Model-Informed Biomarker Qualification: Alzheimer and Parkinson Disease Imaging Biomarkers

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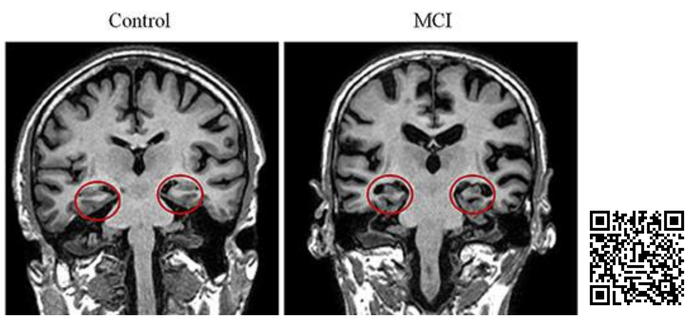
Background

- Disease-modifying/preventative treatments for Alzheimer disease (AD) and Parkinson disease (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.
- Here, we present pharmacometric analyses examining the enrichment utility of intracranial-adjusted-hippocampal volume (ICV-HV*) for mild cognitive impairment (MCI), and dopamine transporter (DAT**) neuroimaging for early stage PD trials, respectively (**Figure 1**).

(A) Hippocampal Volume (ICV-HV) Neuroimaging



(B) Dopamine Transporter (DAT) Neuroimaging

Figure 1. Candidate enrichment biomarkers in (A) MCI, and (B) PD.
ICV-HV is determined by magnetic resonance imaging (MRI); DAT deficit is determined by single-photon emission computed tomography (SPECT).

Objectives

Obtain regulatory qualification of enrichment biomarkers that select subjects most likely to exhibit clinically relevant disease progression.

* Results for ICV-HV in MCI are preliminary and subject to modifications.

** Results for DAT in early stage PD have been published at **Ref. 1**.

References:

(1) Conrado DJ *et al*. Clin Transl Sci. (2017). [Epub ahead of print]
(2) The Parkinson Progression Marker Initiative (PPMI). Prog. Neurobiol. 95, 629–635 (2011).
(2) Parkinson Study Group PRECEPT Investigators. Neurology 69, 1480–1490 (2007).
(3) Conrado DJ, Denney WS, Chen D, Ito K. J Pharmacokinet Pharmacodyn. 41(6):581-98 (2014).

Methods

- **Data**: C-Path assembled subject-level, longitudinal, CDISC-standardized datasets.
  - *Early stage PD*: data came from the Parkinson's Disease Progression Markers Initiative [PPMI (**Ref. 2**)] observational study and from the Parkinson Research Examination of CEP-1347 trial [PRECEPT (**Ref. 3**)].
  - *MCI*: data from 1093 subjects came from the Alzheimer's Disease Neuroimaging Initiative-1 (ADNI-1), ADNI-2 observational studies and the Investigation into Delay to Diagnosis of Alzheimer's disease with Exelon (InDDEx) clinical trial.
- **Endpoint**:
  - *Early stage PD*: Harmonized Part III score of the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS, or motor scores) (**Ref. 1**).
  - *MCI*: Clinical Dementia Rating–Sum of Boxes (CDR-SB).
- **Model**:
  - *Early stage PD*: Mixed-effects model to estimate and compare the endpoint rate of progression between subjects with a scan without evidence of DAT deficit (SWEDD) and those with DAT deficit (**Ref. 1**).
  - *MCI*: Mixed-effects beta regression model to estimate and compare the endpoint rate of progression between subjects with 'high' and 'low' ICV-HV values based on various cut-offs.
- **Enrichment**: Utility of biomarker enrichment was determined by various model outputs including statistical and clinical significance of the estimated covariate effect, and reduction in trial size by Monte Carlo simulations (**Ref. 1**).

Results

- The selected base models to describe the progression of early stage PD and MCI are described in **Table 1**.
- Predictors of rate of progression in early stage PD and MCI are presented in **Table 2**.

