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Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of Alzheimer's Disease Novel Methodologies/biomarkers for BMS-708163

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Background

The European Medicines Agency 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 pharmaceuticals R&D.

The Qualification team was: Prof. Cristina Sampaio (coordinator), Dr Armin Koch, Dr David Neil, Dr Christine Gispen-de Wied, Prof Fernando de Andrés Trelles, Dr Bertil Jonsson. CHMP peer reviewer was Prof. Luca Pani. The EMA Scientific Administrator was Dr Maria Isaac.

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 categorize) subjects for trials in early Alzheimer's Disease (AD) as having a high probability of being in the prodromal stage of the disease.

The vast majority of the data used in CHMP's evaluation have been submitted by the Company that requested the qualification (BMS) and are all published literature available in the public domain. In a few circumstances they have been supplemented by papers searched for by members of the qualification team.

Given the extent of the literature in this field CHMP restricted the analysis to prospective longitudinal studies that were set to evaluate the sensitivity and specificity of the mentioned CSF biomarkers in the long term (>1 year).

There are some constraints in this exercise since the field has been dominated for many years by the concept of minimal cognitive impairment (MCI), as defined by the Petersen Criteria, and only recently the concept of prodromal AD as defined by the Dubois Criteria (2007) has arisen. The difference between the Petersen Criteria and the core clinical Dubois Criteria is that the Dubois Criteria uses a specific cognitive test for episodic memory impairment and therefore the population selected by the core clinical Dubois Criteria is more specific than the MCI population defined by Petersen.

All the prospective longitudinal studies that informed the accuracy of CSF biomarkers were performed in populations defined by the Petersen criteria and were therefore less specific than those populations which will be enrolled in future trials.

From a meta-analysis of all prospective studies based on the population defined by the Petersen Criteria , the sensitivity of the combination Aβ1-42+total tau to predict AD type dementia was 0.87, 95% CI 0.80 -0.95, the specificity 0.70, 95% CI 0.57-0.83 and the positive predictive value of 0.65, 95% CI 0.53-0.77.

Based on these data and despite the fact that the populations were not defined with exactly the same criteria we consider that CSF Biomarkers are Qualified for selecting patients in the context of clinical trials.

The Company BMS requested Qualification of Novel Methodology namely amyloid biomarkers as related to the application of the Dubois Criteria for prodromal AD.

Scope

The Dubois Criteria (2007) envisage a stepwise approach as follows:

"In the absence of completely specific biomarkers, the clinical diagnosis of AD can still be only probabilistic, even in the case of typical AD. To meet criteria for probable AD, an affected individual must fulfill criterion A (the core clinical criterion) and at least one or more of the supportive biomarker criteria such as abnormal cerebrospinal fluid biomarker.

The Dubois Criteria (2007) bring the diagnosis of Alzheimer's disease to a stage of disease when

[1] There is a point for clarification about the use of the two biomarkers in study Aβ1-42 and total tau. For all studies that have been analyzed the patients despite being in a relative early stage of the disease they were sufficiently advanced to have changes in both biomarkers thus they are connected by AND. However recent models suggest that there are a temporal succession for changes in these biomarkers and that in very early stages, before prodromal, Ab42 changes before than total tau, yet that temporal window is earlier than the one we are discussing here therefore the 2 biomarkers are connected by AND.

dementia is not yet present. It is important to note that these criteria rely centrally in the clinical assessment and the biochemical and other markers are described as supportive.

Recently in a clarification paper the same group of authors elaborated the most appropriate terminology Dubois et al. (2010) and on the role of the supportive markers. Accordingly, "Prodromal AD (also called "pre-dementia stage of AD") refers to the early symptomatic, pre-dementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterized by a free recall deficit on testing not normalized with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the presence of AD pathological changes. This phase is now included in the new definition of AD. The term of prodromal AD might disappear in the future if AD is considered to encompass both the pre-dementia and dementia stages.

As it can be understood from the explanation above to fulfill the Dubois Criteria the subject must meet both the clinical and at least one of the supportive criteria.

