April 5, 2013

To: Division of Dockets Management (HFA-305)
Re: Docket # FDA- 2013-D-0077

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to provide comments on the February 2013 FDA's Draft Guidance for Industry, titled *Alzheimer's disease: developing drugs for the treatment of early stage disease*.

We are pleased to submit comments and questions received from ISCTM members. This document is divided into two sections: (1) General comments are provided in bullets below and (2) comments on specified lines are contained in the table that follows.

The ISCTM formed a Working Group, chaired by Steven Romano, MD, to review and provide comments. Authors (in alphabetical order):

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GENERAL COMMENTS ON THE REVISED DRAFT GUIDANCE DATED February 2013:

- The ISCTM appreciates the FDA's effort to guide drug development activities in clinically relevant populations of patients at risk for, or in earlier stages of, Alzheimer's disease.
- The ISCTM appreciates the FDA's acknowledgement that functional impairment may be minimal, or at least challenging to measure, in these earlier stages of Alzheimer's disease. In fact, the ISCTM notes that current diagnostic constructs for symptomatic conditions, for example MCI due to Alzheimer's, underscore impairment in one or more cognitive domains (example, episodic memory), but with general preservation of independence in functional abilities.

- The ISCTM agrees with the FDA that standard approaches to measurement, i.e. those used historically to support the approvals of medicines for the treatment of Alzheimer's patients in the mild to moderate stages of dementia, have limitations regarding measurement of drug effect in earlier stages of Alzheimer's disease.
- Alzheimer's disease is a progressive, neurodegenerative condition. As such, drugs currently being developed for disease modification are not expected to improve cognition or function over a baseline state. There are a number of references to "improvement" in the document. The ISCTM suggests that the guidance be more explicit regarding the need to measure a drug-placebo difference rather than "improvement". This clarification is important and has implications regarding the choice of measurements (based on psychometric properties) as well as approaches to measurement and analysis.
- The ISCTM acknowledges that much progress has been made to delineate earlier stages of Alzheimer's disease, whether symptomatic (*prodromal AD* or *MCI due to AD*) or preclinical. We would like to note, however, that the full spectrum of the disease progresses on a continuum and that certain considerations applied to earlier, non-demented symptomatic patients may also apply to patients with mild AD. For example, mild AD patients with minimal functional impairment (while meeting the diagnostic criteria for dementia) may still benefit from experimental therapies, though the benefit may be captured more reliably on cognitive measures or a composite measure and not on historically used measures of function (current guidelines for development programs in mild AD require co-primaries). Perhaps the FDA could consider expanding this guidance to address this milder end of the AD dementia spectrum.
- The ISCTM acknowledges that since the issuance of this guidance the FDA has stated that it is intended as a starting point for continued dialogue with interested stakeholders. Given the development challenges in this important area, would the FDA consider holding a public meeting before the guidance is finalized? Such a meeting would provide FDA the opportunity to discuss key issues from the guidance with committed members of the research community, industry, and other patient and provider groups.

COMMENTS ON SPECIFIC LINES IN THE REVISED DRAFT GUIDANCE:

Lines	Comments/Issues/Questions
131-134	In the case that a single, composite measure assessing both cognition and function (such as the CDR-SB) is utilized in a symptomatic early AD population, how would those findings be captured in labeling, in particular the indication?
147-150	Similar to the above, in the case that an isolated cognitive measure is used to establish benefit in a preclinical population, how would those findings be captured in labeling, in particular the indication?
144-153	Could the FDA expand their discussion regarding the potential design of "additional and well-controlled studies" that would need to be completed following the approval of a drug for preclinical AD using an isolated cognitive measure? In the case of a continuation of a pivotal study used for approval, what would constitute a reasonable time for continuation of treatment in order to establish a "persistent benefit" or to demonstrate that the effect on an isolated cognitive measure "positively affects the overall course" (and presumably without a placebo arm given the submission of the trial for the initial indication)? Could consideration be given to use of modeling or historical controls in the case of discontinuation of a placebo arm

	following submission of the "pivotal" component of the trial? The length of time for continuation of a trial to establish a "persistent benefit" post-approval might be based on the actual effect seen and the timing of that effect for the particular drug studied, as an example. Some greater discussion of these points as well as others would allow for a sponsor to more fully assess the feasibility of such a post-approval program/commitment. Additionally, in the case that a defined, initial benefit leading to an accelerated approval in a particular population was found to wane as patients progressed into later stages of the disease (during post-approval assessment), what would be the implications for the original indication and labeling?
192-194 202-204	In the section referring to the potential use of a biomarker as a single primary surrogate efficacy measure, the FDA references the need for "widespread evidence-based agreement in the research community". It may be helpful to expand the discussion regarding the evidence requirements, acknowledging that this is a dynamic space with multiple and expanding lines of evidence generation.
216-217	Acknowledging that the FDA has not reached a conclusion regarding comparisons of rates of change (based on slopes), it would be helpful to provide a more thorough review of the FDA's current considerations given that this issue continues to be considered as potentially useful by some.
221	We agree that, for ethical reasons, a randomized-start design would be a more appropriate approach versus randomized-withdrawal as an alternative to the standard parallel-arm study. We would like to bring your attention to a publication which proposes an approach to the use of such a design in disease modifying AD trials, as this may be useful to consider (Zhang RY, Leon AC, Chuang-Stein C, Romano SJ. "A new proposal for randomized start design to investigate disease-modifying therapies for Alzheimer disease." Clinical Trials. 2011 Feb. 8(1):5-14. doi: 10.1177/1740774510392255. < http://www.ncbi.nlm.nih.gov/pubmed/21335586 >).
226-227	For reference, we are aware of a trial which utilized this design in another neurodegenerative condition (Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E, ADAGIO Study Investigators. "A double-blind, delayed-start trial of rasagiline in Parkinson's disease." New England Journal of Medicine. 2009 Sep 24;361(13):1268-78. doi: 10.1056/NEJMoa0809335. <http://www.ncbi.nlm.nih.gov/pubmed/19776408>).

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