16 August 2018

To: Food and Drug Administration, HHS

Re: Docket No. FDA-2018-D-1919

The International Society for CNS Clinical Trials and Methodology (ISCTM) welcomes this opportunity to respond to the FDA request for comment: Major Depressive Disorder: Developing Drugs for Treatment Guidance for Industry.

The 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, comprised of scientists, clinicians, trialists, statisticians and drug developers from both industry and academia, 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 Carla Canuso, Amir Kalali and Jonathan Rabinowitz to review and provide comments on behalf of the Society. Authors (in alphabetical order):

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COMMENTS ON THE MAJOR DEPRESSIVE DISORDER: 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 Major Depressive Disorder (MDD). Expanding on previous guidance related to trial design, sub-populations, clinical endpoints, and biomarkers will be useful in the design of future programs. We appreciate that this document aims to address areas that are quickly evolving, such as the recent advent of research on rapid-acting antidepressants, as well as topics where there has been regulatory precedent with limited explicit guidance, such as trial designs for studies of partial response and treatment resistance. The ISCTM looks forward to the ultimate adoption of guidance that clearly advances the methodology and efficiency of antidepressant drug development and would readily participate in further public debate to achieve this goal.

I. Introduction

II. Background

Although the document states in lines 30-32 that this guidance does not contain discussion of statistical analysis, and that this topic is addressed in the ICH guidance for industry E9 *Statistical Principles for Clinical Trials,* the ISCTM would be interested on the applicability of the ICH E9 addendum (estimands) to clinical trials in MDD.

This document describes MDD as "chronic" illness (line 49). It would perhaps be more accurate to describe the condition as "a debilitating, recurrent and, in some cases, chronic illness."

III. Development Program

A. General Considerations

The ISCTM welcomes the guidance on the development of rapid-acting antidepressants, and the acknowledgement that trial design issues and regulatory considerations for these agents may differ from previously approved antidepressant drugs. We agree that approximately 1 week is an appropriate time frame to define rapid onset and suggest that this be specified in line 77.

However, from a theoretical perspective, onset of efficacy of an antidepressant drug may take place over a continuum from virtually immediately to several weeks after initiation of treatment, depending on the biology involved. The ISCTM recommends using language that recognizes that onset of efficacy may occur over a continuum of time, and that, depending on the temporal aspects of onset of efficacy and how the drug is intended to be used in clinical practice, the appropriate endpoints, study design and requirement for demonstration of maintenance of effect should be agreed with the Agency.

B. General Pharmacological and Clinical Safety Considerations

Line 92 states that "NMDA receptor antagonists have been found to cause Olney lesions." Unless this is an established class effect, we would suggest modifying the statement to "some NMDA receptor antagonists."

Under Clinical Pharmacology Considerations (line 113), we propose using the term "call for" rather than "involve." Additionally, in line 115 the document states that sponsors "should conduct pharmacodynamic studies, such as in vivo receptor binding studies or biomarker studies." The ISCTM recommends this statement be modified to allow for the possibility of a drug without a known ligand and/or biomarker.

Regarding a dose-finding trial (line 118), the ISCTM has concerns about the proposed requirement for a fixed-dose design with at least three doses. Placebo response is known to increase with the number of active treatment arms in a trial (Rabinowitz et al., 2018). We recommend an approach that looks at the totality of the data, including PK modeling. Our proposed language is: "Sponsors should generally evaluate at least three fixed doses for clinical efficacy. This may be achieved through one or more dose-finding studies." Additionally, it would also be appreciated if the Agency could comment on the acceptability of adaptive design studies for dose-finding.

C. Specific Efficacy Trial Considerations

The ISCTM agrees with the choice for placebo-controlled short-term efficacy trials. However, given the high placebo response rate in antidepressant trials, it would be beneficial if the Agency added language encouraging sponsors to consider implementing strategies and techniques that have been

either empirically or theoretically proposed, aimed at managing placebo and nocebo responses among subjects.

