CRITICAL PATH FOR PARKINSON'S: REGULATORY PATH TO ENABLE TARGETING THE RIGHT PATIENTS IN CLINICAL TRIALS OF EARLY STAGES OF PARKINSON'S DISEASE

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(1) Critical Path Institute, (2) NINDS, (3) Biogen, (4) Takeda Pharmaceuticals International, Inc., (5) Pfizer, Inc., (6) Parkinson's UK, (7) FDA, (8) GE Healthcare, (9) IXICO, (10) ADM Diagnostics, LLC.,
(11) Institute for Neurodegenerative Disorders, (12) Teva Pharmaceuticals, Ltd., (13) Boehringer Ingelheim Pharmaceuticals, Inc.

Background

- One of the primary issues for Parkinson's disease (PD) drug development is identifying patients at early stages prior to advanced neurodegeneration. As therapeutic trials aim at earlier stages of PD, appropriate patient selection based purely on clinical criteria is a significant challenge.
- The Critical Path Institute's Critical Path for Parkinson's (CPP) Consortium is a multinational consortium of scientists from industry, patient advocate groups, academia, and government. CPP aims to accelerate drug development with focus on early stages of Parkinson's disease (PD), a time when there is a promise of opportunity to delay disease progression. A key goal of CPP is to qualify novel translational biomarkers and quantitative drug development platforms with regulatory agencies for use in clinical trials in order to enable efficient investigation and development of novel therapeutic candidates (Ref 1).

Objectives

- CPP's PD imaging biomarker team aims to achieve regulatory endorsement with FDA and EMA for the application of reduced dopamine transporter (DAT) density, measured by SPECT imaging, as a prognostic biomarker for PD clinical trial enrichment. The target population is aimed at in early motor stages of Parkinson's disease soon after diagnosis when therapies hold promise for delaying progression.

Methods

- CPP's PD imaging biomarker team seeks to qualify the use of DAT imaging biomarker to enrich subjects with early motor PD who are participating in clinical trials of novel PD therapies. The team is advancing this project through formal drug development tool biomarker qualification review programs as per guidance documents:

  FDA:
  http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284076.htm

  EMA:
  http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004201.pdf

- The proposed **context-of-use** is to identify early motor PD subjects for inclusion into clinical trials for PD therapeutics by applying visual assessment of DAT SPECT images to identify patients for enrollment who have reduced DAT uptake and exclude those subjects who are defined as SWEDD.
- **Literature Review:** A comprehensive literature review was conducted to identify observational and clinical studies that utilized DAT imaging per specifically defined inclusion and exclusion criteria. The rate of scans without evidence of dopamine deficit (SWEDD) cases in published reports of clinical trials to date was reviewed. Figure 1 outlines the decision tree for the decision tree.

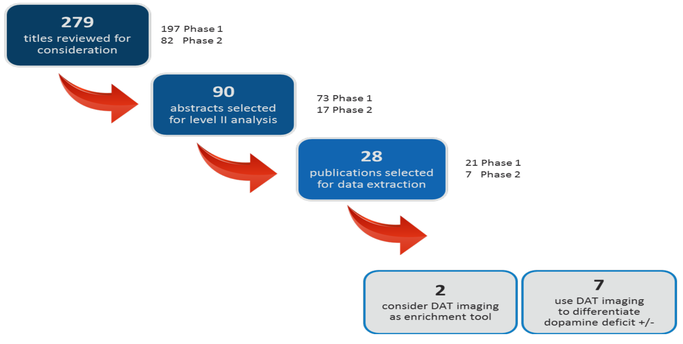


Figure 1: Comprehensive literature review carried out to support Qualification of the Biomarker

- **Data sources:** *Observational cohort:* PPMI. *Randomized Clinical Trial:* Teva generously provided to C-Path the de-identified individual patient level data from PRECEPT, a large multicenter trial of the MLK inhibitor CEP1347 (Ref 2) (Ref 3).
- **Research Plan:** The CPP team developed a comprehensive statistical analysis plan including longitudinal analysis of PRECEPT and the PPMI study to estimate the degree of enrichment and impact on future trials in subjects with early motor PD.

Results

CPP proposes that DAT deficiency assessed by SPECT imaging is a useful drug development tool; an enrichment biomarker for clinical trials targeting early motor Parkinson's Disease.

CPP PD Imaging Biomarker Qualification Team Progress to date:

- Comprehensive literature review
- Meta-analyses of supportive studies (FDA)
- SWEDD in trials to date (Figure 4)
- PRECEPT and PPMI studies, preliminary results (Figure 5)
  - Comparison of diagnostic / inclusion criteria (Figure 3)
- Proposed flow diagram for use of DAT in clinical trials
- Biomarker Reproducibility and Reliability
  - Imaging Methodology Validation Study (qualitative vs quantitative)
- FDA Letter of Support, EMA Scientific Advice (Figure 7)

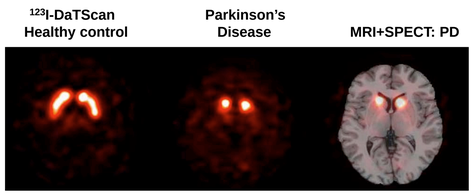
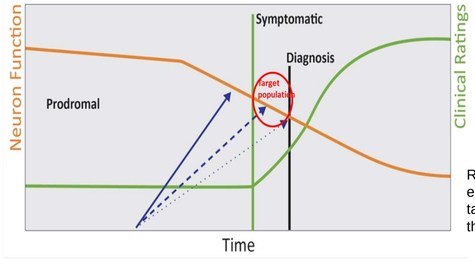


