17 May 2018

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2013-D-0077

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment: Early Alzheimer's Disease: Developing Drugs for Treatment Guidance for Industry.

The International Society for CNS Clinical Trials and Methodology (ISCTM) offers these comments for consideration based on our experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group received compensation for comments provided. Comments represent personal opinions and not that of the institution, agency, or company affiliation of group members.

The ISCTM formed a group, led by Adam Butler, Stephen Brannan and Steven Potkin to review and provide comments on behalf of the Society. Authors (in alphabetical order):

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COMMENTS ON THE EARLY ALZHEIMER'S DISEASE: DEVELOPING DRUGS FOR TREATMENT GUIDANCE FOR INDUSTRY:

General Comments

ISCTM welcomes this guidance, and is encouraged that the FDA has provided a number of new areas for drug developers and researchers to consider related to new treatment development for Alzheimer's Disease. Expanding on previous guidance related to diagnosis, clinical outcome measures, and biomarkers, will be useful in the design of future programs. We feel that this document provides a reasonable amount of discretion around many areas that are changing rapidly, such as which scales and biomarkers may be appropriate in certain situations, without narrowing options for those who are pursuing novel approaches.

II. Background

This document uses the terms "clinically meaningful" and "clinical meaningfulness" in several areas. While clinically meaningful is generally defined well by the FDA, it may be helpful to expand on how the agency views "clinically meaningful" in the context of the proposed stages for AD as this may provide further clarity on meaningfulness.

Beginning on line 69: this paragraph could be clarified. The paragraph states first that cognition "is most certainly meaningful in terms of daily function." The sentences that follow state, "more marked cognitive changes may represent impairment that is clearly clinically meaningful." However, this raises an 'issue of concern' around how these cognitive deficits are measured and appears somewhat inconsistent with earlier statements by indicating, "cognition is meaningful, but when measured using conventional approaches with sensitive tools directed at particular domains, the meaningfulness of measured changes may not be apparent." Additional clarification would be helpful as episodic memory deficits are the core concern of Alzheimer's disease patients early on in the disease course, and are readily measured by many sensitive neuropsychological tests.

In general, this document appears to leave more flexibility for developers and researchers to identify biomarkers that may be useful for an individual study or compound. Expanding on what criteria would be used for biomarker evaluation specific to Alzheimer's disease could be useful.

III. Diagnostic Criteria

Regarding line 111, how can we show that entry criteria for a study "reliably define a population with early AD", particularly before the study has completed?

IV. Outcome Measures

It is welcomed that the agency is proactively sharing its thinking regarding different stages of the AD continuum and attempting to pair them with appropriate outcome measures. The ISCTM agrees that different outcome measures will be appropriate for different stages of the continuum. A somewhat minor structural consideration that might help decrease confusion would be to not present the stages in the reverse order of the previous section, as well as a brief statement that "Stage 4" does not represent earlier stages and thus seems adequately covered by previous guidance and precedent regarding outcome measures and requires no further discussion. ISCTM recognizes that the staging closely follows that which was recently published from the NIA-AA Research Framework.

Stage 3

The (continued) proposal of a single primary endpoint for approval again brings up the discussion of an integrated scale in 171-173. Likewise, on the following page (5, 175-177) the guidance provides additional clarification of what this scale may look like. However, the draft guidance would be more helpful if the agency were willing to provide the category(s) that this type of hypothetical measure falls into [e.g., Performance Outcome Measure], as the guidance appears to imply this would be a performance-based functional measure. That is, a neuropsychological test that measures a cognitive domain and function, but that is also clinically meaningful at the patient level (e.g., an episodic memory list learning task consisting of medication instructions), might be acceptable. Inclusion of this additional granularity would be welcomed and most helpful to those designing and running interventional clinical trials.

An example of cognition and functionality may be demonstrated in the Financial Capacity Instrument - short form (FCI-SF, Marson et al.) Authors note that functional change in subtle financial skills decline in preclinical stage (as early as stage 1), is reflected in slower task completion times (a cognitive measure) and is related to biomarker status (e.g. amyloid PET).

However, the assertion/implication that an improvement in cognition using neuropsychological tests is not by itself a meaningful index of a drug's functional benefit (167, 179-181) does not seem to recognize recent (and not so recent) developments in the field. There are papers which appear to quantify deficits in neuropsychological tests that are associated with known functional benchmarks; for example, intoxication with a range of agents, (Cook et al., 2005; Thapar, Zacny, Thompson, & Apfelbaum, 1995), (Ginani et al., 2011; Pompeia, Pradella-Hallinan, Manzano, & Bueno, 2008; Roth, Roehrs, Koshorek, Sicklesteel, & Zorick, 1987), (M.J. Mattila & Patat, 1996; M.J. Mattila, Vanakoski, Kalska, & Seppala, 1997),sleep deprivation (Tucker, Whitney, Belenky, Hinson, & Van Dongen, 2010), as well as the benefits of caffeine intake (Kassis, Katz, Ravid, & Pillar, 2013; Lane, 1997). Thus, it appears that correlation to function may not be as uncertain as the guidance claims. As the guidance appears to acknowledge (175-177), currently there are no adequate functional outcome measures for this stage (which by earlier definitions had no functional deficit). Thus, current tools for measuring functional

change in stage 3 patients are less precise, more subjective, and poorly correlated with cognitive measures; whereas cognitive measures reflect the hallmark of the disease, correlate with its pathophysiology, and measure functions that patients and caregivers almost uniformly regard as meaningful. (Ropacki, Hannesdottir and Hendrix, 2017). ISCTM would suggest that the FDA allow the more recent, updated conceptualizations and findings in this area to be incorporated rather than solely hope for rapid development of new outcome measures that may not be ready for some time (and apparently will be redefining functionality to acknowledge new levels of subtle impairment). We acknowledge that the FDA appears to be more open to this possibility for "Stage 2 Patients".

