Global Regulatory Agencies Support the Use of Dopamine Transporter Neuroimaging for Subject Selection in Clinical Trials Targeting Early Stage Parkinson's Disease

on behalf of the Critical Path for Parkinson's (CPP) Consortium

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Objective

- The Critical Path for Parkinson's Consortium's (CPP) overarching goal is to advance drug development tools for use in Parkinson's disease (PD) clinical trials.
- CPP's PD Imaging Biomarker Team aims to achieve regulatory endorsement for the application of reduced dopamine transporter (DAT) binding as a biomarker for PD clinical trial enrichment.

Background

- As therapeutic trials aim at earlier stages of PD, appropriate patient selection based purely on clinical criteria poses significant challenges.
- Use of biomarkers can be effective in enabling improved accuracy in selecting appropriate subjects for enrollment in clinical trials, and increase the likelihood of approval (**Figure 1**).

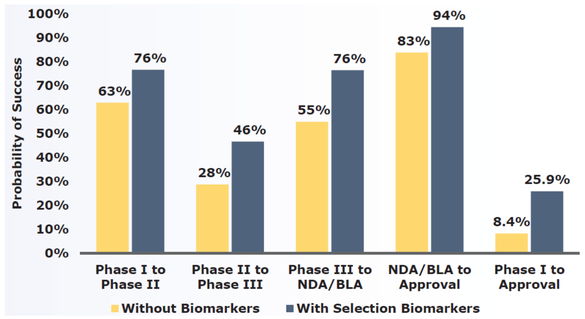

Figure 1. Probability of success in clinical development with/without selection biomarkers (adapted from **Ref. 1**).

Methods

- **Regulatory history:** A team of pharmaceutical companies, academic key opinion leaders, government agencies and advocacy organizations formally submitted to the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) documentation supporting the use of DAT SPECT imaging in PD. Regulatory documents included a comprehensive literature review, a proposed statistical analysis plan of both observational and clinical trial data, and an assessment of biomarker reproducibility and reliability.
- **Target population**: Subjects with early motor stage PD defined as (a) baseline Hoehn and Yahr stage I or II, (b) two of the following signs: resting tremor, bradykinesia, rigidity; or (c) either asymmetric resting tremor or asymmetric bradykinesia.
- **Data**: Subject-level data from the Parkinson's Disease Progression Markers Initiative [PPMI (**Ref. 2**)] study and from the Parkinson Research Examination of CEP-1347 trial [PRECEPT (**Ref. 3**), placebo data only] were mapped to CDISC (Clinical Data Interchange Standards Consortium) PD data standards and integrated for analyses. The analysis dataset included a total of 672 subjects diagnosed with early stage PD and a total of 4521 observations (**Table 1**).
- **Biomarker**: Visual reads of DAT binding in putamen using of FP-CIT (PPMI) and β-CIT (PRECEPT).
- **Clinical Endpoint**: Harmonized MDS-UPDRS (Movement Disorder Society - Unified Parkinson's Disease Rating Scale) (PPMI) and UPDRS (PRECEPT) Part III according to Goetz et al. (**Ref. 4**), referred to as 'harmonized motor scores'.
- **Statistical analysis**: Longitudinal linear mixed-effects regression to compare the rate of progression on the harmonized motor scores between subjects without evidence of DAT deficit (SWEDD) and those with DAT deficit. Utility of biomarker enrichment was determined by various model outputs including statistical and clinical significance of the estimated biomarker status effect on the rate of progression, and reduction in trial size by Monte Carlo simulations.

Table 1. Baseline subject characteristics by study

Baseline	PPMI	PRECEPT
Sample size	481	191
Sex (%)	Female (35), Male (65)	Female (34), Male (66)
Age in year, mean (range)	61 (33, 84)	59 (31, 84)
DAT deficit (%)	Yes (87), No (13)	Yes (86), No (14)
Harmonized motor scores, mean (range)	20 (2, 51)	21 (5.3, 52)

Results

- DAT deficit in PD subjects is associated with statistically and clinically significant larger worsening of the harmonized motor scores when compared to that of SWEDD subjects (**Figure 2**).
  - Subjects with DAT deficit have an average monthly progression in the harmonized motor scores that is 0.18 point/month (90% CI: 0.14, 0.21) *versus* 0.05 (90% CI: -0.04, 0.13) point/month in SWEDD subjects.
  - Subjects with DAT deficit have an average of 3.16 points higher (worse) change from baseline score at 24 months than SWEDDs, which is greater than the minimal clinically important difference of 3 points (**Ref. 5**).

