pTau181 plasma biomarker performance as an inclusion criterion in the RETHINK-ALZ and REFOCUS-ALZ trials in mild-to-moderate Alzheimer's disease

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BACKGROUND

Alzheimer's disease (AD) biomarkers have enabled more accurate, timely diagnoses and improved staging of disease, supporting clinical trials as inclusion criteria and secondary endpoints. While cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers are commonly used to demonstrate AD neuropathology, these biomarkers are invasive and have limited availability and scalability. By contrast, blood-based biomarkers are non-invasive, scalable, and are increasingly used both for diagnosis and entry into clinical trials. Advances in ultrasensitive detection techniques for blood biomarkers have facilitated the development of assays to detect and quantify AD-specific phosphorylated Tau proteins, including Tau phosphorylated at threonine 181 (pTau181).[1,2] We have established superior analytical and clinical performance of a new research use only (RUO) plasma pTau181 single molecule array (SIMOA) assay on a well-characterized clinically diagnosed AD cohort.[3,4] We evaluated the clinical performance of this RUO pTau181 assay to qualify mild-to-moderate AD patients in the RETHINK-ALZ and REFOCUS-ALZ clinical trials.

OBJECTIVE

To evaluate the clinical performance of a new plasma pTau181 assay to confirm AD pathology as an entry criterion for two large Phase 3 clinical trials.

METHODS

The University of British Columbia (UBC) biobank plasma samples from clinically diagnosed AD patients were used to establish clinical and analytical validity of the pTau181 plasma assay per CLSI guidelines.3,4 We assessed the analytical measurement interval, clinical reportable range, linearity, intra-laboratory precision, specimen stability, interference, and clinical performance. RETHINK-ALZ and REFOCUS-ALZ subject plasma samples, along with clinical diagnosis, MMSE and PET data were also used to evaluate performance of the assay and the pTau181 biomarker.

RETHINK-ALZ will randomize 750 subjects (1:1) to placebo or simufilam 100 mg and REFOCUS-ALZ will randomize 1083 subjects (1:1:1) to placebo or simufilam 50 or 100 mg. Subjects are MMSE ≥ 16 and ≤ 27, age 50-87 in both studies.

RESULTS

Table 1: Analytical and clinical performance of plasma pTau181 SIMOA (RUO)

Performance Characteristics:
Analytical Measurement Interval: 6.17 to 60 ng/L
Clinical Reportable Range: 6.17 to 300 ng/L
LoB: 5.0 ng/L; LoD: 6.14 ng/L; 20% LoQ: 22.5 ng/L
Linearity: assay is linear to 60 ng/L
Hook effect: TBD
Repeatability: Within-laboratory precision above the LoQ ≤ 20% CV
Reproducibility: TBD
Interference: No interference detected to the maximum concentrations tested for the following materials: Bilirubin, conjugated and unconjugated; biotin; hemoglobin; lipid
Cut-off: Cut-off established as 43.7 ng/L, with an AUC of 0.89, sensitivity of 88.1%, specificity of 82.0%, and accuracy of 83.2%.
Clinical Performance: On a total of 22 autopsy confirmed specimens, sensitivity for AD of 92.9% and specificity for AD of 82.5%

