Characterizing Disease Progression for Parkinson’s Disease to implement efficient trial designs

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Objectives: A quantitative assessment of the patient characteristics and enrichment of clinical trials evaluating disease-modifying therapies for neurodegenerative disorders are critical to improve trial efficiency. CPP is pursuing regulatory qualification of prognostic enrichment biomarkers and characterize disease progression in early stage Parkinson’s Disease (PD) to enable selection of the most appropriate patient population. The objective of this work is to develop a disease progression model and identify relevant patient characteristics to inform trial design for Phase 2/3 trials that evaluate therapeutic candidates for early stage PD.

Methods: C-Path assembled subject-level longitudinal data from 410 subjects with early-stage PD and dopamine transporter deficit from the PPMI study. Beta regression analyses, an extension of the generalized linear model, was used to characterize the time course of MDS-UPDRS Part II plus III due to its ability to evaluate bounded scores. Covariates included demographic factors, genetic status and background medications. Monte Carlo simulations were performed to compare the statistical power by trial size with relevant covariates.

Results: A series of models were tested including linear, exponential and logistic models. A logistic (non-linear) model was chosen based on goodness-of-fit plots and Bayesian information Criteria (Figure). The progression rate increased with time until the inflection point and the maximum progression rate was estimated to be ~0.25 points/month. Preliminary covariate analysis indicated that age had a significant effect on baseline, and gender and GBA mutation had a significant effect on the slope.

Figure1: VPC of the disease progression in early stage PD patients

Conclusions: A logistic model described the disease progression in early stage PD. The insights from this model represent valuable information to inform the entry criteria and enrichment strategies for long-term trials.