA |
| 2 | European College of Neuropsychopharmacology (ECNP) |
| 3 | Roche, Ltd. |
| 4 | GE Healthcare Ltd |
| 5 | Elan Pharma International Limited |
| 6 | Gorazd Bernard Stokin, MD, PhD |
| 7 | EFNS Dementia Panel. Prof. Philip Scheltens, MD, PhD. Chairman of panel |

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# 1. General comments – overview

| Stakeholder no. *(See cover page)* | General comment (if any) | Outcome (if applicable) |
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| 1 | EFPIA welcome the opportunity to comment on the draft qualification opinion that EMA released on a biomarker intended to identify patients who can be recruited for clinical trials of treatments for pre-dementia Alzheimer's disease (AD). This qualification opinion is an important development in enabling CSF biomarker use for enrichment of clinical trial populations in prodromal AD studies.<br><br>**EFPIA have the following major comments:**<br>• This document should not be restricted to BMS-708163 only. Instead, this opinion should allow for broader acceptance of these biomarkers in other clinical development programs in pre-dementia AD with drugs impacting amyloid burden. Therefore, we recommend that BMS- 708163 be removed from the title of this opinion. In addition, this opinion should obviate the need for others to submit qualification packages for the same biomarkers for this same context of use. Finally, clarity is sought for future clinical studies that there is now an expectation from the Regulators that a biomarker signature of low Aβ1-42 and high tau (rather than one or the other biomarker) is required for inclusion of patients.<br><br>• The document states in a footnote (line 11) that in all studies that have been analysed the patients despite being in a relative early stage of the disease were sufficiently advanced to have changes in both biomarkers, Ab42 and Tau. However this is still controversial and is addressed more in detail in the document where a more flexible definition of "a positive CSF biomarker signature" which could be considered qualified for prodromal AD patient selection is proposed based on recently published data (Okonkwo, 2011).<br><br>• The studies examining the relationship between biomarkers and conversion used different assays and different cut-off values to optimize their predictive validity. What data will be required from a Sponsor to demonstrate that appropriate cut-off values have been applied within a trial to enrich the population? The document | 1. First comment Accepted. The opinion title has been changed.<br>2. The rest of the comments are related to further Qualification Opinions or Scientifc Advice. We hope that further companies, academics and consortiums will add to the qualification opinion new information. Thus, the rest of the comments are not applicable at this stage of the qualification of the Dubois criteria for enrichment of studies. |

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| | strongly suggests that Sponsors adhere to internationally-established guidelines for collection, storage and measurement, but does not define cut-off values.<br>○ Does the CHMP anticipate that cut-off values will become universal for this assay?<br>○ Clarity is sought on what is meant by 'low' Aβ1-42 and 'high' tau and what ratios would be acceptable for cut-off.<br><br>• Does the CHMP consider use of the Dubois or Peterson criteria, coupled with biomarker assessments, equivalent to enrich the population?<br>• It is noted that the AD conversion rate in cognitively impaired Aß/tau-positive patients per year is approximately triple that of unselected patients. However the qualification opinion largely focuses on trial of longer than one year duration. What is the shortest treatment duration trial for which CHMP considers these biomarkers qualified for enrichment purposes? Is there a recommended trial duration for which these biomarkers can be considered qualified?<br><br>• Would use of an enriched population be permitted for proof-of-concept trials and registration studies? If enriched populations are used in registration studies, what are the implications for regulatory approval/labelling regarding the diagnosis of patients where clinical programmes including biomarker selected patients have delivered a positive outcome? What specificity/sensitivity figures would be needed for a biomarker to be an approved diagnostic tool?<br><br>• Would other potential biomarkers also be considered for enrichment strategies if a Sponsor could demonstrate that alone the biomarker had equivalent sensitivity and specificity to those proposed in the document or that addition of a biomarker to markers proposed here increased sensitivity or specificity?<br><br>• The current Alz Ass QC program, an international effort led by Kaj Blennow with the participation of pharmaceuticals and academics should be discussed in this document. The aim of the QC program | |