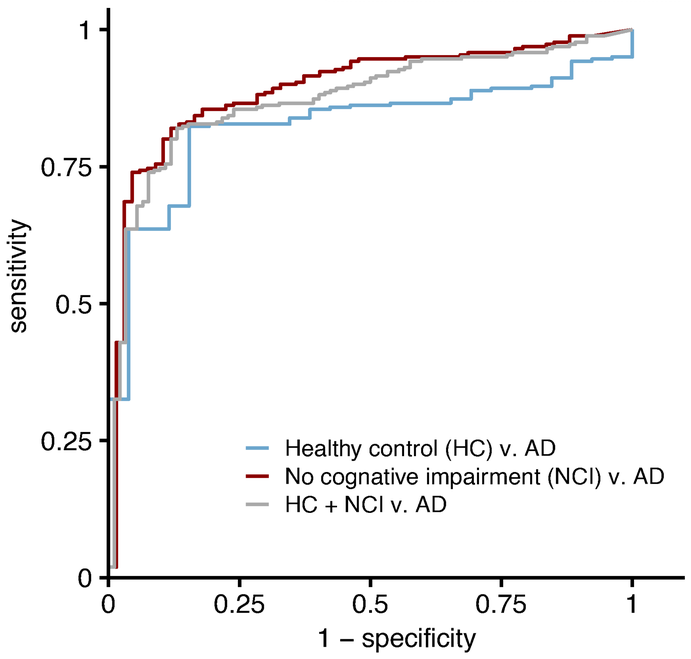

Figure 1: Receiver operated curve (ROC) for healthy control (HC) and no-cognitive impairment (NCI) cohorts compared to clinical diagnosis AD patient plasma samples. The area under the curve (AUC) for each curve is listed and ranges between 0.83 and 0.89. N = 25 healthy control samples, N = 66 NCI samples, and N = 262 clinically diagnosed AD samples.

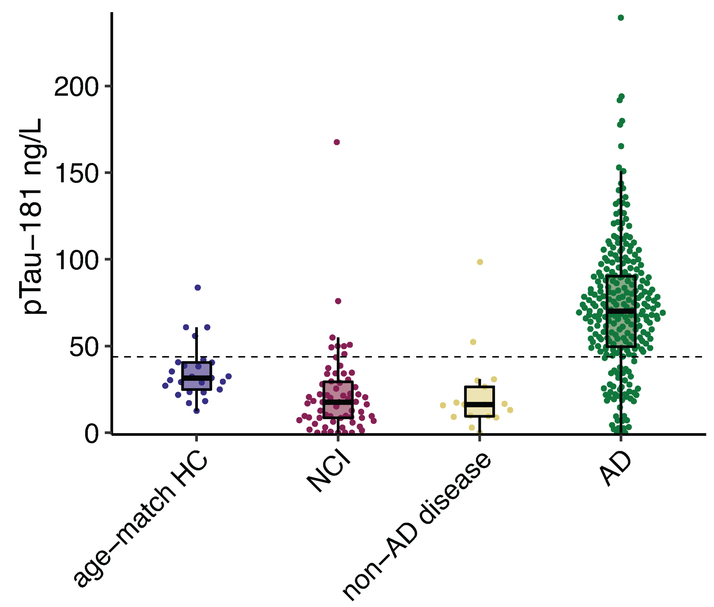

Figure 2: Clinical performance of pTau181 SIMOA. Dots represent individual data points. The dotted-line shows the Youden's threshold of 43.7 ng/L determined by the highest specificity and sensitivity from the ROC curves (figure 1).

Table 2: Autopsy confirmed AD diagnosis compared to plasma pTau181 concentration based on the clinical decision point of 30 ng/L.

N = 22 (BCNI biobank)	pTau181 predicted non-AD	pTau181 Predicted AD
Autopsy confirmed non-AD	7	1
Autopsy confirmed AD	1	13

The cut-point (≥ 30 ng/L) had 100% sensitivity and 88% specificity for AD diagnosis in 22 autopsy-confirmed samples

CONCLUSION

This pTau181 plasma assay provides a robust and accurate biomarker approach for independent determination of AD, with an AUC of 0.92 in a validation study. This pTau181 assay appears to be performing well as a screening method for inclusion of mild-to-moderate AD subjects in two large Phase 3 clinical trials. This robust plasma biomarker measured by our RUO assay has great potential both as a diagnostic tool and to streamline clinical trials in AD.

Table 3: RETHINK-ALZ & REFOCUS-ALZ trial screening data using pTau181 plasma conc. as of October 2022 enrollment. Based on a cut-point of 30 ng/L.

Phase 3 trial	Sample total (n)	Below cut-point	Above cut-point	% passing
RETHINK-ALZ	556	92	464	83.5%
REFOCUS-ALZ	637	78	547	85.9%

pTau181 concentrations were elevated (> 50 ng/L) in all subjects with prior Tau or amyloid-beta PET confirmation of pathology (8 of 8) enrolled in these studies, suggesting an excellent correlation of plasma pTau181 with AD neuropathology.

REFERENCES

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