



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2022
EMADOC-1700519818-955717
Executive Director

Letter of Support for a Model-based Clinical Trial Simulation Platform to Optimize Design of Efficacy Evaluation Studies in Parkinson's Disease

On May 10, 2022, the Applicant Critical Path for Parkinson's (CPP) Consortium requested scientific advice for their "*Model-based Clinical Trial Simulation Platform to Optimize Design of Efficacy Evaluation Studies in 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 January 12, 2022, the SAWP agreed on the advice to be given to the Applicant.

During its meeting held on June 23, 2022, the CHMP adopted the advice to be given to the Applicant.

Background and rationale for the proposed tool

Model-informed drug discovery and development (MID3) can improve research and development (R&D) decision-making. Examples of the application of MID3 to R&D include: (a) understanding of disease-related targets; (b) selection of dose, schedule and regimens; (c) stage-gate (go/no-go) decisions; (d) optimization of study design; (e) patient selection; and (f) bridging studies in special populations.

A rich pipeline of promising therapeutic candidates are being advanced for Parkinson's disease many of which aim to target the underlying pathophysiology of the disease. Previous findings from natural history studies and legacy PD clinical trials can be used to comprehensively inform and design new PD trials; however, translation of legacy data is challenging. Without a data-driven framework for planning and optimizing trials, Applicants are challenged with designing informative clinical trials of appropriate and reasonable size, duration, and cost that will adequately evaluate potentially transformational therapies.

The current endpoint that is uniformly employed across PD clinical trials is the Movement Disorders Society Unified Parkinson's disease rating scale (MDS-UPDRS), a measure that represents a combination of clinical observed and patient reported assessments of motor and non-motor symptoms characteristic of Parkinson's disease. This submission represents the most comprehensive and robust evaluation of MDS-UPDRS Part II and MDS-UPDRS Part



III progression in early motor PD to date, with a goal to optimize clinical trials assessing MDS-UPDRS Part II or III progression that will facilitate a regulatory endorsement of optimal study characteristics, including design, inclusion criteria, trial size and duration.

Proposed Context of use

General Area: Clinical trial simulation.

General Description: A model-based clinical trial simulation platform describing the progression of early motor PD as measured by two endpoints: The Movement Disorder Society Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Parts II and III, incorporating the following relevant sources of variability specific to each endpoint:

- Part II: PD duration, presence of obesity, Hoehn and Yahr stage at baseline, medication use, age at time of clinical diagnosis, and sex
- Part III: PD duration, Hoehn and Yahr stage at baseline, medication use, age at time of clinical diagnosis, sex, evidence of dopamine deficiency through neuroimaging (e.g., presence of scans without evidence of dopaminergic deficit [SWEDD] status)

Target Population for Use: Patients with early motor PD within five years of clinical diagnosis.

Stage of Development for Use: All clinical efficacy evaluation stages of therapeutic interventions for use in early motor PD, including early signs of efficacy, proof-of-concept, dose-ranging, and registration studies.

Intended Application: Perform clinical trial simulations to help inform trial design, including inclusion/exclusion criteria, enrichment, and stratification approaches, for trials intended to evaluate the efficacy of symptomatic and disease-modifying therapeutic candidates. In the absence of regulatory-approved disease-modifying therapeutics, the CTS platform incorporates functionality for sponsors to introduce a non-data-driven therapeutic effect that modifies the rate parameter for both parts II or III of the MDS-UPDRS.

Out-of-scope: Approval of therapeutic interventions without the actual execution of properly conducted trials in PD patients. The CTS platform consisting of two PD drug-disease-trial models is not intended to support synthetic control arms or labelling claims for individual specific drug candidates. In addition, the CTS platform is not intended to inform or mandate specific endpoint selection; such decisions will be linked to therapeutic targets and will be informed by Applicant-specific interactions with EMA.

Sources of Data

- The Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) clinical trial
- The Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN) study
- Investigation of Cogane (PYM50028) in Early-stage Parkinson's Disease (CONFIDENT-PD) clinical trial
- The Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism (DATATOP) clinical trial
- Long-Term Dopamine Transporter Imaging and Clinical Assessment of Parkinson's Disease Progression--Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) clinical trial