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| | is to standardize CSF biomarker measurements to increase the analytical precision and improve the longitudinal stability for biomarker measurements. The program will allow direct comparisons of biomarker levels between laboratories and, thus, between publications.<br>http://www.neurophys.gu.se/english/departments/psychiatry_and_neurochemistry/Neurochemical_pathophysiology_and_diagnostics/TheAlzAssQCProgram | |
| 2 | We feel that essentially this review is helpful and that it provides a useful update on current information about potential biomarkers for AD. The report is nicely aligned with the suggested revised criteria for AD. The issue is of extreme importance, but it probably deserves more detailed attention and critical comments.<br><br>Whilst the expressed view is that CSF biomarkers indicate the pathologic processes underlying AD, it is also important to keep in mind that for example, APOE genotype affects the degree of pathological change, in particular amyloid accumulation in the brain, with APOE4 carriers having more accumulation. Accordingly APOE4 non-carriers may also show less prominent changes in CSF.<br><br>From the presented data it seems that use of CSF marker is an unavoidable step for a correct and early diagnosis and this is necessary to enrich the population that should be enrolled in clinical trials. However the data reported show only the positive results, with no negative comments or discussion on potential pitfalls.<br><br>Uncritical support without showing areas of uncertainty or controversy could be misleading, in helping to improve subsequent RCT design. The HR in longitudinal studies shows an extremely large confidence interval, which is not so supportive of the utility of monitoring | |

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| | biomarkers at the individual level.<br><br>Furthermore, a recent paper by Schneider et al (Alzheimer's and Dementia 6: 367-377, 2010) performed on data from ADNI, simulated different clinical trials with mild cognitive impairment and clearly showed that adding CSF evaluation did not increase dramatically the efficiency of trial. In addition the same paper emphasised how this could also affect also the outcome at the level of the single patient (being positive to marker could be translated in a more severe disease less responsive to treatment…and type of treatment could be affected by this).<br><br>We contend that using CSF assays as a mandatory aspect for performing randomised controlled trials in AD could therefore be a double-edged weapon and more studies are probably needed before CSF examination should be required, either as a screening criterion or as a surrogate marker. | |
| 3 | This qualification opinion is an important development in enabling CSF biomarker use for enrichment of clinical trial populations in prodromal AD studies.<br><br>The opinion is based on a review of multiple prospective studies evaluating the use of the core CSF biomarkers ( Aβ1-42, T-tau and P-tau) for identification of prodromal AD patients. The qualification focuses on a combination of CSF Aβ1-42 and T-tau which in this analysis seemed to perform best in predicting the likelihood that a given individual who is suffering from a specific amnestic disorder will evolve to develop a full blown dementia of the Alzheimer's type in a relative short time window of up to 2 years. At this stage, although | |

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| | there is no doubt that CSF biomarkers are useful in identifying patients in the pre-dementia phase of AD there is still no sufficient evidence to indicate which marker combination would ultimately provide the best selection criterion. There are certain caveats in the multiple published studies: substantial variation in the definition of MCI, of pathological CSF and corresponding biomarker cut-offs (i.e. single marker vs. combination of markers, continuous variables versus ratios), differences in analytical procedures, and in general only a modest improvement of the accuracy of predicting AD provided by the addition of tau to Aβ. In addition to that, a recent publication assessing the performance of CSF biomarkers in the ADNI dataset (amnestic MCI patients with a 3 years clinical follow-up) reported that amyloid abnormalities but not tau alterations were associated with cognitive deterioration, disease progression, and increased risk of conversion to AD dementia (Okonkwo, 2011). Additional prospective studies with sufficient duration and sample sizes will be necessary to define the best performing biomarkers for this purpose; definition of cut-offs will also be essential to enable clinical use of these biomarkers. We thus propose the use of a more flexible definition of "a positive CSF biomarker signature", which will be considered qualified for prodromal AD patient selection, i.e. low Aβ1-42 OR a combination of low Aβ1-42 and high T-tau (or even P-tau which was not assessed in this qualification but may also contribute to a better patient selection).<br>We agree with the conclusion that standardization of pre-analytical and analytical steps is critical for obtaining reliable CSF biomarker measurements. In addition to establishing defined processes, development of highly standardized assays with accepted cut-off values as well as availability of international reference material/controls are a prerequisite for the wide use of CSF | |

