Overview of comments received on Draft Qualification Opinion for Centiloid measure of Amyloid PET to quantify brain amyloid deposition

Comments from:

Name of organisation or individual
1. **Alzheimer's Association**
2. **Jiri Cerman, MD, PhD and Jakub Hort, MD, PhD, FEAN;** Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital
3. **Neuroimaging committee from the European Association of Nuclear Medicine**
4. **Oskar Hansson, Professor [1], Ruben Smith, Associate Professor [1], Rik Ossenkoppele, Associate Professor [1, 2]** Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden. [2] Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands
5. **Eli Lilly and Company**

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1. General comments

Stakeholder number	General comment (if any)	EMA response
Jiri Cerman, MD, PhD and Jakub Hort, MD, PhD, FEAN; Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital	In general we consider the centiloid scale very important and useful, especially in borderline cases. We would like to note that the field is very dynamic and AI models are gradually being introduced in image processing tasks. Fully automated centiloid pipelines may emerge soon with automated quality control and this should be reflected.	The comment is noted. It is not agreed that at this stage automated Centiloid pipelines or quality control approaches should be mentioned. Appropriate validation data will be needed.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 3-5	**Alzheimer's Association**	The Alzheimer's Association welcomes this document, and agrees with CHMP consideration that "the Centiloid Unit for the measurement of brain amyloid level can be considered a validated measure of global amyloid load in the brain for enrichment in clinical trials, if properly used with quality control procedures." The document is of relevance to other initiatives. For example, in 2013, a task force convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging developed Appropriate Use Criteria (AUC) to define the types of patients and clinical circumstances in which amyloid PET could be used, and, importantly, clinical scenarios in which amyloid PET was felt to be inappropriate. In 2024 the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging is publishing updated AUC for amyloid PET based on additional data that have emerged in the decade since the original AUC were published, including advances in therapeutics designed to lower cerebral amyloid burden. This article will all be inclusive of AUC for tau PET, recognizing that this is a relatively novel technology and that data on its clinical utility are currently limited.	The comment is acknowledged and welcomed. It is noted that the qualification opinion statement refers to a clinical trial setting. It is agreed that other imaging markers may also be of relevance in this setting in the future.

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Line 657 *(To provide a potential baseline measure for future therapy monitoring/follow up scanning)*	**Alzheimer's Association**	In addition, in August 2023, the Alzheimer's Association gathered a group of clinicians and scientists with expertise in clinical trials and biomarkers of Alzheimer's disease and related dementias. This group aims to summarize the current knowledge on patients with depleted amyloid biomarkers following anti-amyloid treatment, identify gaps in knowledge, and make recommendations on the naming and operationalization of this entity and its implementation in clinical settings. This working group has been carefully reviewing publications and presentations reporting data on treatment-related amyloid-PET clearance from clinical trials. It has become clear that the clinical benefits observed in clinical trials of anti-amyloid therapies are related to the drug's ability to remove amyloid (as measured with PET) from the brain. Differences in clinical benefits across drugs correlate with the drug effect on amyloid-PET reduction (Boxer & Sperling, Cell 2023). Recent data from the donanemab trials shows that baseline levels of amyloid burden, as measured in centiloids in amyloid-positive patients, is related to the time needed to reach amyloid negativity (Shcherbinin et al JAMA Neurol 2022). In this phase 2 trial, patients who reached amyloid negativity after 24 weeks of treatment had a baseline burden of 92.8 CL, versus 117.4 for those who were still amyloid positive at 24 weeks. While outside the context of use for the current consideration, this, together with data	The comment is acknowledged and it is noted that additional data on response to treatment emerge. Monitoring treatment response is not in the qualified context of use. No change to the qualification opinion is envisaged.

