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Executive Director

Letter of support for Model-based CT enrichment tool for CTs in aMCI

On March 14, 2018, the applicant Critical Path for Alzheimer's Disease (CPAD) Consortium requested qualification advice for a Model-based Clinical Trial Simulation Tool to Optimize Clinical Trial Design in Amnestic Mild Cognitive Impairment (aMCI). During its meeting held on July 10 2018, the SAWP agreed on the advice to be given to the applicant. During its meeting held on July 23-26 2018, the CHMP adopted the advice to be given to the applicant. The current Letter of Support is issued on the basis of the qualification advice.

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.
Failures in trials for Alzheimer disease (AD) may be attributable to inadequate dosing, uninformative population selection, lack of drug efficacy, or suboptimal design.
This submission expands CPAD's efforts in MID3, with the goal herein to develop a clinical trial simulation tool that is based on a comprehensive disease progression model for aMCI.

Proposed Context-of-Use statement for the proposed tool:
General Area: Clinical trial simulation (CTS).
General Description: A quantitative CTS tool, based on a disease progression model, which integrates estimates of placebo effect and drop-outs.
Target Population for Use: Subjects with amnestic mild cognitive impairment (aMCI) based upon clinical signs and symptoms. For this purpose, amnestic mild cognitive impairment is specifically defined as: Mini-Mental State Examination (MMSE) scores between 24-30 (inclusive), with a memory complaint, objective memory loss measured by education adjusted scores on the Wechsler Memory Scale Logical Memory II, a global Clinical Dementia Rating (CDR) of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia (ADNI [Alzheimer's Disease Neuroimaging Initiative] criteria). Patients with or without the

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Alzheimer disease pathology may be included in this context; the expected proportion of amyloid negative patients is 30 to 50% based upon data from multiple studies.
Stage of Drug Development for Use: All clinical efficacy evaluation stages of drug development for aMCI, including early efficacy, proof-of-concept, dose-ranging, and registration studies.
Intended Application: The tool will be used to perform clinical trial simulations. Simulations based on this model will allow sponsors to optimize clinical trial design, perform power and sample size calculations, inform entry criteria, define enrichment strategies, define stratification approaches, and determine the operating characteristics of the different simulated studies.
Out of Scope: Use to predict response to treatments without execution of clinical trials.

Status of development and EMA Assessment

The CPAD team has developed a non-linear mixed effects model for the longitudinal trajectory of Clinical Dementia Rating – Sum of Boxes (CDR-SB), based on patient-level data from the ADNI-1 and ADNI-2 trials. The Investigation Into Delay to Diagnosis of Alzheimer's Disease With Exelon (InDDEx) trial was used as an external validation dataset. The model accounts for baseline intra-cranial volume-corrected hippocampal volume (ICV-HV), apolipoprotein E4 (*APOE*-ε4) carrier status, baseline MMSE scores, baseline age and CDR-SB, as well as sex as other relevant covariates. This model allows the user to perform simulations to inform sample size estimation and power calculations, as well as evaluating enrichment strategies, over a varied range of assumptions and trial design options. Current approaches for sample size estimation, based on literature metadata of the estimated standard deviation for the clinical endpoint and the expected effect size, do not account for differences in clinical and demographic characteristics of the enrolled trial population, disease worsening profile over time, and the different levels of variability (e.g., between-study, between-subject, and residual variability). The current version of the model accounts for the contribution of the aforementioned aspects and is being used to develop a web-based aMCI 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. The resulting tool will be submitted to version control and made available to qualified researchers, upon appropriate vetting of requestors, through the Critical Path Institute's (C-Path) webpage. Once vetted, qualified researchers will have access to the tool with a user-friendly graphical user interface (GUI) and detailed instructions for use, the model code, and related publications. An expansion of the modeling analysis dataset with contemporaneous patient-level clinical trial data will strengthen the representativeness of the patient population and allow the description of additional components such as placebo response and dropout profile. Such intended data sources would ideally include individuals in the aMCI stage of disease, with baseline and longitudinal follow-up using the CDR-SB, baseline MMSE measures, *APOE*-ε4 genetic status and baseline ICV-HV.

The EMA supports the primary objectives of the applicant and has decided to issue a Letter of Support to the CPAD Consortium to encourage industry sponsors to share the patient-level data from completed phase II and III clinical trials in the intended target population as defined in the COU statement, including active and control arms, with CPAD. This will allow the CPAD team to complete the development and validation of the proposed quantitative novel methodology in drug development, while also encouraging the CPAD team to disseminate and provide access to the current version of the model for implementation by sponsors actively designing clinical trials in aMCI.

Yours sincerely,

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