The statement "A substantially earlier or larger effect could be demonstrated in an active-control superiority trial" (lines 144-145) requires clarification for several reasons. First it is unclear what is meant by "substantially earlier." Additionally, is the intent of this statement that an active-control superiority trial could be considered (or is required to be) an alternative to a placebo-controlled study, and serve as one of the two well- controlled studies for an efficacy claim? Would such as study require a placebo arm? Finally, would two such studies be required for a superiority claim?

In the section "Timing of effect," regarding rapid-acting antidepressants, line 161 states "Durability of effect beyond the initial response should be characterized." We suggest this sentence be modified to read "Durability of effect beyond the initial response should be characterized to ensure clinical meaningfulness". Additionally, clarity is needed around the definition of "initial response" and "durability of effect." Further, the text in lines 165-166 would be clearer if it stated, "The precise studies depend on how the drug is intended to be used, for example as a ~~predecessor~~ *short-term treatment given in advance of the full treatment effect of* a conventional antidepressant or as a drug for ~~repeated~~ *continued* use."

The section on Maintenance treatment lines 175-176 states, "studies of conventional antidepressants are actually assessments of the ability of the drug to reduce the rate of recurrence of depression." However, earlier within the document (line 74) maintenance is explained as "(i.e. relapse prevention)." Since relapse typically refers to return of symptoms within the current episode (i.e. without a period of at least two months without or with minimal symptoms) and recurrence the return of symptoms after such period of remission, we suggest that the terms not be used inter-changeably and be used consistently with the European Medicines Agency guidelines which make a distinction between the two. Additionally, line 177 states "studies should be at least 6 months in duration." However, it is unclear whether the 6-month duration refers to the randomized period or to the total study duration.

The proposed guidance on maintenance treatment for rapid-acting antidepressants is limited to lines 181-183 stating, "there is interest in whether the rapid effect does in fact persist for the episode." It would be helpful for the Agency to distinguish this statement from the need to characterize the durability of effect of rapid-acting antidepressants described in line 161 of the section on short-term treatment. Further, it is not clear whether such a study of rapid-acting drugs would be required pre-approval as opposed to a maintenance study conducted as a post-marketing commitment.

Lines 189-190 state that the "FDA is interested in studies that explore whether treatment response can be maintained with a lower dose of the drug than is needed for short-term efficacy, and whether a lower dose may improve tolerability." Having to evaluate different doses during a maintenance study will increase sample size and timelines. The ISCTM suggests that the exploration of lower doses be requested on a case by case basis, rather than set forth in guidance.

The ISCTM has several comments about the proposed guidance on partial response and treatment-resistant depression (TRD) (beginning on line 204). As indicated in the document, antidepressant response exists on a continuum and the distinction between partial responders and non-responders

is arbitrary. Publications have shown similar degree of improvement between these two patient groups with adjunctive therapy (Nelson et al., 2012; Papakostas, 2016). Even modest degrees of response (<25% improvement) could be clinically relevant and worth preserving by maintaining the responsible agent. Therefore, from this clinical standpoint adjunctive therapy could be viewed as appropriate even where there is little response to baseline treatment (i.e., in treatment-resistant populations). In addition, it is conceivable that a novel medication may be effective as adjunctive therapy and ineffective as monotherapy, even if there has not been an adequate response to the baseline antidepressant treatment. Therefore, the ISCTM strongly suggests that the guidance allow for the sponsor to determine whether the investigational antidepressant is best suited to a monotherapy or adjunctive therapy paradigm, irrespective of the target population (i.e., partial responder or treatment resistant). This determination should be based on scientific and clinical evidence accumulated in the course of the drug's development.

