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【Overview presentation】

15th Clinical Trials on Alzheimer's Disease (CTAD)

Three group classification of participants based on fully automated plasma β-amyloid measurements to achieve high positive and negative predictive values

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Overview presentation	**Backgrounds** Blood-based biomarkers that can predict brain β-amyloid (Aβ) status are in high demand not only for the recruitment of participants into Alzheimer's disease (AD) clinical trials but also for ensuring that appropriate AD patients can receive disease-modifying therapies in the future as they become available. Recently, we reported that plasma $Aβ_{1-42}$ (Aβ42) to $Aβ_{1-40}$ (Aβ40) ratio measured by our fully automated immunoassay platform (HISCL™ series) predicted brain Aβ status defined by amyloid positron emission tomography (PET) as assessed by Centiloids (CL). Area under the curves of 0.932 and 0.922 were obtained in two clinical studies (discovery and validation studies). In the previous analysis, we determined a cut-off value of 0.102 using the Youden index in the discovery study. Using this cut-off value, we achieved high negative predictive value (NPV) of 97.6% and 94.0%, and moderate positive predictive value (PPV) of 80.6% and 79.6% in the discovery and validation studies, respectively. Considering use in the screening of participants for clinical trials, higher PPV would be preferable. In this study, we combined discovery and validation studies to one dataset, and classified participants into three groups (positive, intermediate, and negative Aβ groups) depending on their plasma Aβ42/Aβ40 ratio, in order to improve PPV of our plasma Aβ assay.

	Objectives To evaluate the performance of our plasma Aβ42/Aβ40 ratio in predicting amyloid PET status upon classifying participants into three groups. **Methods** Plasma Aβ40 and Aβ42 were measured using a fully automated immunoassay platform in a set of plasma samples sourced from participants in the screening phase of the elenbecestat Phase 3 program. Participants were clinically diagnosed with mild cognitive impairment and mild dementia. In this analysis, we combined datasets from previously reported discovery and validation studies to make one dataset that included 172 amyloid PET positive participants and 199 negative participants. Brain Aβ status was determined by amyloid PET scans as assessed by the Centiloid method (cut-off value defined previously as 32.21 CL). Here, we determined the cut-off value of our plasma Aβ42/Aβ40 ratios that would result in a PPV of 90% or more. We then utilized this cut-off value and the prior reported cut-off value as the thresholds to divide participants into positive, intermediate, and negative Aβ groups. **Results** A cut-off value was determined based on the criteria to achieve a PPV of at least 90%, and we used this cut-off value and the prior reported cut-off value to classify participants into positive, intermediate, and negative Aβ groups. In this analysis, PPV in positive Aβ group and NPV in the negative Aβ group were both more than 90%. **Conclusion** Our Aβ assay achieved PPV and NPV ≥ 90% by classifying participants into the three groups. Majority of participants were classified as positive or negative Aβ groups by plasma Aβ42/Aβ40 ratio, indicating that our assay may contribute to reduce amyloid PET scan or CSF Aβ testing, which could be helpful in applications such as the recruitment step of clinical trials.
Session	Poster, Clinical Trials: Biomarkers including plasma（LP84A）