Stage 2

We agree with the FDA that for the defined Stage 2 patients, "with only subtle cognitive deficits" detectable (187-188) that it is currently very difficult to envision how to establish a clinically meaningful effect for differences in cognitive (or functional) outcomes in trials of "reasonable duration".

The discussion regarding how the convergence of neuropsychological test findings (199-202) or "a large magnitude of effects on sensitive measures of neuropsychological performance" may be helpful to making a compelling case to the agency could be more useful if augmented with some examples of what constitutes subtle detectable abnormalities either at the individual level (e.g., amount of deviation from age- and education-corrected norms) or group level (e.g., trend or statistical significance level required). Similarly, though it was not explicitly stated here, changes in biomarkers of AD pathophysiology would be judged similarly. ISCTM notes that this stance is not dissimilar to other data that the FDA monitors and it may be helpful to explicitly state this.

It also appears that studies at this stage may need to end up being longer than typical trial duration, leading to the difficult discussion of the certainty of future clinical course and its relationship to the changes seen (207-211 and later 263-289). These uncertainties currently make it hard to envision how one can currently make a credible argument and we urge the agency to find different terms than "certainty" and "inevitability", which appear on the surface to be a very high threshold for biological systems.

Stage 1

From the current definition of Stage 1 Patients, it would appear that the only way to show an effect is through biomarker changes. ISCTM appreciates the agency's willingness to consider such an approach as well as its assessment that the current understanding of biomarker progression is not yet fully established regarding the uncertainties mentioned in the previous section and that precompetitive collaboration may be needed to evolve our understanding of the various biomarkers that might be associated with the Alzheimer's continuum. ISCTM feels that the standard mentioned of (line 231) "reasonably likely to predict clinical benefit" is appropriate both here and in the previous section. Further clarification regarding thinking about "post approval requirements" for full approval if this first step is successful would be helpful.

Biomarkers

NIH working group defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention" (BDWG, 2001). Biomarkers can be used to aid in diagnosis, to staging an illness, to predict diagnostic conversion or to predict and monitor clinical response to treatment (FDA, 2014). It may be more productive to identify subgroups of individuals who share biological patterns in common that may predict preferential response to targeted treatments. In order to guide treatment, biomarkers should

reflect disease mechanisms that are relevant to the selection of therapeutic options. If measured early enough, biomarkers for these factors might identify individuals at risk in order to modify or halt progression of the aberrant process.

The FDA's guidance on Drug Development Tools (DDT; Qualification Process for Drug Development Tools (FDA, 2014)) identifies two separate processes necessary to develop novel biomarkers for drug development. The first step is analytical validation of assays and the second step defines how the biomarker should be used in the context of clinical management or drug development and includes the biomarker's purpose, its boundaries, the conditions of qualified use, and its interpretation. In the clinical research literature, statistically significant differences in mean values of analytes or imaging findings between target populations and controls groups are often interpreted as potential biomarkers. However, the predictive value of a biomarker depends on many factors, including generalizability across clinical populations, the reliability of the biomarker, the sensitivity and specificity for the specific target population and on the relative prevalence of the target population. Due to issues of poor reliability and generalizability, many promising biomarkers have failed replication and for those biomarkers that have successfully achieved replication, overlap in values between groups may be great enough to make the biomarker of little or no clinical value. Very few publications provide the positive predictive value (PPV), i.e., the ratio of the number of true or accurate positive predictions / total number of positive test predictions (both true and false).

Even biomarkers that are not related to drug targets may be useful in enriching a clinical trial sample by removing unwanted variability.

> *Biomarker Refs*
> *BDWG, B.D.W.G., 2001. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 69, 89–95.*
> *FDA, 2014. Guidance for Industry and FDA Staff- Qualification Process for Drug Development Tools. In: U.S. Department of Health and Human Services, F.a.D.A., Center for Drug Evaluation and Research (CDER) Ed. Silver Spring, MD.*
> *Time to Event & Assessment of Disease course*

The discussion of the assessment of disease course is welcomed but could benefit from a discussion on the agency opinion concerning the use of longitudinal cohort study (LCS) designs (e.g., IMI-EPAD LCS, CHARIOT-PRO) in interventional clinical trials. Previously, Dr. Janet Woodcock had publicly supported verbally the use of these data as run-in data for an eventual clinical trial as long as the LCS was done to GCP, and these same patients entered the follow-on interventional clinical trial. However, agency clarification on these statements in writing within the draft guidance would be most helpful for the field.

Establishing a bar of "permanence" for the expected effect of a drug on disease course, and that that effect continue in absence of drug exposure, seems high and inconsistent with other clinically meaningful interventions.

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