Among the supportive criteria listed by Dubois et al., are the CSF biomarkers: low amyloid β1-42 concentrations, increased tau concentrations, or increased p-tau concentrations or a combination of these three. The use of these biomarkers was meant to increase the specificity of the diagnosis of AD or, in practice, the use of these biomarkers as tools to increase the likelihood to correctly predict that a given individual who is suffering from a specific amnestic disorder will evolve to develop a full blown dementia status of the Alzheimer's type in a relative short time window of up to 2 years.

For the time being the use of these biomarkers is restricted to enrich cohorts and to allow the design of more efficient clinical trials. Although this is not the remit of the current evaluation, there are already discussions in the literature about the diagnostic value of such biomarker at the individual level Forlenza et al. (2010).

BMS presented two types of amyloid related biomarkers in the context described above. In this document we are set to evaluate the data on pathologic CSF Biomarkers (low CSF Aβ1-42, high total-tau [t-tau], phosphorylated tau [p-tau] and their combinations).

After analyzing all the data submitted and data in public domain, the CHMP thinks that the evidence available is strong enough to issue an opinion regarding CSF biomarkers at this point in time.

Scientific Discussion & Methodology

The issue at stake in the decision to quality the CSF amyloid related biomarkers - low CSF Aβ1-42, high total-tau [t-tau], phosphorylated tau [p-tau] and their combinations - 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 a specific amnestic disorder 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 generalizable.

It is recognized that the type and number of CSF amyloid related biomarkers are much larger than the selection chosen here, Hampel et al. (2010). The CHMP, however recognizeS that these are the ones for which the largest amount of accumulated data is available and therefore it is reasonable to start with them.

The following table summarizes all longitudinal studies that evaluated the predictive value of at least one of the CSF Biomarkers under consideration - (low CSF Amyloid β1-42 [Aβ], high total-tau [T-tau], phosphorylated tau [P-tau]) that have been published.

Study	Year	Location	Marker	Sample Size	Baseline Subjects	Follow Up (Yrs)	Nº Convert	H.R.□(95% CI)	Sensitivity	Specificity	AUC
Bouwman	2007	Netherlands	CSF-Aβ	59	MCI	18 mos.	30	5.0□(1.4 - 18.0)			
			Total-τ	59	MCI	18 mos.	30	5.3□(1.5, 19.2)			
			T-τ / Aβ	59	MCI	18 mos.	30	3.0□(1.7-7.9)			
Fagan	2007	US	CSF-Aβ	61	Cog Normal	3	13	0.99□(0.99 - 1.01)			
			Total-τ	61	Cog Normal	3	13	1.00□(1.00 - 1.01)			

			P-τ	61	Cog Normal	3	13	1.02□(0.99 - 1.04)			
			T-τ / Aβ	61	Cog Normal	3	13	5.21□(1.58 - 17.22)			
			P-τ / Aβ	61	Cog Normal	3	13	4.39□(1.62 - 11.86)			
Buchhave	2008	Sweden	CSF-Aβ	148	MCI	4	63	6.83□(2.40 - 19.4)			
Vemuri	2009	US	CSF-Aβ	186	aMCI	2	60	1.3□			
			T-τ	186	aMCI	2	60	1.7□(1.1 - 2.6)			
			P-τ	186	aMCI	2	60	1.8□(1.1 - 2.9)			
			T-τ / Aβ	186	aMCI	2	60	2.0□(1.1 - 3.4)			
Hansson	2006	Sweden	T-┃/ A®	137	MCI	4	57	17.7□(5.3 - 58.9)	95%	83%	
			P-┃/ A®	137	MCI	4	57	16.8□(5.0 - 56.5)	95%	81%	
			(T- A®) / P-τ	137	MCI	4	57	19.8□(6.0 - 65.7)	95%	87%	
Hansson	2007	Sweden	A®	137	MCI	4	57	8.97□(3.2-24.9)	93	53	0.77
Hansson	2009	Sweden	T-τ / A®	167	MCI	4	69	13.4□(4.0 - 45.1)	95%	83%	
Visser	2009	Multi-centre EU	T-τ / A®	100	aMCI	3	35	26.8 (Odds Rat)□(1.6-456.4)			
Bloom	2009	Sweden	CSF-A®	28	MCI	3	14		85%		
			Total-τ	28	MCI	3	14	7.0 (Rel Risk)□(1.7 - 38.6)		86%	
			P-τ	28	MCI	3	14	3.5 (Rel Risk)□(1.2 - 10.1)		83%	
			A®, P-τ, and T-τ	28	MCI	3	14		64%	79%	
Mattsson	2009	12 EU Memory Clinics	CSF-A®	750	MCI	2	271		79%	65%	0.78
			Total-τ	750	MCI	2	271		86%	56%	0.79
			P-τ	750	MCI	2	271		84%	47%	0.76
			T-τ / A®	750	MCI	2	271	5.2 (Rel Risk)□(3.9 - 6.9)	83%	72%	