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		presented at ADPD 2024, suggest that baseline quantification of amyloid-PET signal could help estimate duration of treatment, and inform follow-up with amyloid PET or other biomarkers.	
Lines 496-498 *("intermediate C: zone names 'gray zone")* and Lines 575-578	**Alzheimer's Association**	We fully agree with the conclusion presented here on the impossibility to derive a single threshold value for all purposes. This idea of an indeterminate zone was also added to the "revised criteria for diagnosis and staging of Alzheimer's disease" based on the Alzheimer's Association workgroup to emphasize that i. criteria for cut point selection depends on intended use and ii. a level of diagnostic uncertainty exists for values at or near any cut point. This approach is also illustrated in the Lumipulse CSF assay, which results are provided as 3 categories: negative, positive, and likely positive	The comment is acknowledged and welcomed.
Lines 207-209	**Alzheimer's Association**	The use of the Centiloid scale is not restricted to the 3 FDA-approved tracers but is also used for 11C-PIB (the tracer of reference) and 18F-Flutafuranol (NAV-4694), which are both widely used in research studies.	The comment is noted. Answers to questions by the applicant and qualification opinion are based on data for the substances included in the documentation. Statements on variabilities do not apply to 11C-PIB that is used as reference.
Line 309	**Alzheimer's Association**	The appropriate reference is La Joie et al, Alzheimers Dement 2019, not Neurology 2018.	The comment is noted and the qualification opinion revised.

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Line 25 *(technical recommendations)*	**Jiri Cerman, MD, PhD and Jakub Hort, MD, PhD, FEAN;** Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital	Some of the methods or steps in recommended pipelines might be outdated. For example the SPM method yields better R squared with SMP8 than SPM12 (which is closer to truth in our opinion) Although in our experience it is possible to validate both pipelines according to the "Klunk tolerances"	The comment is noted. It is not intended to recommend specific imaging software packages but to provide general recommendations. No change to the qualification opinion is envisaged.
Line 611-614	**Jiri Cerman, MD, PhD and Jakub Hort, MD, PhD, FEAN;** Department of Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital	We actually consider longitudinal measurements and amyloid load change important, especially when anti-amyloid treatments are introduced in order to not to "overtreat" patients when the amyloid is cleared.	The comment is noted. An assessment of amyloid accumulation or monitoring of response to treatment is not included in the Context of Use.
Line 139	**Neuroimaging committee from the European Association of Nuclear Medicine**	The centiloid measure uses a late static-frame which is an easily adoptable method to obtain information about the amyloid status and the amyloid load. It is clinically useful for inclusion in studies and future anti-amyloid drugs. It is robust across tracers in the Alzheimer's disease continuum and therefore practical and valuable in clinical routine. However, it is important to acknowledge that the centiloid measure provides only rough information that can be ameliorated by kinetic parameters using dynamic scans (PMID 35652962, 28674847, 23940304). Thus it may be valuable to include kinetic parameters especially in serial	The comment is acknowledged. Dynamic scanning methods were not in the scope of this qualification procedure. Based on the provided information monitoring of response to treatment is not included in the Context of Use, although technical recommendations for longitudinal assessments are provided.

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		imaging when aging or treatment impacts cerebral blood flow. However, centiloids using a late static-frame after anti-amyloid treatment showed association with therapy success (PMID: 36655336) and may already provide clinically useful information on drug response.	
Line 170	**Neuroimaging committee from the European Association of Nuclear Medicine**	The centiloid measure is a global measure without any regional information. Therefore, it is important to consider the centiloid measure as an adjunct to visual reading or to provide a "regional" centiloid analysis.	The comment is noted. Use of regional data is not generally proposed for application of Centiloid units. The qualification only covers validation of the methodology as a global measure.
Line 349	**Neuroimaging committee from the European Association of Nuclear Medicine**	Longitudinal evaluations should be performed using the same acquisition and reconstruction settings.	The comment is welcomed. Recommendations for longitudinal assessments are included in the qualification opinion.
Line 402	**Neuroimaging committee from the European Association of Nuclear Medicine**	As there is a large bias using the pons as reference region, it is important to stress that the pons should not be used as reference region in this setting.	The comment is acknowledged and the answer to question 3 was amended.
Lines 1-9	**Oskar Hansson, Professor [1], Ruben Smith, Associate Professor [1], Rik Ossenkoppele, Associate**	There are several benefits supporting the use of quantitative metrics when assessing beta-amyloid PET scans. The first and most important reason is that while visual reads are user dependent and are likely to be different between experienced and inexperienced readers supporting quantitative metrics are likely to provide a more comparable	The comment is acknowledged. The benefits mentioned are referred to in the qualification opinion and technical recommendations are provided.