Furthermore, the proposed monotherapy study design for TRD within the draft guidance is problematic as it is likely to lead to differences between the two treatment arms in baseline characteristics, including severity of depressive symptoms. With such a design, since the comparator group would continue on the active treatment they were previously receiving, inherently this group would be enriched for tolerability (as potential subjects who had not tolerated the medication would have previously discontinued the medication). Additionally, since subjects assigned to the new treatment arm would be withdrawn from their previous antidepressant, their baseline depression scores may differ (i.e., worsen) compared to subjects who continue on their previous treatment. This could lead to unreliable study results and potentially reduce the difference in treatment effect for any medication being developed for patients with TRD. Indeed, this could hamper the development of new treatments for the MDD sub-population with the highest unmet need and greatest health burden.

Finally, while the Agency does not specify the need for a prospective treatment failure in the proposed TRD monotherapy study design, operationally it would be very difficult to blind the treatments to which the subjects would have failed using an all-comers design (i.e., allowing the comparator agent to be whatever antidepressant the subject happened to be on). Alternatively, narrowing the comparator arm to a pre-specified set of antidepressants would impact enrollment and generalizability.

Regarding Study Population and Entry Criteria, the ISCTM agrees that study populations should reflect a broad population of MDD patients and should avoid unnecessary restrictions, such as the systematic exclusion of subjects with a history of suicidal ideation and behavior and concomitant illnesses. We also appreciate the Agency's flexibility in allowing sponsors to provide a rationale for more restrictive entry criteria. At the same time, the ISCTM would welcome more insight on how anticipated events related to these symptoms and comorbidities would impact labeling, and what additional monitoring might be required. We note this proposed guidance does not address safety monitoring with respect to suicidal ideation and behavior. In supporting the inclusion of patients with a history of suicidal ideation and behavior in clinical trials, the Agency may also wish to reference the 2012 guidance on the prospective assessment of suicidal ideation and behavior in clinical trials within the new MDD guidance document.

The section on Selection and Adjudication of Efficacy Endpoints identifies the currently accepted clinician-rated outcome measures utilized as primary endpoints in phase 3 studies (lines 244-246) and specifies that other endpoints may be acceptable based on advice received prior to initiating studies. The ISCTM would appreciate an explication of the Agency's position on the use of validated patient-reported depression measures as a primary or key secondary endpoint in phase 3 studies. Likewise, it would be useful to have insight into the Agency's stance on the potential use of Quality of Life outcomes, as well as digital measures based on new technology, as regulatory endpoints. Finally, it would be helpful to understand what requirements, if any, are needed to validate primary efficacy endpoints for rapid-acting antidepressants.

Line 258 would read more clearly if the word "CGI-S" were added after the word "baseline." This would clarify that the value being referred to is the difference of two ratings on the CGI-S.

In lines 270-271 of the Statistical Considerations section, for clarity we recommend modifying the statement to read "…should provide documentation that the analysis plan was not developed or altered with *unblinded* efficacy data in hand."

Concerning the study of pediatric subjects (beginning line 297), we agree that some controlled clinical efficacy and safety data are needed. However, given the recruitment challenges in most pediatric studies and the high medical need for safer and more effective antidepressants, especially for adolescents, the ISCTM would like the Agency to consider more leniency in the proposed requirement for two independent adequate and well-controlled short-term clinical trials in pediatric patients. Alternatively, we suggest evaluating the need for two separate studies on a case by case basis, depending on the strength of the data in both adults and pediatric populations. The ISCTM would also be interested in any commentary that the Agency may have about the study of TRD in pediatric populations.

We are also pleased that the Agency has included considerations of biomarkers in this draft guidance, even though no surrogate endpoints for the assessment of antidepressant effectiveness are available at this time.

References:

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Papakostas, George. (2016). Identifying patients with depression who require a change in treatment and implementing that change, Journal of Clinical Psychiatry. 2016 Feb;77 Suppl 1:16-21

Rabinowitz, Jonathan et al. (2018). Determinants of antidepressant response: Implications for practice and future clinical trials. *Journal of Affective Disorders*, Volume 239, 79 - 84