Bouwman et al. (2007), presented a follow-up of 64 subjects diagnosed as MCI according to the Petersen Criteria, using Elisa commercial kits to measure Aβ1-42 and tau, with cut-off for Aβ1-42 < 495 pg/mL and for tau > 356 pg>mL. They found an increased risk of progression to dementia of about 3-fold.

Fagan et al. (2007), is a study focused on cognitively normal individuals thus less relevant for the predicated here. Nevertheless, a sub analysis in this study correlated findings of Pittsburgh Compound B (PIB) PET imaging with CSF biomarkers showing a good correlation that are relevant and interesting for a later discussion of the PET markers. The conclusion of this study stated that the very mildest symptomatic stage of AD exhibits the same CSF biomarker phenotype as more advanced AD. In addition, levels of CSF Aβ1-42, when combined with amyloid imaging, augment clinical methods for identifying in individuals with brain amyloid deposits whether dementia is present or not. Importantly, CSF tau/Aβ1-42 ratios show strong promise as antecedent (nonclinical) biomarkers that predict future dementia in cognitively normal older adults.

Buchhave et al. (2008), studied a population of MCI subjects defined by Petersen Criteria however the interest of the authors was to combine different markers, cognitive tests, PET and CSF biomarkers; therefore the data for the CSF marker alone is not presented by itself. A commercial kit was used to

measure Aβ1-42 and the cut of was < 640ng/l. They concluded that combinations of the cube copying test with MMSE, rCBF and CSF Aβ1-42 measurements could help in identifying subgroups of MCI subjects with either substantially reduced or increased risk for future development of AD.

In Vemuri et al. (2009), data from the Alzheimer's Disease Neuroimaging Initiative were used to study cross-sectionally the correlations of both MRI and CSF biomarkers with clinical diagnosis and with cognitive performance in cognitively normal (CN), amnestic mild cognitive impairment (aMCI), or AD cohorts with both CSF and MRI. Baseline CSF (t-tau, Aβ1–42, and p-tau181P) and MRI scans were obtained in 399 subjects (109 CN, 192 aMCI, 98 AD). Structural Abnormality Index (STAND) scores, which reflect the degree of AD-like features in MRI, were computed for each subject. Aβ1–42 did not have an ordered relationship of time to conversion by quartiles that were biologically sensible, which might be due to the significant nonlinear relationship. The authors concluded that CSF and MRI biomarkers independently contribute to intergroup diagnostic discrimination and the combination of CSF and MRI provides better prediction than either source of data alone. However, according to their results, MRI provides greater power and better correlation with general cognition and functional status cross-sectionally than the CSF biomarker tested.

Hansson et al. (2006), assessed a series of 180 consecutive patients with MCI (Petersen Criteria), 137 of them underwent successful lumbar puncture at baseline. Patients at risk of developing dementia were followed clinically for 4–6 years. Additionally, 39 healthy individuals, cognitively stable over 3 years, served as controls. The authors analysed CSF concentrations of Aβ1–42, total tau (T-tau), and phosphorylated tau (P-tau181) using Luminex xMAP technology. The cut-off values that best indicated a relative risk of progression to incipient AD were T-tau> 350 ng/L and Aβ1–42 <530 ng/L, which defined pathological (or Alzheimer's disease-indicative) CSF. The combination of T-tau and Aβ1–42/P-tau181 ratio yielded closely similar results (sensitivity 95%, specificity 87%, hazard ratio 19.8).