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	Professor [1, 2] Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden. [2] Alzheimer Center Amsterdam, Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC location VUmc, Amsterdam, The Netherlands	result between readers with different experience. Second, in borderline cases a dichotomous result into positive and negative does not convey the information that the result is borderline. A quantitative result with a value closer to the cut-off will retain this information and the clinician will then have the information that even though the result is positive or negative it is close to the cut-off. When it comes to the type of quantitative metric used, the Centiloid metric is a robust measure with clearly defined and published instructions for implementation at different sites. Another benefit of the Centiloid metric is the possibility to use the method with several different beta-amyloid tracers with a uniform scaling for normal/abnormal.	
Lines 578, 93-97	**Eli Lilly and Company**	The qualification opinion provides apparently conflicting statements with respect to centiloid (CL) cutoffs. On one hand, there is the statement in response to Question 3 "No definitive thresholds can be singled out for a broad application." Yet earlier in the document it states, without qualification, that <10 CL may be used to rule out amyloid load, and other cutoffs above 10 CL can be used. These are strong statements based on relatively limited data. This could lead to inappropriate application of the cutoffs provided. See specific comments.	The comment is acknowledged. The qualification opinion was revised to align the statements, including a more comprehensive discussion This is taking into account the specific comment on Lines 93-96 and 315-316 below.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 36-52, 96-97	**Eli Lilly and Company**	It is agreed that optimal estimates of longitudinal variability using CL are likely to be obtained using same tracer and scanning pipeline. However, it is also true based on the information provided in the same Draft Opinion that, for instance discussing possible between-pipeline variability, the maximum observed bias was observed for Florbetaben-PET to be 8.77CL (Line 68), in cases with positive visual read. In a longitudinal application measuring a large change in amyloid load, as for instance in the context of a patient undergoing an efficacious amyloid-targeting therapy, the impact of the expected bias introduced by a change in pipeline would likely be attenuated. As an example, in the donanemab TRAILBLAZER-ALZ2 Phase III Trial (Sims et al., 2023 JAMA), patients treated with donanemab showed a decrease of ~87CL (combined population, 76 weeks). We suggest that it would be appropriate to elaborate on these nuances. See specific comments. Reference: Sims, et al. Donanemab in Early Symptomatic Alzheimer Disease The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023;330(6):512-527	The comment is noted and partially agreed. The general statement that for longitudinal assessments use of the same pipeline is recommended is maintained. A discussion of expected differing variability across the range of the Centiloid units is included in the qualification opinion, which may allow deviation from the recommendation.
Line 36	**Eli Lilly and Company**	To add clarity to introductory sentence that these recommendations are important when variability is intended to be minimized.	The comment is noted and not fully agreed. The objective is also to minimise potential bias.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Suggested text (edits in bold): The applicant provides a set of technical recommendations for utilizing the CL method **intended to minimize variability:**	
Lines 38-39	**Eli Lilly and Company**	To add clarity to introductory sentence that these recommendations are important when variability is intended to be minimized. Suggested text (edits in bold): Longitudinal evaluation of amyloid levels should be performed with the same tracer and scanning pipeline **as possible when variability is intended to be minimized (eg, longitudinal disease progression studies with relatively small expected changes in amyloid over time)**	The comment is noted and partially agreed. The general statement that for longitudinal assessments use of the same pipeline is recommended is maintained. A discussion of expected differing variability across the range of the Centiloid units is included in the qualification opinion, which may allow deviation from the recommendation.
Lines 40-41	**Eli Lilly and Company**	Propose rephrasing to make it clear that authors mean harmonizing inherent resolution of different scanners, resulting from individual acquisition and reconstruction parameters, to the same effective resolution by using phantoms. Suggested text (edits in bold): Consider harmonizing (e.g., using phantoms) the data when comparing CL data obtained across different scanners **where effective resolutions may be different**.	The comment is acknowledged and the document was revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 45	**Eli Lilly and Company**	Motion and other artifacts are the most common reasons for failed image QC. Suggested text (edits in bold): …may bias CL values (e.g., **motion or other artifacts**, wrong positioning of the ROIs, atrophy, etc.).	The comment is acknowledged and the document was revised accordingly.
Lines 51-52	**Eli Lilly and Company**	While it is agreed as described, that there are possible between-pipeline differences and the estimated technical variability should be considered, the recommendation (lines 51-52) is in contrast with the Centiloid approach (Lines 5-8) and reflected in comments to Work Section A (Lines 386-388), where it is concluded, despite the variability that: "The overall conclusion that the approach proposed by Klunk et al. is still appropriate to derive CL calibration equations can be supported" We agree that the ideal scenario when combining CL values for multicenter studies is the ability to use CL values obtained with the same pipeline. Changes to the given pipeline progressively impact comparability of CL values, although the calibration itself should at least attenuate this impact. Suggested text (edits in bold): If comparing data collected from other sites, do not use different pipelines **~~(~~without** check**ing** for **~~consistency~~ impact** of pipeline used for CL measure**~~)~~**.	The comment is acknowledged. The meaning of the original statement may not have been fully clear and a revision along the proposal was implemented.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 93-96, 315-316	**Eli Lilly and Company**	The statements on line 93 that a cutoff of 10 CL may be used to rule out amyloid load, or on line 315 that CL<10 corresponds to absence of amyloid plaques, are strong statements based on relatively limited data, (Amadoru, 2020 and LaJoie, 2018). It is our belief that the CL values for subjects with no and sparse plaques (interpreted here as amyloid absent or present but not pathological) may overlap and may range up to values of 20 CL. For example, Clark et al 2012 showed the CERAD neuritic plaque scores and SUVr values for florbetapir cases followed to autopsy. These SUVr can be converted to CL values using the formula given by Navitsky et al. (2018). In this study, 5 of 15 cases with no CERAD neuritic plaques had SUVr >1.02 (>10 CL) with a high value of SUVr =1.09 (approximately 22 CL), and all 5 cases with CERAD sparse plaques had SUVr <=1.02 (<10 CL.). We think a more appropriate statement would be that CL in the range of 20-30 has been associated with at least moderate neuritic plaque density (pathological plaques). We would not object to a statement that CL values just below this range (e.g., 10-20) should be interpreted cautiously as they may reflect a biological grey zone where amyloid is approaching a pathological level. References: Clark, C.M., et al. Florbetapir PET for Detection of Amyloid Neuritic Plaques, Comparison to Neuropathology at Autopsy: A Prospective Cohort Study, The Lancet Neurology, 2012; 11: 669–78.	The comment is acknowledged. The qualification opinion was revised to align the statements, including a more comprehensive discussion (see above).

