Model-Informed Biomarker Qualification: Alzheimer Disease (AD) and Parkinson Disease (PD) Imaging Biomarkers

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Objectives:

Disease-modifying/preventative treatments for AD and PD are expected to be most effective at early disease stages. Early stage selection of the right subjects is challenging due to pathophysiological uncertainty or patient heterogeneity. CAMD and CPP are pursuing regulatory qualification of prognostic enrichment biomarkers that select subjects most likely to exhibit clinically relevant disease progression. Here, we present pharmacometric analyses examining the enrichment utility of intracranial-adjusted-hippocampal volume (ICV-HV) for pre-dementia-AD, and dopamine transporter (DAT) neuroimaging for early-stage-PD trials, respectively.

Methods:

C-Path assembled subject-level, longitudinal, CDISC-standardized datasets. For early-stage-PD, data from 672 subjects came from the PPMI and PRECEPT studies. For pre-dementia-AD, data from ~800 subjects came from the ADNI-1, ADNI-2 and InDDeX studies. Mixed-effects model-based meta-analyses were chosen to describe AD and PD progression in Clinical Dementia Rating–Sum of Boxes (CDR-SB) and motor scores (UPDRS/MDS-UPDRS), respectively. Additional covariates based on biological plausibility/knowledge were included for each disease imaging approach. Utility of biomarker enrichment was determined by various model outputs including statistical and clinical significance of the estimated covariate effect, reduction in trial size by Monte Carlo simulations.

Results:

Subjects with and without DAT deficit have an average monthly progression in motor scores of 0.18 (90%CI: 0.14, 0.21) and 0.05 (90%CI: -0.04, 0.13) point/month, respectively. To detect a drug effect of 50% reduction in progression rate with 80% probability at α=0.05, a DAT-based enrichment strategy allows ~24% reduction of trial size (Figure). Preliminary ICV-HV results will be presented in the poster.

Conclusions:

Model-informed analyses of potential enrichment biomarkers can streamline the pathway towards regulatory qualification, and improve clinical trial design efficiency.