Hansson at el. (2007) is the same cohort as Hansson et al. (2006) but it provides further data on the diagnostic accuracy concerning Alzheimer's dementia. The CSF Aβ1–42 concentration identified incipient AD in the MCI cohort with a sensitivity of 93% (95% CI, 82– 98) and a specificity of 53% (95% CI, 41–64) when an optimal cut-off value of 0.64 ng/mL, as identified by the Youden method, was used. The positive likelihood ratio was 2.0 and the negative likelihood ratio was 0.14 for Aβ1–42. The Aβ1–42 / Aβ1–40 ratio resulted in a sensitivity of 87% (95% CI, 76–95) and a specificity of 78% (95% CI, 67–86) for prediction of AD among the MCI patients using the optimal cut-off value 0.95. The positive likelihood ratio was 3.9 and the negative likelihood ratio was 0.16 for the Aβ1–42 / Aβ1–40 ratio. When comparing the diagnostic performance of these two approaches, the area under the curve was larger for the Aβ1–42 / Aβ1–40 ratio (0.87; 95% CI, 0.80–0.92) than for AB42 alone (0.77; 95% CI, 0.69–0.84), which was statistically significant ($p < 0.05$).

Hansson et al. (2009), is a study aimed to identify preclinical AD in patients with MCI using measurements of both regional cerebral blood flow (rCBF) and cerebrospinal fluid (CSF) biomarkers. Baseline rCBF assessments ((133)Xe method) were performed in 70 patients with MCI who were cognitively stable for 4-6 years, 69 patients with MCI who subsequently developed AD, and 33 healthy individuals. CSF was collected at baseline and analyzed for Aβ1–42, total tau and phophorylated tau. In contrast to patients with stable MCI, those who subsequently developed AD had decreased rCBF in the temporo-parietal cortex already at baseline. The relative risk of future progression to AD was particularly increased in MCI patients with decreased rCBF in parietal cortex (hazard ratio 3.1, P<0.0001). Subjects with pathological levels of both CSF tau and Aβ1–42 were also at high risk of developing AD (hazard ratio 13.4, P<0.0001). The MCI patients with a combination of decreased parietal rCBF and pathological CSF biomarkers at baseline had a substantially increased risk of future development of AD, with a hazard ratio of 24.3 (P<0.0001), when compared to those with normal CSF biomarkers. Moreover, decreased parietal rCBF (but not CSF biomarkers) was associated with a more rapid progression to AD. The authors concluded that the combination of rCBF and CSF biomarkers improves the risk assessment of progression to AD in patients with MCI.

Visser et al. (2009), for the DESCRIPA study, investigated the prevalence of a CSF AD profile in patients with subjective cognitive impairment (SCI), non-amnestic mild cognitive impairment (naMCI) or aMCI and the association of this profile with cognitive outcome in each group. Patients with SCI, naMCI, aMCI, and neurologically healthy controls were recruited from 20 memory clinics across Europe, between January 2003 and June, 2005, into this prospective cohort study. A CSF AD profile was defined as an abnormal ratio of Aβ1-42/tau. Patients were assessed annually up to 3 years. Outcomes measures were changes in memory, overall cognition, mini-mental state examination (MMSE) score, daily function, and progression to AD-type dementia.

The CSF AD profile was defined as a score below 1, calculated with the formula Aβ1-42/(240+[1·18×T-tau]). This formula can distinguish patients with AD from controls or from patients with other types of

dementia and can identify patients with potential AD-type dementia among patients with MCI at a sensitivity in the range of 88–91% and a specificity in the range of 52–90%.

All patients who were diagnosed with AD-type dementia at follow-up had CSF AD profile at baseline. A CSF AD profile in patients with a MCI was associated with an increased risk for AD type-dementia (Odds ratio OR, 26.8% 95% CI 1.6-456.4; p=0.02).

