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

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

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[1]Critical Path Institute, [2]AbbVie Inc., [3]ADM Diagnostics, LLC, [4]Biogen, [5]Served as advisor to CPP, [6]U.S. FDA , [7]GE Healthcare, [8]IXICO, [9]Michael J Fox Foundation, [10]Institute for Neurodegenerative Disorders, Molecular NeuroImaging LLC, [11]Merck & Co. Inc, [12]NIH/NINDS, [13]Parkinson's UK, [14]Pfizer, [15]UCB Pharma, [16]University of Glasgow, [17]GSK, [18]Lundbeck

Objective

- A key goal of the Critical Path for Parkinson's Consortium's (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 clinical trial enrichment for clinical trials in early motor PD.

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 enable improved accuracy in selecting appropriate subjects for enrollment in clinical trials, and to decrease the enrolment number required to ascertain efficacy (**Figure 1**).

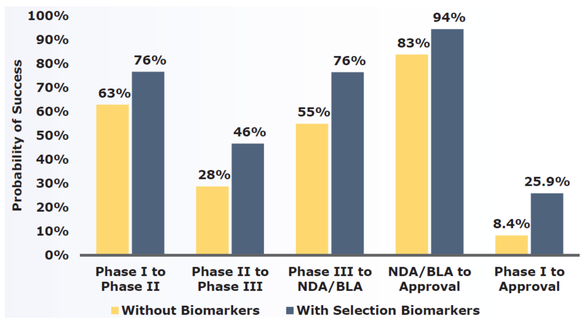


Figure 1. **Probability of success in clinical development with/without selection biomarkers (Ref. 1).**

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 for FDA 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. With EMA, documentation extended to the submission of the final model-based results.
- **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. Criteria align with PPMI.
- **Data:** Subject-level data from the Parkinson's Disease Progression Markers Initiative [PPMI (**Ref. 3**)] study and from the Parkinson Research Examination of CEP-1347 trial [PRECEPT (**Ref. 4**), 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 assessed with categorical classification of SPECT scans using either 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. 5**), referred to as 'harmonized motor scores'. Clinically important difference followed as per **Ref. 6**.
- **Statistical analysis:** Longitudinal linear mixed-effects regression to compare the rate of progression on the harmonized motor scores between subjects who had scans without evidence of dopamine deficit (SWEDD) and those with DAT deficit. See **Ref. 2** for methodology details.

Table 1. **Baseline subject characteristics in longitudinal and clinical trial studies**

Baseline	**PPMI**	**PRECEPT** (placebo)
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

- The rate of worsening in the motor scores between DAT deficient and SWEDD subjects was different both statistically and clinically (**Figure 2**).
  - Subjects with DAT deficit have an average monthly progression in the harmonized motor scores that is 0.18 (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. 6**).

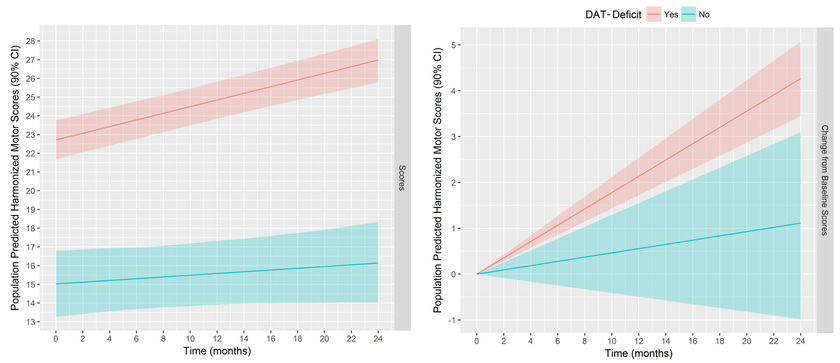


Figure 2. Population-predicted harmonized motor scores. Shaded area is the 90% confidence interval (CI). Predictions are for a randomized controlled clinical trial (similar to PRECEPT) with average baseline age of 60 years old.

- Sample size estimates: enrichment strategy using baseline DAT deficiency for subject inclusion was estimated to allow a meaningful reduction of trial size (e.g., 24% in the example showed in **Figure 3**).

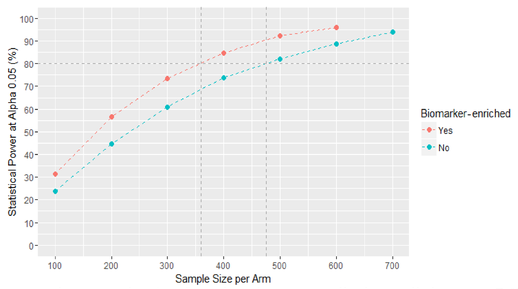
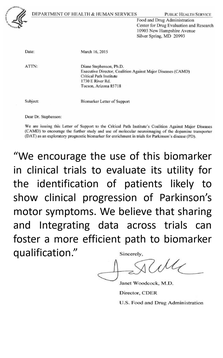


Figure 3. Statistical power by sample size for placebo-controlled parallel group DAT imaging enriched and non-enriched clinical trials with a drug effect of 50% reduction in the progression rate with an 80% probability (type II error or β=0.20) at α=0.05.