Table 1. Selected base models

Disease	Model	Structure
Early stage PD	Linear*[1]	$\frac{dScore_i}{dt} = r_i$
MCI	Generalized logistic (Richards)*[2]	$\frac{dScore_i}{dt} = r_i \times Score_i \times \left[1 - \left(\frac{Score_i}{max(Score_i)}\right)^{\beta}\right]$

*[1] Details are provided at **Ref. 1**.
*[2] Details on the Richards model can be found at **Ref. 4**.

Table 2. Predictors of rate of progression

Disease	Rate Predictors
Early stage PD	DAT deficit status: yes or no
MCI	ICV-HV, age, gender, MMSE, *APOE* ε4 genotype

Results (cont.)

- *Early stage PD*:
  - Subjects with and without DAT deficit have an average monthly progression in scores of 0.18 (90%CI: 0.14, 0.21) and 0.05 (90%CI: -0.04, 0.13) point/month, respectively (**Figure 2A; Ref. 1**).
  - Under reasonable assumptions, a DAT-based enrichment strategy allowed a ~24% reduction of trial size to detect a drug effect of 50% reduction in progression rate with 80% probability at α=0.05 (**Figure 2B; Ref. 1**).

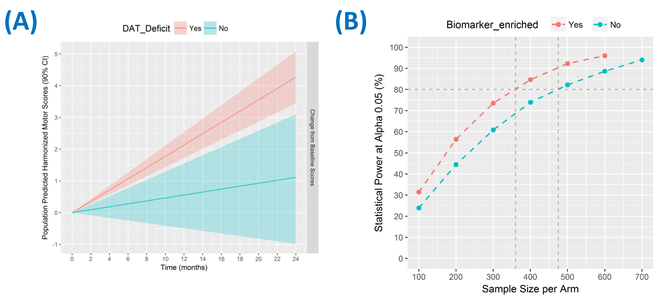


Figure 2. DAT imaging enrichment in early stage PD
(A) Population predicted harmonized motor scores.
(B) Statistical power *vs*. sample size. Simulated placebo-controlled DAT imaging enriched and non-enriched clinical trials with a drug effect of 50% reduction in the progression rate (N = 2,000 simulations). Non-enriched clinical trials include 15% of DAT non-deficient subjects, while enriched include only DAT deficient subjects.

- *MCI*:
  - ICV-HV values (cm^3) related to the rate of CDR-SB progression via a linear function, and the estimated effect was -0.884 (95% CI: -1.30, -0.47). This means that for each 1 cm^3 decrease in the ICV-HV, the progression rate increases by ~88% (**Figure 3**).
  - ICV-HV enrichment (inclusion of subjects with ICV-HV < 5.25 cm^3) allowed a sample size per arm of ~200 (*vs*. ~500 without enrichment) in a 2-year parallel arm study design to detect a drug effect of 50% reduction in rate with 80% probability at α=0.05 .

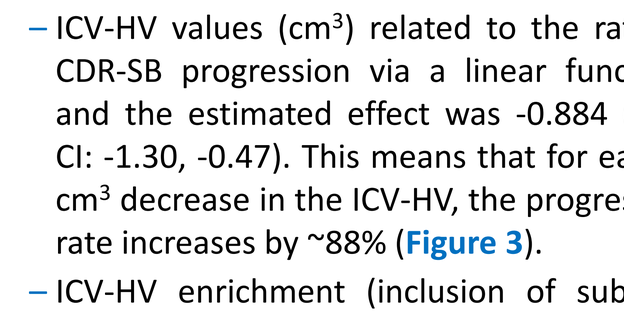


Figure 3. Visual predictive check stratified by ICV-HV.
5.293 cm^3 is the mean ICV-HV value of the dataset. Dropout has been included. One thousand simulations were performed. Open circles are observed scores; solid lines are the 10th, 50th and 90th percentiles of the observed scores; shaded areas are the 95% inter-percentile ranges of the simulations.

Conclusions

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

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