Bloom et al. (2009), using ELISA, measured the CSF biomarkers in 47 AD patients, 58 patients with MCI (Petersen Criteria) and 35 healthy control subjects. Twenty-eight MCI patients revisited the clinic and half of them progressed to AD during a period of 3–12 years. Results corroborate an increased risk for progression from MCI to AD with elevated CSF T-tau and P-tau and with the presence of the APOE E4/E4 genotype, but not with decreased Aβ1-42. This paper demonstrated that MCI subjects with high CSF T-tau or P-tau and APOE E4 homozygosity progressed faster from MCI to AD. Therefore these biomarkers can be considered robust predictors of AD and associated with a more rapid progression from MCI to AD.

Mattsson et al. (2009), investigated the diagnostic accuracy of CSF Aβ1-42, total tau protein (T-tau), and tau phosphorylated at position threonine 181 (P-tau) for predicting incipient AD in patients with MCI. This study had 2 parts: a cross-sectional study involving patients with AD and controls to identify cut points, followed by a prospective cohort study involving patients with MCI, conducted 1990-2007. A total of 750 individuals with MCI, 529 with AD, and 304 controls were recruited by 12 centers in Europe and the United States. Individuals with MCI were followed up for at least 2 years or until symptoms had progressed to clinical dementia. Main outcome measures were sensitivity, specificity, positive and negative likelihood ratios (LRs) of CSF Aβ1-42, T-tau, and P-tau for identifying incipient AD.

Of the patients with MCI, 420 did not progress to dementia (stable MCI) when followed up for at least 2 years (median, 3; range, 2-11 years). During follow-up, 330 cases with MCI showed progression of cognitive symptoms to clinical dementia. Of these, 271 were diagnosed as having AD (i.e., had incipient AD at base- line), and 59 with other types of dementia, including 28 with vascular de-mentia, 14 with dementia with Lewy bodies, 7 with fronto temporal dementia, and 10 with neurological diseases and dementia. In the MCI sample, the annual rate of AD diagnosis was around 11% in the first 4 study years. The median time to conversion was 24 months (range, 2-126 months) in AD, 30 months in vascular dementia (range, 6-77 months), 12 months in dementia with Lewy bodies (range, 7-52 months), 22 months in fronto temporal dementia (range, 6-37 months), and 36 months in other dementias (range 24-60 months).

Following recommendations in the Standard for Reporting Diagnostic Criteria, Bossuytt et al., (2003) cutoff levels for individual biomarkers were established for all AD patients vs. all controls, with sensitivity for the index test set at 85%. Positive CSF T-tau and P-tau test results were defined as values above the cutoff (T-tau>320 ng/L and P-tau> 52 ng/L, respectively), and positive CSF Aβ1-42 as values below the cutoff (<482 ng/L).

Aβ1-42 had a sensitivity of 79% (215 of 271; 95% CI, 74%-84%), a specificity of 65% (321 of 479; 95% CI, 61%-69%), a positive Likehood Ratio (LR) of 2.3 (95% CI, 2.0-2.6), and a negative LR of 0.32 (95% CI, 0.28-0.36). P-tau had a sensitivity of 84% (227 of 270; 95% CI, 80%-88%), a specificity of 47% (225 of 479; 95% CI, 42%-52%), a positive LR of 1.6 (95% CI, 1.4-1.8), and a negative LR of 0.34 (95% CI, 0.31-0.37). T- tau had a sensitivity of 86% (232 of 271; 95% CI, 82%-90%), a specificity of 56% (268 of 479, 95% CI, 51%-61%), a positive LR of 1.9 (95% CI, 1.7-2.2), and a negative LR of 0.26 (95% CI, 0.23- 0.29). The area under the receiver operating characteristic curve was 0.78 (95% CI, 0.75-0.82) for AB42; 0.76 (95% CI, 0.72-0.80) for P-tau; and 0.79 (95% CI, 0.76-0.83) for T-tau.

