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

On 06 February 2016 the applicant Critical Path for Parkinson's (CPP) requested qualification of molecular neuroimaging of the dopamine transporter (DAT) as an enrichment biomarker for clinical trials for early Parkinson's disease pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 4 – 7 July 2016, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 18 – 21 July 2016, the CHMP adopted the advice to be given to the applicant.

The biomarker letter of support is issued on the basis of the qualification advice.

Background and rationale for the biomarker:

The current status of drug discovery in Parkinson's disease (PD) is at a juncture where novel candidate genes and promising therapeutic targets are being discovered. Innovative strategies are needed for success, particularly in light of the recent failures of late-stage clinical candidates. The prolonged duration of disease progression, heterogeneity of the patient population, and risk of adverse drug events in an elderly patient population, when combined with the expensive and lengthy drug development process, contribute to the challenges of advancing new therapies for PD. It is acknowledged that novel disease modifying therapies will be efficacious only if one can initiate treatment early in the course of disease. To date, significant challenges have occurred in assessing effects of therapies in patients with early symptomatic PD, largely due to the difficulty of identifying patients based upon clinical evaluations alone. The estimates of numbers of patients needed to achieve meaningful drug efficacy is not possible without employing novel approaches to identify and exclude those patients that do not truly have PD. Emerging advances in biomarkers are now facilitating identification of patients in the early symptomatic phase of the disease and targeting this population for clinical trials. Pharmaceutical companies in conjunction with academic experts and advocacy organizations are aggressively exploring a multitude of biomarkers to aid in diagnosis, as indices of drug mechanism, and as potential measures of central target engagement.

Letter of support for Molecular Imaging of the Dopamine Transporter for Parkinson's disease clinical trials

The proposed biomarker is the dopamine transporter (DAT), with its level measured by FP-CIT ([123I]N-omega-fluoropropyl-2β-carbomethoxy-3β-{4-iodophenyl}nortropane, DaTscanTM, GE Healthcare), a SPECT ligand approved for use in a clinical setting by both the FDA and EMA. Ligands specific for DAT, located on dopaminergic presynaptic nerve terminals, directly measure dopamine terminal integrity and degeneration, the hallmark of PD pathology. Significant clinic pathologic findings illustrate that reductions in DAT assessed by neuroimaging are an index of dopaminergic nerve terminal degeneration in PD patients and that reductions precede onset of clinical symptoms. Patients presenting with two or more motor signs of PD, plus reduction of DAT expression as measured by visual assessment of DaTscanTM SPECT images, will be identified as suitable candidates for PD clinical trials, while biomarker negative subjects will be identified as not likely to show clinically relevant disease progression, i.e., motor deterioration over the course of phase II and phase III clinical trials. Patients with striatal dopamine deficit will be identified at the earliest signs of clinical motor impairment, when candidate therapeutic drugs presumably would more effectively disrupt the progressive neurodegenerative and declining clinical trajectory.

The CPP submission included a literature review, description of data sources, proposed context-of-use, preliminary data and analysis plan. The literature review, preliminary data, and analysis plan presented suggest that this biomarker, in conjunction with clinical criteria (at least two motor features characteristic of PD) and patient factors such as baseline age, baseline disease severity, etc.) may be used in predicting disease progression trajectories, to identify subjects more likely to show disease progression during the course of a clinical trial.

The goal in applying this biomarker according to its 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 for dopaminergic deficit (SWEDD) cases in future trials aims to enrich clinical trial populations with idiopathic PD patients, improve statistical power, and spare subjects who do not have PD from being exposed to novel therapeutic agents.

The methodology of SPECT neuroimaging is well established as the DaTscanTM tracer is used for enhancing decision making in clinical practice. Procedures will be in accordance with the tracer manufacturer's specifications and consistent with the methods currently being employed in the multisite observational Parkinson's Progression Markers Initiative (PPMI) studies. The proposed analysis of the scan is by visual inspection. Based on existing data to date, this approach is expected to generate a sufficiently accurate, reproducible, reliable and robust assessment for decision making in recruiting subjects into a clinical trial.

The EMA supports the primary objectives of the applicant and has decided to issue a letter of support to the Critical Path for Parkinson's (CPP) Consortium to encourage further development and validation of the proposed Biomarker.

Sincerely,

Guido Rasi
Executive Director

(Signature on file)

Letter of support for molecular imaging of the dopamine transporter biomarker as an enrichment
biomarker for clinical trials for early Parkinson's disease
EMA/506726/2016   Page 2/2