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| | biomarkers in clinical trials. | |
| 4 | GE Healthcare recognises the importance of the dedicated EMA biomarker qualification procedure and welcomes this approach for qualification of a biomarker for Alzheimer's Disease. We agree that the CSF biomarkers are very useful to define inclusion criteria for Alzheimer's clinical trials but highlight that there are issues with the reliability of the measurement methods which are currently not solved for using them on a large scale. High variability has been found for the CSF biomarkers not only between centres but also within centres (Verwey et al 2007).<br><br>In contrast, amyloid PET imaging has the potential to overcome those issues as suggested by the high test-retest performance using the 18F-labelled Pittsburgh compound B (PiB) derivative 18F-flutemetamol (Vandenberghe et al 2010), while providing similar information as CSF. Indeed, a tight inverse correlation between PiB PET and CSF Aβ42 measures has been observed in every study where the two measures have been compared (Jack et al 2010). In addition amyloid PET is recognized as a pathophysiological biomarker of Alzheimer's in the emerging revised diagnostic criteria, as indicated in Dubois et al (2010). Pathophysiological markers correspond to the two aetiological degenerative processes that characterise Alzheimer's pathology: the amyloidosis path to neuritic plaques and the tauopathy path to neurofibrillary tangles. They include CSF measures of reduced concentrations of amyloid β, increased total tau, and increased phosphotau, and amyloid PET scanning with PiB or other radioligands (florbetaben, ¹□F-AV-45, etc).<br>1. Verwey NA et al 2007. A worldwide multicentre comparison of assays for cerebrospinal fluid biomarkers in Alzheimer's disease. Ann | PET biomarker is not part of this qualification opinion. |

| Stakeholder no. *(See cover page)* | General comment (if any) | Outcome (if applicable) |
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| | Clin Biochem 2009; 46: 235–240.<br>2. Vandenberghe R et al 2010. 18F-Flutemetamol Amyloid Imaging in Alzheimer Disease and Mild Cognitive Impairment A Phase 2 Trial. Ann Neurol: 68; 319-329.<br>3. Jack CR et al 2010. Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. Brain: 133; 3336–3348.<br>4. Dubois B et al 2010. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol: 9; 1118-1127. | |
| 5 | Elan welcomes the opportunity to comment on the draft Qualification Opinion of Alzheimer's Disease novel methodologies/biomarkers.<br><br>Biomarkers remain a key research focus in the area of AD, as diagnostic and enrichment criteria but also as potential indicators of an alteration in the pathology of the disease following therapeutic intervention. While this latter hypothesis is not currently validated it is important that there is no ambiguity to sponsors of the continued value of on-treatment assessment of scientifically important biochemical markers. As the current document represents the first qualification opinion by the agency in this area, the company believes an important clarifier is that the qualification of low Aβ1-42 and high T-tau as predictors of evolution to dementia in MCI patients is not to the exclusion of their potential value in other contexts in interventional trials.<br><br>The company also believes that while there is evidence that low Aβ1-42 and high T-tau are appropriate predictors as described by the agency, there remains the possibility of alternative criteria also being proven as applicable. Therefore the company suggests that where | The company is advised to come for qualification opinion or advice to discuss these issues further. |

| Stakeholder no. *(See cover page)* | General comment (if any) | Outcome (if applicable) |
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| | robustly justified, other approaches may also remain feasible.<br><br>Finally there is potential confusion within the document with respect to which population the opinion applies to, given multiple references to MCI, the criteria of Dubois and the applicant request in respect of prodromal AD. The company feels the document would benefit from a discussion of the application of these criteria in clinical development and the regulatory implications in terms of product labelling. This could be achieved through a Question & Answer document. | |
| 6 | Think tau and p-tau interchange is a bit confusing, truly most studies have been carried out using tau, but p-tau is probably more sensitive, possibly above all in the presymptomatic phase (although there is no study to confirm thisat this point), I would not reject the use of p-tau in favor of tau merely based on older or luck of studies | |
| 7 | The panel applaud the EMA for having this analysis being done as a response to BMS in the context of conducting a clinical trial in prodromal AD as defined by the Dubois criteria. Our main points of criticism focus on:<br>-The use of tau instead of p-tau<br>-the lack of stress on standardisation issues<br><br>The analysis focuses on tau and abeta and not on p-tau. The authors inform us on line 282 that they have chosen only total TAU because it is supported by 8 studies. This is hardly an argument since at least 5 relevant studies have appeared that included also p-tau. This is especially relevant since the general assumption is that p-tau offers specificity over total tau in discriminating AD from non-AD. Since MCI in the document is not distinguished between non- and amnestic forms, specificity towards AD is crucial. | We hope that the scientifc community and companies will add to the current information and the opinion can be updated. |

