DEPARTMENT OF HEALTH & HUMAN SERVICES

June 12, 2013

Diane Stephenson, PhD
Executive Director, Coalition Against Major Diseases
Critical Path Institute

Dear Dr. Stephenson:

Please refer to your submission, provided on behalf of the Coalition Against Major Diseases (CAMD), which contains a package intended to support the utility of a trial simulation tool for planning certain clinical trials involving patients with mild to moderate dementia of the Alzheimer's type.

We have completed our review of your submission and have determined it is fit-for-purpose in the contexts, and with the caveats and constraints, outlined in this letter.

Goal and Intended Applications
The goal of the proposed simulation tool is to serve as a public resource for sponsors designing trials of new therapies for Alzheimer's disease (AD). CAMD intends that this simulation tool will provide quantitative support in the design and planning of clinical trials involving subjects with mild to moderate AD. The submission further suggests that the proposed tool could be used during all clinical stages of AD drug development, including proof-of-concept, dose-ranging, and confirmatory trial design and could encompass various types of treatment mechanisms (e.g. symptomatic and disease-modifying).

The submission outlines several intended applications of the proposed tool:
- Sample size calculations
- Determination of optimal trial durations and treatment effect measurement times
- Comparison of the sensitivity of competing trial designs to assumptions about the types of expected treatment effects (time to maximal effect, effects that increase or decrease over time)
- Determination of the most appropriate data analytic methods for novel trial designs

FDA Assessment
Quantitative disease-drug-trial models are potentially useful tools to represent the time course of clinical outcomes, placebo effects, drug pharmacologic effects and trial execution characteristics. The CAMD quantitative AD model was developed based on patient-level and summary data to support the design of future drug development studies in patients with mild to moderate AD. Different data resources (e.g., derived from literature, the AD Neuroimaging Initiative (ADNI), and CAMD database) were used to build up the current model and describe longitudinal changes in ADAS-Cog.

Previous interactions between the Agency and CAMD include an initial meeting with the CAMD Coordinating Committee on November 3, 2009 and a face-to-face meeting on April 28, 2010. On March 27, 2012, FDA sent comments to the submission entitled "Drug Development Tool for Trial Simulation in Cognitive Trials in Mild to Moderate Dementia of the Alzheimer's Type" of November 22, 2011. On August 23, 2012, CAMD submitted responses to the information request and questions posed by the Agency. On January 14, 2013, CAMD submitted their simulation tool for evaluation.

Based on an evaluation by a multidisciplinary Center for Drug Evaluation and Review (CDER) team, the following are noted:

1. CAMD's ADAS-cog disease progression and dropout model and predictive check were reviewed. This tool provides a quantitative rationale for selection of study design and inclusion criteria in mild and moderate dementia of AD patients. The tool can be used in planning clinical trials in AD, and as a tool to simulate the phenomenology of the disease restricted by certain assumptions. Assumptions used in the model should be transparently noted in any user interface such that future users of the tool can make informed judgments of the tool's output in the context of their particular drug development question.

2. CAMD's trial simulation and power calculation was reviewed and suggest:
   a) Under the assumption of only symptomatic drug effects, a parallel design may be as short as 6 weeks and a cross-over design has to be 15 weeks at minimum. The cross-over design has relatively smaller sample size while maintaining appropriate power to demonstrate drug effect (if one exists).

   b) Under the assumption of only disease modifying drug effects, the power is higher for 78-week parallel design than that for the randomized start design (52 weeks) because the comparison between the two arms is scheduled at a later time.

   c) CAMD's model was implemented across the different developing platforms (from MAC cluster to Windows server and Linux parallel environment using Open Grid Engine scheduler); we replicated CAMD's submitted figures and tables.

We find the submitted drug development tool scientifically supported and suitable for the purpose of aiding in the design of future clinical trials in patients with mild to moderate AD. This model can be used to explore the effect of important design features such as trial duration, patient evaluation frequency, endpoint selection, and sample size. Clinical trial simulations relying on this model can provide support for the choice of trial design features, and can facilitate protocol review by CDER staff. End-of-Phase 2A meeting requests can be supported through the use of trial simulations based on this model or a modified version when clearly described.

We suggest that as CAMD makes the tool more widely available, it includes a detailed description of the model. Finally, we would strongly suggest that each sponsor update this tool with the most current assumptions regarding parameter uncertainty and variability prior to its application and their understanding of the new molecular entity (NME) under development.

General Use of Quantitative Disease-Drug-Trial Models
A precise description of a modeling tool and what decisions are intended to be driven by the results is valuable in interactions between FDA and drug developers.

We note that disease models are not intended to have a static construction and characteristics. Modelers have generally intended that the disease model is continuously refined over time as additional knowledge about the disease, important covariates, and mechanisms and characteristics of drug actions is gained. In addition, it is expected that for many models there will be additional empirical data from clinical studies of various types that can be incorporated into the body of empirical data that is the basis for the disease model quantitative key parameters. Furthermore, this evolution of the model is intended to increase the model's predictive capability in some manner (e.g., more accurate quantitative prediction, more realistic early response description, extended timeframe for prediction) and the model will be applied to take advantage of this improvement.

The results from disease modeling may not be the determining factor in deciding how to develop a drug or select the design parameters (e.g., sample size, number of dose groups, duration of study, analysis method) for a study. Disease models are intended to be one of the useful pieces of information incorporated in the thinking about how to develop a new drug, and selecting a specific design for the next clinical study in a drug's clinical development program.

As a prerequisite for future scientific evaluation of quantitative disease-drug-trial models, interested parties should contact the Division of Pharmacometrics (Office of Clinical Pharmacology | Translational Sciences).

Sincerely,
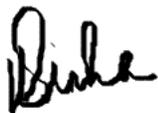
Vikram Sinha, PhD
Director, Division of Pharmacometrics, Office of Clinical Pharmacology

Issam Zineh
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Attachments
Discipline Reviews: Pharmacometrics, Biostatistics, Medical