Figure 2: DAT Imaging illustrating reduced uptake in PD patients



Red circle represents early motor PD, the target population for this qualification

Figure 3: Target Population Proposed to Regulators

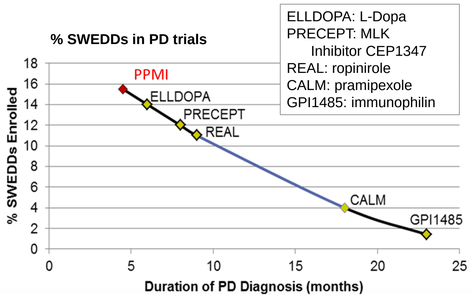


Figure 4: Rate of SWEDD in PD clinical studies

Table 1: SWEDDs in PD Trials

Study	Stage-PD	Dur DX at Baseline (mo)	% SWEDD
Elldopa-CIT	Denovo	6	21/142 (14%)
PRECEPT	Denovo	8	91/799 (12%)
REAL-PET	Denovo	9	21/186 (11%)
Calm-CIT	Start of DA Rx	18	3/82 (5%)
GPI1485	Treated Stable Responder	23	3/212 (1.4%)

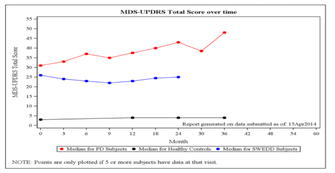
ELLDOPA: Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N. Engl. J. Med. 2004 Dec 9;351(24):2498-508.
PRECEPT: Marek K, Innis R, van Dyck C, Fussell B, Early M, Eberly S, Oakes D, Seibyl J. [123]Ibeta-CIT SPECT imaging assessment of the rate of Parkinson's disease progression. Neurology. 2001 Dec 11;57(11):2089-94.
CALM-PD: Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. Arch Neurol. 2004 Jul;61(7):1044-53.
REAL-PET: REAL-PET Study Group Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann. Neurol. 2003 Jul;54(1):93-101.

A higher incidence of SWEDDs is observed as the duration since PD diagnosis decreases

What is the Fate of SWEDD Subjects in PPMI?

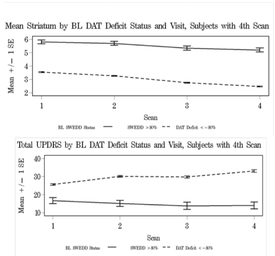
- SWEDDs do not progress / MDSUPDRS

Longitudinal course of MDS-UPDRS in healthy controls, PD, and SWEDD



- SWEDDS do not have PD biomarker profile

PRECEPT study – Follow up at 72 months

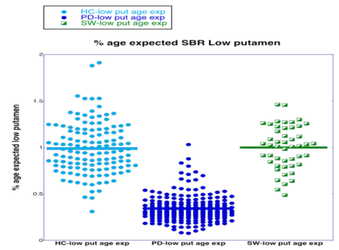


SWEDD
N=42,
% Ann Change from Baseline -7.3% (sd 11.5)

DAT Deficit
N=374,
% Change from Baseline -30.3% (sd 11.3)

Figure 5: Clinical trajectories of SWEDD cases in relevant clinical studies (Ref 2)

DAT Imaging results from PPMI Subjects at Baseline shows Reliability of the Measure



Baseline PRECEPT – % Age expected Putamen [123I] β-CIT uptake

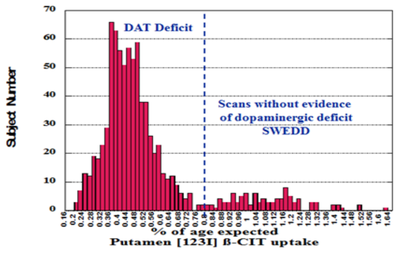
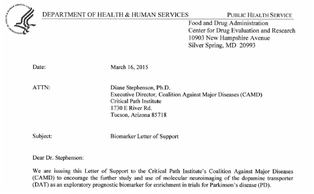


Figure 6: DAT Imaging data in studies to support regulatory qualification goals



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 it's 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

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm434382.htm

Figure 7: FDA issues Letter of Support for use of DAT imaging as prognostic biomarker in PD trials

Conclusion

- Exclusion of SWEDD subjects in future clinical trials aims to enrich clinical trial populations with subjects more likely to show relevant disease progression, improve statistical power, and spare subjects who do not have PD from being exposed to novel therapeutic agents.
- Advantages of the consortium approach to achieving regulatory qualification include: sharing of costs and risks, sharing of precompetitive data, and consensus building on standardization and harmonization.
- Regulatory science focus of the precompetitive consortium initiative CPP promises to increase the probability of success in future PD therapeutic trials aimed at tools to enable treatments in early stages of the disease.

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(2) Marek, K., Seibyl, J., Eberly, S., Oakes, D., Shoulson, I., Lang, A.E., Hyson, C., Jennings, D.. Parkinson Study Group PRECEPT Investigators. Longitudinal follow-up of SWEDD subjects in the PRECEPT Study. Neurology; 2014; 82(20) :1791-1797.
(3) Parkinson Study Group. PRECEPT Investigators. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. Neurology; 2007; 69(15): 1480-1490.

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