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| | Another issue is the assay itself: in the survey carried out by Hort et al., 2010 " The use of CSF biomarkers across Europe " revealed the lower heterogeneity in its assessment and in establishment of normative values for this particular marker, as opposed to total tau. According to a very recent meta-analysis (Van Harten 2011), comparing to controls, tau concentrations are moderately elevated in DLB, FTLD and VaD, while phospho TAU concentrations are only slightly elevated in DLB and not elevated in FTLD and VaD. Over all p-tau reached higher specificity over tau in all comparisons.<br><br>The authors recommend enforcement of guidelines for sample processing and collection, but do not mention the problems with cut-off values and control groups as revealed also in our European survey Hort et al., 2010. In addition, results from EU initiatives on standardisation show disappointing results (Verwey 2009). In lines 298-300 this is touched upon, but not further elaborated. We stress that only when using a central laboratory for these assays reliable results can be obtained. This should be an pertinent requirement when performing trials using these biomarkers and added to the conclusions in lines 302-314<br><br>References to be included for consideration<br>Van Harten AC, Kester MI, Visser P-J, Blankenstein MA, Pijnenburg YAL, Van der Flier WM, Scheltens P. Tau and p-tau as CSF biomarkers in dementia: a meta-analysis. Clin Chem Lab Med 2011;49(3):xxx-xxx Epub printed ahead of publication DOI 10.1515/CCLM.2011.086<br><br>Hort J, Bartos A, Pirttilä T, Scheltens P. Use of cerebrospinal fluid biomarkers in diagnosis of dementia across Europe. Eur J Neurol 2010;17:90-96. | |

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| | Verwey NA, Van der Flier WM, Blennow K, Clark C, Sokolow S, De Deyn PP, Galasko D, Hampel H, Hartmann T, Kapaki E, Lannfelt L, Mehta PD, Parnetti L, Petzold A, Pirttila T, Saleh L, Skinningsrud A, Van Swieten JC, Verbeek MM, Wiltfang J, Younkin S, Scheltens P, Blankenstein MA. A worldwide multicentre comparison of assays for cerebrospinal fluid biomarkers in Alzheimer's disease. Ann Clin Biochem 2009; 46:235-240. | |

