The Critical Path for Parkinson’s Consortium: Understanding Motor Disease Progression through Quantitative Medicine

**Objective**
- The goal is to develop and obtain regulatory endorsement of a computation tool for PD clinical trial enrolment.
- This tool will be based on a PD progression model and will inform entry criteria, enrichment strategies, and stratification approaches.

**Background**
The Critical Path for Parkinson’s (CPP) consortium (Figure 1) is based on the value of sharing patient-level data from cohorts and clinical trials in Parkinson disease (PD), and transforming those data into generalizable and applicable knowledge for PD therapeutics (Figure 2).

**Methods**

- **Studies**: Selected studies herein are the Parkinson’s Progression Markers Initiative (PPMI), the Parkinson Research Examination of CEP-1347 Trail (PRECEPT), Oxford PD Centre (OPDC) Discovery Cohort; the Cambridgeshire Parkinson’s Incident from GP to Neurologist cohort (CamPaIGN); Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation—PD (ICICLE-PD) and Tracking Parkinson’s (the ProBaND study) (Figure 3).
- **Data integration**: The PD Clinical Data Interchange Standards Consortium (CDISC) standards will enable the integration of the studies in a unique database.
- **Model**: The time course of the harmonized parts II and III of the Unified Parkinson’s Disease Rating Scale (UPDRS) and MDS-UPDRS will be described using a non-linear mixed-effects regression.
- **Covariates**: Subjects’ demographic, genetic, biomarker, and clinical characteristics to be tested as predictors of disease severity at baseline or intrinsic rate of disease progression are presented on Figure 4.

**Results**
- Up to this moment, patient-level data of PPMI, PRECEPT, and CamPaIGN have been integrated using PD CDISC standard. Integration of ICICLE-PD, OPDC, and Tracking Parkinson’s study will follow.
- The CPP integrated global database will result in a total of >6000 subjects into a unified database. Such database will expand the understanding of PD progression and allow a comprehensive investigation of subjects characteristics that predict disease severity and rate of disease progression.
- An analysis of integrated subset — PRECEPT (n=191) and PPMI (n=481) — demonstrated that subjects defined as SWEDD (scans without evidence of dopamine transporter deficiency) have an average linear monthly progression in the harmonized motor scores that is 0.05 (90% CI: -0.04, 0.13) point/month or 0.13 point/month lower than that in subjects with dopamine transporter deficit (0.18 point/month; 90% CI: 0.14, 0.21) (Figure 5). The work herein will provide a comprehensive evaluation of the findings in the presence of additional studies and covariates, accounting for potential non-linearity in disease progression.

**References**