Results (continued)

- Regulatory milestones for CPP include publicly-posted letters of support by the FDA (March 2015) and EMA (October 2016) and a qualification opinion by EMA (now posted for public review and comment).



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service — Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Avenue, Silver Spring, MD 20993

Date: March 16, 2015

ATTN: Diane Stephenson, Ph.D., Executive Director, Coalition Against Major Diseases (CAMD), Critical Path Institute, 1730 E River Rd, Tucson, Arizona 85718

Subject: Biomarker Letter of Support

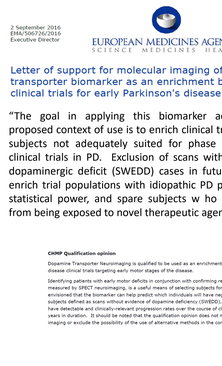
Dear Dr. Stephenson:

We are issuing this Letter of Support to the Critical Path Institute's Coalition Against Major Diseases (CAMD) to encourage the further study and use of molecular neuroimaging of the dopamine transporter (DAT) as an exploratory prognostic biomarker for enrichment in trials for Parkinson's disease (PD).

"We encourage the use of this biomarker in clinical trials to evaluate its utility for the identification of patients likely to show clinical progression of Parkinson's motor symptoms. We believe that sharing and Integrating data across trials can foster a more efficient path to biomarker qualification."

Sincerely,

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration



2 September 2016
EMA/565262/2016
Executive Director

EUROPEAN MEDICINES AGENCY
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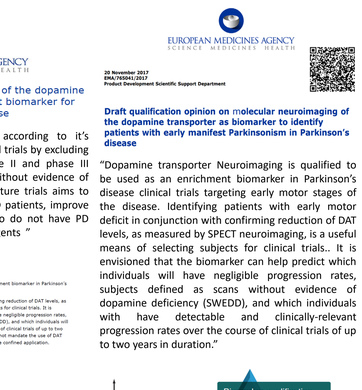
Letter of support for molecular imaging of the dopamine transporter biomarker as an enrichment biomarker for clinical trials for early Parkinson's disease

"The goal in applying this biomarker according to it's proposed context of use is to enrich clinical trials by excluding subjects not adequately suited for phase II and phase III clinical trials in PD. Exclusion of scans without evidence of dopaminergic deficit (SWEDD) cases in future trials aims to enrich trial populations with idiopathic PD patients, improve statistical power, and spare subjects w ho do not have PD from being exposed to novel therapeutic agents "

CHMP Qualification opinion

Dopamine Transporter Neuroimaging is qualified to be used as an enrichment biomarker in Parkinson's disease clinical trials targeting early motor stages of the disease.

Identifying patients with early motor deficits in conjunction with confirming reduction of DAT levels, as measured by SPECT neuroimaging, is a useful means of selecting subjects for clinical trials. It is envisioned that the biomarker can help predict which individuals will have negligible progression rates, subjects defined as scans without evidence of dopamine deficiency (SWEDD), and which individuals will have detectable and clinically-relevant progression rates over the course of clinical trials of up to two years in duration. It should be noted that the qualification opinion does not mandate the use of DAT imaging or exclude the possibility of the use of alternative methods in the confined application.



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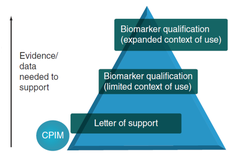
SCIENCE MEDICINES HEALTH

20 November 2017
EMA/765041/2017
Product Development Scientific Support Department

Draft qualification opinion on molecular neuroimaging of the dopamine transporter as biomarker to identify patients with early manifest Parkinsonism in Parkinson's disease

"Dopamine transporter Neuroimaging is qualified to be used as an enrichment biomarker in Parkinson's disease clinical trials targeting early motor stages of the disease. Identifying patients with early motor deficit in conjunction with confirming reduction of DAT levels, as measured by SPECT neuroimaging, is a useful means of selecting subjects for clinical trials.. It is envisioned that the biomarker can help predict which individuals will have negligible progression rates, subjects defined as scans without evidence of dopamine deficiency (SWEDD), and which individuals with have detectable and clinically-relevant progression rates over the course of clinical trials of up to two years in duration."

Figure 4. **Regulatory Pathways to encourage the use of biomarkers in drug development (Ref. 7)**
(CPIM – Critical Path Innovation Meeting, FDA)



Conclusions

- The application of DAT imaging at baseline for subject selection was found to enrich for subjects more likely to demonstrate motor progression, allowing trial enrichment and meaningful reduction of trial size.
- Exclusion of subjects identified as SWEDD in future clinical trials targeting early motor PD subjects is expected 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 an early symptomatic target population.

References

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