## 2. Specific comments on text

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| Line 11, footnote 1 | 1 | Comments:<br><br>The footnote states that in all studies that have been analysed the patients despite being in a relative early stage of the disease were sufficiently advanced to have changes in both biomarkers, Ab42 and Tau. However this is still controversial; a recent publication assessing the performance of CSF biomarkers in the ADNI dataset (amnestic MCI patients with a 3 years clinical follow-up) reported that amyloid abnormalities but not tau alterations were associated with cognitive deterioration, disease progression, and increased risk of conversion to AD dementia (Okonkwo, 2011). e.g. in ADNI not all amnestic MCI patients who later converted to AD had abnormal tau at baseline (Okonkwo, 2011)<br><br>  <br>Okonkwo 2011.pdf<br><br>Additional prospective studies with sufficient duration and sample sizes, and with cut-offs definition could be necessary to define the best performing biomarkers and enable their clinical use. It is thus proposed the use of a more flexible definition of "a positive CSF biomarker signature" which will be considered qualified for prodromal AD patient selection, i.e. low Aβ1-42 OR a | The opinion is related to the information related and the stay of the art at the time of the opinion. |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | combination of low Aβ1-42 and high T-tau (or even P-tau which was not assessed in this qualification but may also contribute to a better patient selection).<br><br>Proposed change (if any): | |
| Lines 91,106,251 | 1 | Comments:<br><br>Varying terminology has been used regarding 'cut-off'. It is recommended to correct to single terminology 'cut-off'.<br><br>Proposed change (if any): | Accepted |
| Line 258-261 | 1 | | |
| Line 298-300 and 306-310 | 1 | Comments: Standardisation of detailed procedures and the importance of assay robustness are key. However, the draft Opinion appears to contain a conflicting message. In line 299 it reads that 'limitation and impact on the qualification decision are acknowledged' and yet by line 309 states that 'guidelines must be enforced'. Although the CHMP working party only 'touched upon the issues' according to line 298, the group formed a sufficiently strong opinion to make such recommendations<br><br>Proposed change (if any): We consider it appropriate to include further detail of the issues in the paragraph | Not accepted. |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | beginning line 298, in order to support the recommendations in the later section. | |
| Line 298-300 | 1 | Comments: This passage is vague but could potentially imply a complete reversal of the opinion. The committee's task was to evaluate the usefulness of biomarkers. It should be within the committee's task and expertise to judge whether biomarkers have been measured with sufficient reliability and can be measured with sufficient reliability in the future. The cited passage implies that biomarkers, in the opinion of the committee, are useful but the reliability of measurement is unclear and was not judged by the committee. It is thus recommended to include the issue of measurement reliability fully into the opinion.<br><br>Proposed change (if any): | Not accepted. |
| Line300, 316 | 1 | Comments: Typo.<br><br>Proposed change (if any): Change Berjeke to Bjerke | Accepted. |
| Line 304-305 | 1 | Comments: It is concluded that low CSF Aβ1-42 and high T-tau "is mostly useful for enrichment of clinical trial populations".<br>a) Please specify if this includes placebo controlled drug testing trials designed for drug development and registration.<br>b) Since the word "mostly" implies that the biomarkers are useful for other purposes as well, please specify what those purposes are. | This is part of Scientifc Advice. |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | Proposed change (if any): | |
| Line 307 | 1 | Comments: "It implies…" What implies? The literature implies? 'It' is also used in the same sentence to refer to CSF. Please clarify the meaning of "it"<br><br>Proposed change (if any): | Not accepted. |
| Line 309-310, 314 | 1 | Comments: It is mentioned that international guidelines for the standardization and inter-site concordance of measurements of CSF Aâ1-42 and T-tau have been produced and must be enforced. They are also referred to as "specific International standards". This sentence is phrased vague and it is unclear which "specific International standards" are considered relevant. It should also be noted that e.g. Teunissen et al, 2010 did not publish explicit or specific guidelines, but a report of results from an international workgroup by one participating group. The report specifies commonalities and differences in Elisa practices in an international workgroup and represents a summary from one participating group. This report did not address question of CSF collection and storage. No explicit and specific recommendations /guidelines are made in this article. It may be problematic to regard this article as a "specific International guideline", as the recommendations are at best implicit and thus likely to be subject of interpretation. | Standardization will need further qualification. |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | Proposed change (if any): Please reference the specifics international guidelines that are considered relevant and also specify for which aspect of GCP (e.g. CSF collection, Elisa technique) they are considered relevant. | |
| Line 11, footnote 1 | 3 | Comments: The footnote states that in all studies the prodromal phase of AD the patients were sufficiently advanced to have changes in both Ab42 and Tau, however this is still controversial. E.g. in ADNI not all amnestic MCI patients who later converted to AD had abnormal tau at baseline (Okonkwo, 2011).<br>**References**<br>Okonkwo, 2011 *Arch Neurol.* 2011;68(1):113-119<br><br>Proposed change (if any): | Not accepted. |
