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

Daniela J Conrado1, Jackson Burton2, Timothy Nicholas3, Brian Corrigan2, Kuenhi Tsai2, Danny Chen2, Vikram Sinha2, Sreeraj Macha2, Julie Stone2, Brian Willis4, Ian Watson4, Massimo Bani2, Pierandrea Muglia2, Wenping Wang1, Volker D Kern1, Stephen Arneric1, Diane Stephenson1, Klaus Romero1 on behalf of the Coalition Against Major Diseases (CAMD) and Critical Path for Parkinson’s (CPP)

1Critical Path Institute (C-Path), Tucson, AZ; 2Pfizer, Groton, CT; 3Merck, North Wales, PA; 4Eli Lilly, Indianapolis, IN; 5UCB, Brussels, Belgium; 6Novartis, East Hanover, NJ

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).

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-1637 trial (PRECEPT [Ref. 3]).
  - MCI: data from 1093 subjects came from the Alzheimer’s Disease Neuroimaging Initiative-1 (ADNI-I), ADNI-2 observational studies and the Investigation into Delay to Diagnosis of Alzheimer’s disease with Elenon (InDEx) 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.

Results (cont.)

- **ICV-HV:** values (cm²) 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 cm² decrease in the ICV-HV, the progression rate increases by ~88% (Figure 3).
- **ICV-HV** inclusion (incidence of subjects with ICV-HV < 5.25 cm²) allowed a sample size per arm of ~250 (vs. ~500 without enrichment) in a 2-year parallel study to detect a drug effect of 50% reduction in rate with 80% probability at α=0.05 (N=1600 Monte Carlo simulations).

Conclusions

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

References


* 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.

Table 1. Selected base models

<table>
<thead>
<tr>
<th>Disease</th>
<th>Model</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Stage PD</td>
<td>Linear**</td>
<td>Score pd = f1</td>
</tr>
<tr>
<td>MCI</td>
<td>Generalized logistic (Richards)**</td>
<td>Score r = n1 x Scored x \left(1 - \frac{Score r}{\text{max}}\right)^3</td>
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Table 2. Predictors of rate of progression

<table>
<thead>
<tr>
<th>Disease</th>
<th>Odds reduction</th>
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<tbody>
<tr>
<td>Early stage PD</td>
<td>DAT deficit status: yes or no</td>
</tr>
<tr>
<td>MCI</td>
<td>ICV-HV, age, gender, MMSE, APOE e4 genotype</td>
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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).

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