

Global Regulatory Agencies Support Use of Dopamine Transporter Neuroimaging in Clinical Trials Targeting Early Parkinson's Disease

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- 6 – Eli Lilly
- 7 – U.S. Food and Drug Administration
- 8 – GE Healthcare
- 9 – IXICO
- 10 – Michael J. Fox Foundation
- 11 – Institute for Neurodegenerative Disorders, Molecular Neuroimaging LLC
- 12 – Merck & Co. Inc
- 13 – NIH/NINDS
- 14 – Parkinson's UK
- 15 – Pfizer
- 16 – F. Hoffmann-La Roche Ltd
- 17 – UCB Pharma
- 18 – University of Glasgow
- 19 – GSK
- 20 - Lundbeck

Methodological Question: Regulatory endorsement of imaging biomarker in Parkinson's disease clinical trials targeting early stages of the disease

Objective: A key goal of the Critical Path for Parkinson's Consortium (CPP) is to achieve regulatory endorsement for 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 target earlier stages PD, appropriate patient selection based purely on clinical criteria poses significant challenges. In the absence of a biomarker, there may

be patients enrolled not suitable for an investigational new drug trial and could potentially jeopardize the trial outcome. Use of biomarkers can enable improved accuracy in selecting appropriate subjects for enrollment in clinical trials and to decrease the enrolment number required to ascertain efficacy.

Methods: A team of pharmaceutical companies, academic key opinion leaders, government agencies and advocacy organizations formally submitted to EMA and FDA documentation supporting the use of DAT SPECT imaging in PD. Regulatory documents included a comprehensive literature review, a proposed analysis plan of both observational and clinical trial data, and an assessment of biomarker reproducibility and reliability. The research plan included longitudinal analysis of the Parkinson Research Examination of CEP-1347 Trial (PRECEPT) and the Parkinson's Progression Markers Initiative (PPMI) study to estimate the degree of enrichment achieved and impact on future trials in subjects with early motor PD.

Results: The presence of reduced striatal DAT binding based on visual reads of SPECT scans in early motor PD subjects is an independent predictor of faster decline in UPDRS Parts II and III as compared to subjects without evidence of dopamine deficiency (SWEDD) over 24 months. The FDA (March 2015) and EMA (October 2016) have issued publicly posted letters of support to encourage collection and sharing of relevant data supporting the use of DAT at baseline as an enrichment biomarker. The EMA is poised to issue in early 2018

a full Qualification Opinion for the use of DAT as an enrichment biomarker in PD trials targeting subjects with early motor symptoms.

Conclusions: 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 and biomarker qualification issued by global regulatory agencies encourage broader use of this biomarker by trial sponsors.

As Critical Path for Parkinson's is a precompetitive public private partnership that enables collaborations for which there is no bias for any single stakeholder or product, the authors report no conflicts of interest for this work.