The final index test was an equation for the combination of Aβ1-42/P-tau ratio (y) and T-tau (x), with cutoffs constructed in the training set of all patients with AD vs. all controls, and sensitivity for AD set at greater than 85% based on logistic regression analysis (y = 3.694+0.0105x). This equation was evaluated in MCI patients with incipient AD vs. controls in a first step and in MCI patients only in a final step. As shown in earlier studies, the predictive value of the biomarkers combined was greater than the predictive value of any individual biomarker. In comparing patients with MCI and incipient AD with controls, the cutoff equation achieved a sensitivity of 83% (223 of 270, 95% CI, 78%- 88%), a specificity of 88% (266 of 303, 95% CI, 84%-92%), a positive LR of 7.0 (95% CI, 5.7-8.5), and a negative LR of 0.17 (95% CI 0.14-0.21). When applied to all MCI patients only, the specificity was 72% (345/479, 95% CI, 68%-76%), the positive LR was 3.0 (95% CI, 2.5-3.4), the negative LR was 0.24 (95% CI, 0.21-0.28), the positive predictive value was 62%, and the negative predictive value was 88%. The relative risk for incipient AD in MCI patients with a positive result on this equation was 5.2 (95% CI, 3.9-6.9).

In addition to the studies in the table that are the ones discussed by the Company there is a further analysis of the ADNI data, Shaw et al. (2009). The ADNI is a large, multicenter, longitudinal neuroimaging study, launched in 2004 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations. ADNI includes 819 adult subjects, 55 to 90 years old, who meet entry criteria for a clinical diagnosis of amnestic MCI (n = 397), probable AD (n = 193), or normal cognition (n = 229). Baseline CSF samples were obtained in the morning after an overnight fast from 416 ADNI subjects (AD = 102, MCI = 200, NC = 114 with average [± standard deviation] ages of 75 ± 8, 75 ± 7, and 76 ± 5 years, respectively; Premortem CSF was obtained from separate, ADNI-independent groups of autopsy-confirmed AD cases and additional NC subjects who were matched for age to provide a pathological basis for these biomarker measurements. The CSF t-tau, p-tau181p, and Aβ1-42 concentrations of these individuals were measured using the same reagents and assay system described earlier for the baseline CSF samples from ADNI subjects.

As expected, there were ADNI MCI subjects who converted to a clinical diagnosis of probable AD during the first year of follow-up. As of August 15, 2008, there were a total of 37 MCI subjects who had provided CSF samples at baseline when they entered ADNI and who 12 months thereafter were documented to be converters to AD at the time of their year 1 visit. The average biomarker concentrations and ratio values for these MCI to AD converters were different ($p < 0.0001$) from the corresponding results for the ADNI NC group, and as noted later, they had an AD- like CSF profile incidence comparable with that seen in the ADNI AD group. On the other hand, the three MCI subjects who back-converted to NC status showed an NC-like CSF tau and Aβ profile at baseline. The CSF t-tau values for these MCI subjects were 69, 73, and 83pg/mL, all less than the cutoff value of 93pg/mL; the values for Aβ1-42 were 253, 233, and 285pg/mL, all greater than the cutoff value of 192pg/mL; and the values for p- tau181p were 21, 25, and 20 pg/mL, two less than the cutoff value of 23pg/mL and one slightly more than it. The change in clinical diagnosis for these three MCI individuals was based on an improvement on several cognitive measures including the ADAS-Cog, Mini-Mental State Examination, and memory measures.

Finally, application of the cut points for the three best pathologically based parameters, Aβ1-42, t-tau/Aβ1-42, and the LRTAA logistic regression model, for the presence of an AD-like CSF profile in the ADNI AD, MCI, and NC groups, as well as in the MCI subjects who converted to AD, showed the following incidence of an AD-like CSF profile: 91, 88, and 89%, respectively, for AD; 74, 69, and 70%, respectively, for MCI; 38, 34, and 31%, respectively, for NC; and 86.5, 89, and 86.5%, respectively, for MCI converters to AD.

Conclusions

The prospective data available is very consistent in showing that subjects diagnosed as MCI according to the Petersen Criteria which are less specific for AD than the clinical core of the Dubois Criteria that have a positive CSF biomarker profile based on Aβ1-42 and Tau are more likely to develop dementia in the coming 2 to 3 years. How likely that evolution for dementia is, is still relative uncertain but it is much more frequent than when the CSF biomarker profile is negative. All studies are supportive of the concept that a positive signature predicts the evolution to dementia since they have found that the CSF biomarker signature based on Aβ1-42 and tau predicts the evolution to dementia in cohorts of MCI patients diagnosed according with the Petersen criteria. There are 2 exceptions, one being the study by Vemuri et al. in a subset of the ADNI data the multi factorial model did not find that the CSF signature would add any information to the MRI and the other is by Bloom et al. 2009 in a small sample size study could only find a value for the increased Tau but not for the low Aβ1-42.

