Expected Centiloid Values for Patients with Positive Visual Reads of Amyloid PET Scans

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Introduction

Objective: To determine the expected range of Centiloid (CL) values from amyloid positron emission tomography (PET) scans assessed as positive by visual reads based on published literature and baseline clinical trial results.

Background: While amyloid PET scans can be assessed by visual reads, some clinical trials now use a CL cut-off. The CL scale was developed to standardize comparison across PET tracers, with the intent to approximate a value of 0 for amyloid negativity and an approximate value of 100 for mild to moderate dementia. Recent publications and presentations have investigated the possible reasons for discrepant visual read results and results using a CL cut-off. While most studies use a cut-off of approximately 24 CL units to define positivity, a variety of cut-offs have been employed by different investigators, for instance using a cut-off of 37 in one publication.[1]

We used screening data from the ALTITUDE-AD study to better understand these discrepancies, in particular why individuals with a positive visual read may have CL values <24. We also reviewed the literature to assess the range of CL values that might be expected for scans that were amyloid positive by visual read.

Methods

ALTITUDE-AD (NCT06335173) is an ongoing phase 2 study of sabirnetug (ACU193) that has completed enrollment of 542 participants with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD). Amyloid pathology was confirmed by a visual read of an amyloid PET scan using florbetapir or florbetaben or by amyloid levels in cerebrospinal fluid (CSF).

Preliminary baseline amyloid PET standard uptake value ratio (SUVr) levels were converted to CL for analysis. Cases in which PET scans were assessed as positive on visual read and had CL levels <24 were examined for possible reasons for low CL values.

Additional information regarding discordance between amyloid PET CL levels and visual reads was identified from the literature and recent presentations.

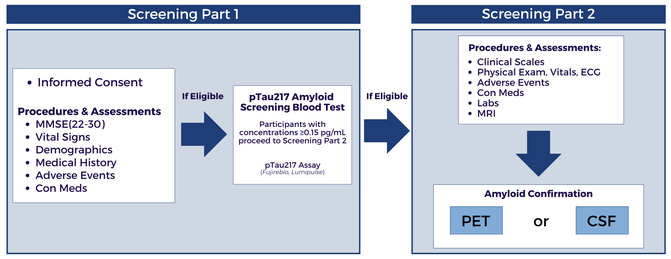
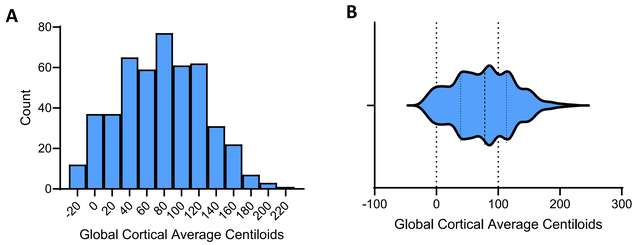


Figure 1. ALTITUDE-AD Screening Visits and Related Procedures. After a qualifying pTau217 blood test (for participants in North America only, n=429), amyloid pathology was confirmed by a visual read of an amyloid PET scan or by amyloid levels in CSF.
Abbreviations: Con, concomitant; CSF, cerebrospinal fluid; ECG, echocardiogram; MMSE, mini mental state examination; MRI, magnetic resonance imaging; PET, positron emission tomography; pg/mL, picograms per milliliter

Results

ALTITUDE-AD Study: Preliminary Centiloid Distribution (Global Cortical Average) at Baseline



n	Mean	Standard Deviation	Median	Minimum	Maximum	Lower Quartile	Upper Quartile
474	76.65	48.47	78.38	-20.37	220.32	39.29	113.35

Reasons for Low Centiloid Values in Participants with Positive Visual Read in ALTITUDE-AD

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Reason for discrepancy		Number of participants (% of all participants)	Mean CL value
Atrophy		5 (0.9%)	3.6
Cerebellar artifact		13 (2.4%)	-0.5
Only 1 ROI positive		59 (10.9%)	-0.1
	Frontal ROI	20 (3.7%)	-1.1
	Parietal ROI	10 (1.8%)	1.6
	Occipital ROI	29 (5.4%)	-0.1
Partial volume effect		4 (0.7%)	2.5
Visual positive		12 (2.2%)	17.7