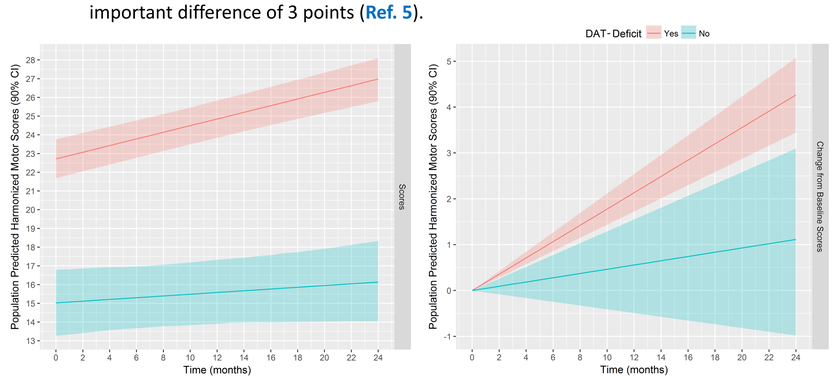

Figure 2. Population predicted harmonized motor scores. Shaded area is the 90% confidence interval (CI). Predictions are for a PRECEPT-like study with average age of 60 years old.

- To detect a disease-modifying drug effect of 50% reduction in the progression rate with an 80% probability (type II error or β=0.20) at α=0.05, a DAT-based enrichment strategy was estimated to allow approximately 24% reduction of trial size (**Figure 3**).

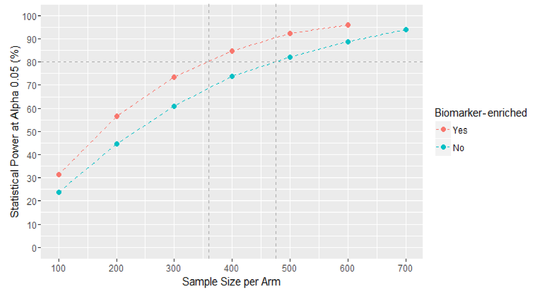

Figure 3. Statistical power by sample size for placebo-controlled DAT imaging enriched and non-enriched clinical trials with a disease modifying drug effect of 50% reduction in the progression rate

Results (continued)

- The FDA (March 2015) and EMA (October 2016) have issued publicly-posted letters of support (**Figure 4**) to encourage collection and sharing of relevant data supporting the use of DAT imaging at baseline as an enrichment biomarker for early PD.

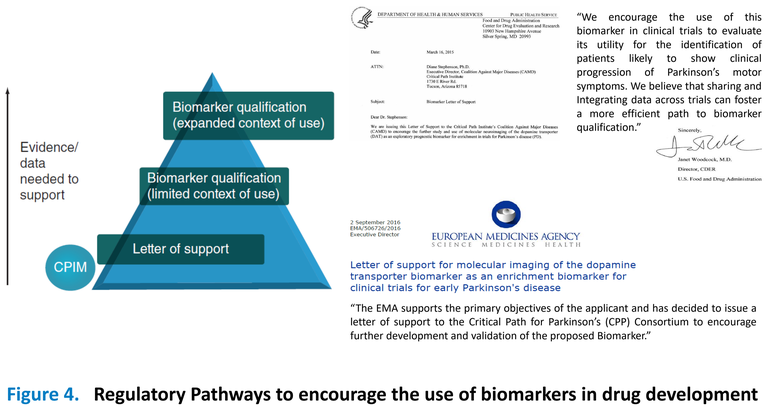

Figure 4. Regulatory Pathways to encourage the use of biomarkers in drug development (left panel adapted from **Ref. 6**) (CPIM – Critical Path Innovation Meeting)

Conclusions

- The application of DAT imaging at baseline served to identify subjects with a steeper worsening of the motor progression, allowing trial enrichment and 24% reduction of sample size.
- Exclusion of SWEDD subjects in future clinical trials targeting early motor PD subjects aims to enrich clinical trial populations with idiopathic PD patients, improve statistical power, and spare subjects who are unlikely to have PD from being exposed to novel test therapeutics.
- Publicly-posted letters of support by FDA and EMA encourage broader use of this biomarker by trial sponsors.
- Qualification of DAT imaging biomarker by regulatory agencies holds promise in improving the efficiency of clinical trials in a target population that is more likely to benefit of treatment.

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