Given the consistency of the data available CHMP concludes that a positive signature of CSF biomarkers, i.e. a low Aβ1-42 and high tau is qualified to predict predictive for an evolution for dementia in patients diagnosed as MCI.

To establish the accuracy of the predictive value of the Biomarkers signature CHMP took advantage of a published systematic review and meta-analysis. While in the discussion above only studies with more than 1.5 years of follow-up were retrieved by the Company in the meta-analysis quoted here, van Rossum IA et al. (2010) all longitudinal studies were considered.

The mean conversion rate to AD-type dementia in the studies was 37% during a mean follow-up of 2.5 years. Cohen's delta show that Aβ1-42, T-tau, p-tau were significant predictors of outcome. The highest OR for AD type dementia was found for the combination of Aβ1-42 and T tau with or without p-tau (OR 18.1, 95% CI, 9.6-34.2). An abnormal combination was defined as an abnormal ratio of these markers or as an abnormal score for at least 2 of these markers; the combination of Aβ1-42 with only p-tau and a slightly lower OR 17.5 (95% CI, 10-30.6). For the individual markers, the OR ranged from

7.54 (AB42) to 8.05 (p-tau). For further analysis the combination Aβ1-42 and T-tau was selected because it was studied in 8 studies with a total of 1236 MCI patients of which 454 converted to AD type dementia. The sensitivity of this combination to predict AD type dementia was 0.87, 95% CI, 0.80 -0.95, the specificity 0.70, 95% CI, 0.57-0.83 and the positive predictive value of 0.65, 95% CI, 0.53-0.77.

Given the values detailed above CHMP considered the positive signature of CSF biomarkers, i.e. a low Aβ1-42 and high Tau qualified to predict the evolution to dementia in patients diagnosed as MCI. The sensitivity will be at least 80% and the specificity 60%.

Overall the accuracy is considered to be sufficient to provide the desirable population enrichment of patients at risk to develop AD dementia. In fact the biomarker signature of low Aβ1-42 and high Tau has a relative high sensitivity what allows the exclusion of subjects with a low likelihood of developing dementia when it is not present. The specificity is not as high, thus the signature is less useful in predicting accurately the development of dementia. However for an individual diagnosed as MCI for whom the CSF status is unknown the probability to convert to dementia is about 15% per year. This rate increases about 3-fold if the CSF biomarkers are positive. In any case given that the signature has a higher sensitivity than specificity its usefulness is greater for trial enrichment.

During the discussions, the SAWP touched upon the issues of reliability of the measurement methods. This topic was not meant to be addressed in depth, thus limitation and impact on the qualification decision are acknowledged (Berjeke et al. (2010), Mattsson et al. (2010), Teunissen et al. (2010)).

CHMP Qualification opinion

In patients with MCI a positive CSF biomarker signature based on a low Aβ1-42 and a high T-tau is predictive of evolution to AD-dementia type. The PPV is at least 60%. Given the relative high sensitivity and moderate specificity the CSF biomarker signature based on a low Aβ1-42 and a high T-tau is mostly useful for enrichment of clinical trial populations.

ELISA methods to measure this CSF biomarkers signature are commercially available but the process of measurement is also complex. It implies the standardization of all steps from liquor collection and the type of vials where it is sampled to the last working procedure in the circuit in order to obtain reliable results. International guidelines have been produced to assure inter-site concordance. These guidelines must be enforced.

The CSF biomarker signature based on a low Aβ1-42 and a high-tau qualifies to identify MCI patients as close as possible to the prodromal stage of AD, Dubois (2007) who are at risk to evolve into AD-dementia. Collection, procedures and measurements of all CSF samples should be done in accordance with Good Laboratory Practices and the specific International standards for these measurements.

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