Abbreviations: ROI, region of interest

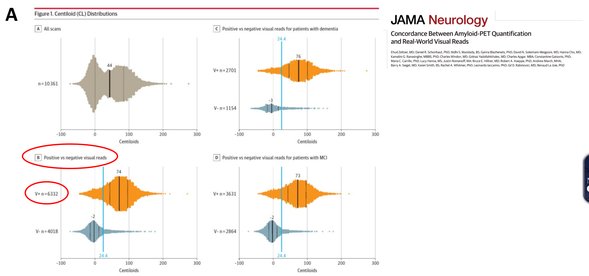
Figure 2. Centiloid values at baseline in ALTITUDE–AD. In ALTITUDE-AD, preliminary baseline CL values ranged from -20.37 to 220.32. Of 542 people enrolled in ALTITUDE-AD, 93 (17.2%) had CL values <24. The reasons for a positive visual read with a low CL value were assessed. Graphs show (A) a histogram of global cortical average distribution with a bin width of 20 and (B) a violin plot of global cortical average distribution at baseline in ALTITUDE-AD. (C) Potential reasons for a positive visual read in participants with low CL value in ALTITUDE-AD.

RESEARCH HIGHLIGHTS

- **Discrepancies between visual reads of amyloid PET scans and positivity as assessed by an amyloid cut-off have been demonstrated in clinical trials and could be expected to occur in clinical practice.**
- **The actual range of CL values for individuals with MCI or mild dementia with visually positive amyloid scans is wider than 0 to 100. The preliminary baseline CL values from the ALTITUDE-AD study are consistent with the published literature.**
- **The most common reason for a positive visual read with a CL value under 24 in ALTITUDE-AD was having a single ROI positive on the PET scan, but other reasons did occur.**
- **For the 542 people enrolled in ALTITUDE-AD, 17.2% of participants had CL values under 24; however, 13.1% had one or more ROI that was visually positive, and only 4.1% had other reasons for low CL values.**

Results

Concordance between amyloid-PET quantification and real-world visual reads



Variability in calculated CL values based on published equations for an SUVr value of 1.15 for florbetapir

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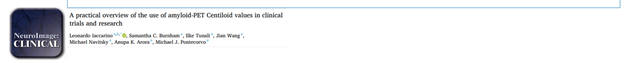
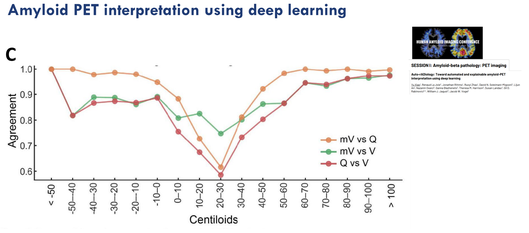
Box 1: Example ^{18}F-florbetapir Centiloid transformation formulas.

Source	Florbetapir formula	Centiloid for SUVr 1.15
Avid/Lilly processing (Navitsky et al., 2018)	183.07 × SUVr–177.26	33.3
Lecanemab phase III (van Dyck et al., 2023)	203.68 × SUVr–207.15	27.1
Aducanumab phase III (Budd Haeberlein et al., 2022)[a]	230.47 × SUVr–233.33	31.7
Gantenerumab OLE SR/MR (Klein et al., 2019)	184.12 × SUVr–233.72	–22
Elenbecestat phase III (Roberts et al., 2021)	205.72 × SUVr–209.63	26.9
CapAIBL (Bourgeat et al., 2018)[b]	174.52 × SUVr–187.26	13.4
ADNI cross-sectional (Royse et al., 2021)	188.22 × SUVr – 189.16	27.3
rPOP IDEAS (Iaccarino et al., 2022)	189.9 × SUVr–211.1	7.3
ADNI PET only (Landau et al., 2023)	208.48 × SUVr–219.41	20.3



Amyloid PET interpretation using deep learning



Discordance between amyloid PET visual read and quantitation

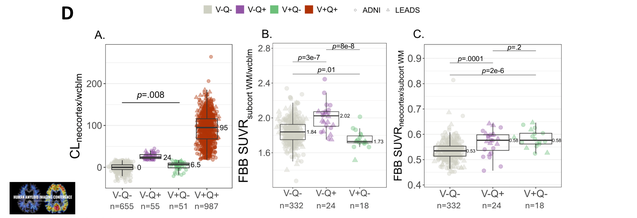


Figure 3. Amyloid PET Centiloid values in AD clinical studies. (A) Variability in CL distribution in Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study.[2] (B) Calculated CL values in clinical trials for an SUVr value of 1.15 for florbetapir. Applying the same SUVr value into published formulas yields wide range of CL values (from -22 to 33.3 CL).[3] (C) Change in agreement between test groups across CL windows in IDEAS study. Discordance is observed between quantitative (Q) and visual read (V) data.[4] (D) Amyloid tracer uptake across V/Q classifications in Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Longitudinal Early-Onset Alzheimer's Disease Study (LEADS).[5]

References

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