- NET-PD Futility Study 1 (FS-1 NET PD) clinical trial
- NET-PD Futility Study-TOO (FS-TOO) clinical trial
- The Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation–PD (ICICLE-PD) study *
- The Oxford Parkinson’s Disease Centre Discovery Cohort (OPDC) study*
- The Parkinson Progression Marker Initiative (PPMI) study*
- The Parkinson Research Examination of CEP-1347 (PRECEPT) clinical trial
- An Open-Label Extension Trial to Assess the Safety of Long-Term Treatment of Rotigotine in Early-Stage Parkinson's Disease (SP512) clinical study
- Rotigotine versus ropinirole to assess the efficacy and safety of the rotigotine CDS patch in subjects with early-stage idiopathic Parkinson’s disease (SP513) clinical study
- Safety, Tolerability and Efficacy Assessment of Dynacirc CR in Parkinson Disease Phase III (STEADY-PD3) clinical trial*
- Study of Urate Elevation in Parkinson's Disease, Phase 3 (SURE-PD3) clinical trial*
- Tracking Parkinson’s (the PRoBaND study) Parkinson's Repository of Biosamples and Network Datasets study*

* Indicates that the study was used in Part II modelling. All studies listed above were used for Part III modelling.

Status of development and EMA Assessment

The CPP team has developed two drug-disease-trial models, one for MDS-UPDRS Part II and one for MDS-UPDRS Part III. To evaluate Part II progression, four contemporary non-interventional studies paired with two interventional randomized controlled trials that collected MDS-UPDRS Part II were evaluated. To evaluate MDS-UPDRS Part III, these six studies were also aggregated with an additional 11 interventional studies that collected UPDRS Part III. Following a harmonization procedure, UPDRS Part III scores were transformed to harmonized MDS-UPDRS Part III scores. Key findings indicated that both the Part II and Part III models robustly describe population-level disease progression while quantifying relevant sources of variability. Such variability includes observable features described above as well as unobservable features (i.e., between-subject variability and residual variability). For both models, underlying disease progression models accurately described baseline severity and rates of progression. A nonlinear disease progression model was utilized for Part II to capture changes in progression rates due to the bounded nature of the scale. In Part III, a linear model was utilized to capture natural disease progression. In conjunction, a placebo-effect model was developed to describe placebo responses in Part III. In both cases, symptomatic drug-effect models were developed to capture the time-varying effects of levodopa and/or dopamine agonist effects on disease progression. Dropout models were developed to predict patient dropout based on the same covariates assessed for disease progression. Extensive diagnostic and validation exercises were performed to establish the robustness of the models through both internal and external validation. In totality, the collection of these models serves as the basis for the proposed CTS platform to enable efficient trial design for clinical trials targeting early motor PD stages of the disease. The current version of the model accounts for the contribution of the aforementioned aspects and is being used to develop a web-based early motor PD clinical trial simulator with a user-friendly graphical interface. This tool will simulate clinical trials based on user-defined trial and subject characteristics at study entry. C-Path will grant public

access to this tool with a user-friendly graphical user interface (GUI) and detailed instructions for use, the model code, and related publications.

An expansion of the modelling analysis dataset with patient-level clinical trial data from contemporary clinical trials including relevant measures will strengthen the representativeness of the patient population and improve the predictive accuracy of the CTS platform to ongoing and future clinical trials. Such intended data sources would ideally include individuals in early motor PD with baseline and frequent longitudinal follow-up, using MDS-UPDRS II and III, biomarkers (fluid and imaging), genetic and additional exploratory measures. In addition, expansion of the modelling analysis dataset with contemporaneous patient-level clinical trial data will strengthen the representativeness of the patient population at a time when biological definitions of the disease are emerging. Incorporation of data that reflects recent innovative advances in the field will be key to enable the description of additional components such as placebo response and dropout profile.

The EMA supports the primary objectives of the Applicant and agrees to issue a Letter of Support to the CPP Consortium to encourage industry sponsors to share with CPP the patient-level data from completed phase II and III clinical trials in the intended target population as defined in the COU statement. This will allow the CPP team to continue to enhance quantitative novel methodology in drug development, while also encouraging the CPP team to disseminate and provide access to the current version of the model for implementation by sponsors actively designing clinical trials in early motor PD.

There is urgency to have effective treatments that halt the disease early in the course of the disease spectrum. There is a sense of optimism about the number of promising candidates advancing to the clinic, yet the field has witnessed the inefficiencies of having quantitative models developed separately by different groups on single studies and limited datasets. There is tremendous value to stakeholders to achieve regulatory acceptance of such drug development tools as a catalyst to the development of both safe and effective medical products for patients suffering from the most rapidly growing brain disease.

The current Letter of Support is issued on the basis of the qualification advice.

Yours sincerely,

Emer Cooke

Executive Director