| Line 10 – 13 | 5 | Comments: Comment: For the purpose of clarity to sponsors the agency is requested to consider the addition of a statement with respect to potential uses of the biomarkers in question in other settings. The example of elevated cholesterol comes to mind whereby this biomarker can be used to assess patients at risk but is also indicative of on-treatment effects.<br><br>Proposed change (if any): The present opinion addresses the question as to whether the use of two cerebral spinal fluid (CSF) related biomarkers (Aβ1-42 and total tau [1]) are qualified in selecting (*i.e.* to | *This topic is outside the scope of the current qualification opinion.* |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | categorize) subjects for trials in early Alzheimer's Disease (AD) as having a high probability of being in the prodromal stage of the disease. *It remains unknown whether on-treatment changes in these biomarkers may be indicative of any alteration in disease pathology; however this topic is outside the scope of the current qualification opinion.* | |
| Line 30 | 5 | Comments: With respect to the meta-analysis conducted, it is important to the integrity of the outcome that all studies considered were of equal quality. The agency is requested to consider adding a statement to reflect the standard of data included in the meta-analysis<br><br>Proposed change (if any): | Not accepted. |
| Line 66-67 | 5 | Comments: Consistent with the general comments raised above, the company proposes some language to confirm the potential for these biomarkers to have other uses if validated in the future.<br><br>Proposed change (if any): For the time being the use of these biomarkers is restricted to enrich cohorts and to allow the design of more efficient clinical trials. *However this does not preclude sponsors from applying these biomarkers in other settings to support the scientific advancement of their use in other contexts as the field advances.* | *Accepted.* |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| Line 287-288 | 5 | Comments: The agency states that the positive signature of CSF biomarkers, i.e. a low Aβ1-42 and high T-tau are qualified to predict the evolution to dementia in patients diagnosed as MCI. Is the company correct in its understanding from the draft opinion that a low Aβ would be <192pg/mL and a high T-tau would be > 93pg/mL.<br>Also the statement refers to Tau but it is assumed should specify T-tau.<br><br>Proposed change (if any): Given the values detailed above CHMP considered the positive signature of CSF biomarkers, i.e. a low Aβ1-42 *(<192pg/mL)* and high T-tau *(> 93pg/mL)* qualified to predict the evolution to dementia in patients diagnosed as MCI. | *This topic is outside the scope of the current qualification opinion.* |
| Line 302-303 | 5 | Comments: The agency refers to the fact that the majority of data supporting the draft opinion was derived from studies applying the Petersen criteria. However the criteria of Dubois are cited as more specific than those defined by the Petersen criteria. It is appropriate that the final qualification statement clarify the nature of definition to which the opinion applies, as Line 30 seems to imply Petersen criteria should be followed. The exact population to which these criteria can be applied in clinical trials warrants specific clarification | *This topic is outside the scope of the current qualification opinion. The opinion is related to the Dubois criteria.* |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | Proposed change (if any): In patients with MCI *as defined by Petersen, Dubois or other clinically justifiable criteria*, a positive biomarker signature based on a low Aβ1-42 and a high T-tau is predictive of evolution to AD-dementia type | |
| Line 311 – 312 | 5 | Comments: The Qualification was requested in relation to prodromal AD. In the final statement patients with MCI 'as close as possible' to prodromal AD are referenced. Given the reluctance of the agency to recognise MCI in the past, it would be helpful to understand the agency perspective on the relative phases of clinical progression in AD.<br><br>Proposed change (if any): | *This topic is outside the scope of the current qualification opinion.* |
| Line 313-314 | 5 | Comments: The agency recommends the collection, procedures and measurements of CSF samples adhere to GLP and International standards. The agency should clarify exactly which guidelines it is referring to here. Also, the ADNI group found that the sample collection method can impact data, and is now implementing a standard method. How do the International standards referred to in the document compare to those standards being applied by the ADNI group? It should also be highlighted that currently, data can not be easily compared across laboratories even when utilizing the same assays. | *This topic is outside the scope of the current qualification opinion.* |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | Can the agency clarify whether it may be necessary for sponsors to systematically check with the agency the "acceptability" of the method chosen?<br><br>Proposed change (if any): Collection, procedures and measurements of all CSF samples should be done in accordance with Good Laboratory Practices and the specific International standards *(add citation)* for these measurements. | |
| Line 267 | 6 | Comments: small sample size<br><br>Proposed change (if any): delete as it adds bias to the interpretation of the results | Not accepted. |
| Line 293 | 6 | Comments: specificity not as high<br><br>Proposed change (if any): give number, percentage, saying not as high is not acceptable in science, which is all about numbers and being exact | Not accepted. |
| Line 294 | 6 | Comments: less useful in predicting development of dementia<br><br>Proposed change (if any): think this is not clearly phrased, it's not only about predicting development of dementia, it's also about false positives, this possibility should be clearly stated | Not accepted. |
| Line 298 | 6 | Comments: method (including the types of antibodies | Not accepted. |

| Line no. | Stakeholder no.<br>*(To be completed by the Agency)* | Comment and rationale; proposed changes | Outcome<br>*(To be completed by the Agency)* |
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| | | used) should be standardized<br><br>Proposed change (if any): there should be an interlab quality control | |