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		Navitsky, M., et al. Standardization of amyloid quantitation with florbetapir standardized uptake value ratios to the Centiloid scale. Alzheimers Dement. 2018; 14: 1565-1571.	
Lines 226-229	**Eli Lilly and Company**	While it is agreed that there is a degree of variability, we do not agree that it is not sufficient to be called "tracer independent". The CL method is valid across all three approved brain amyloid PET tracers as well as 11C-PIB and 11C-NAV4694. In principle, methodology in Klunk., et al 2015 allows for calibration of any new tracer or method to the CL scale as long as they follow guidelines for calibration described in the paper. As per a previous comment, the impact of variability should also be taken into account in terms of the context of use. If one is observing amyloid clearance in response to an ATT, there would be larger changes in amyloid load and thus 8.77 CL variability may not have such a significant impact. Suggested text (edits in bold): However, even if the method has undergone validation work using the currently approved tracers, it may not be sufficient to call it "tracer independent" regarding all possible future tracer developments**~~, as the available local PET data quality and quantitative properties may differ~~. Each new tracer CL equation would need to be derived from and validated by the methods outlined in Klunk, et al. 2015.**	The comment is acknowledged and agreed. The text was revised accordingly.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 277-278	**Eli Lilly and Company**	The statement at these lines should be deleted or corrected. While earlier trials with treatments that achieved less amyloid reduction did not achieve clinically relevant treatment effects, more recently, treatments with significant amyloid lowering have shown clinically relevant results and at least one treatment has demonstrated replication of Phase 2 results in Phase 3 (i.e., donanemab). Suggested text (edits in bold): **Although compounds that reduce amyloid levels have recently shown promise in clinical trials, ~~Finally, as demonstrated in previously failed trials with antibodies against amyloid,~~** a decreased amyloid burden according to PET is not synonymous with clinically relevant treatment effects.	The comment is noted and partially agreed. The statement was revised.