March 30, 2012

Submission of comments on "Guideline on clinical investigation of medicinal products in the treatment of depression"

Comments from:

Name of organisation or individual
International Society for CNS Clinical Trials and Methodology (ISCTM) www.isctm.org

The International Society for CNS Clinical Trials, ISCTM, welcomes the opportunity to comment on the above listed paper. The ISCTM was chartered in fall of 2004 as an international society charged with providing a commercial free forum where key stakeholders from academia, industry and regulatory branches can discuss/resolve challenges specific to the design and methodological issues in CNS clinical trials. Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the guidance.

Work Group members included:
Chair: Andrei Pikalov, MD, PhD, Sunovion
Douglas Feltner, MD
Larry Alphs, MD, PhD, Janssen Pharmaceutical Companies
Tanya Ramey, MD, PhD, Pfizer
Lu Zhang, PhD, Pfizer
Cynthia Siu, PhD, Data Power Inc
James Rawls, PharmD, Sunovion
Michael Detke, MD, MedAvante
Robert Berman, MD, Bristol-Myers Squibb
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Atul Mahableshwarkar, MD, Takeda

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Study population and endpoint: Clarifications are needed for definitions of partial response, non-response, and treatment resistant patients. A definition of Partial Response is not provided.	
	Treatment: Clarifications are needed to distinguish monotherapy in treatment resistant patients vs. augmentation/add-on treatment for partial responders with monotherapy treatment.	
	Long-term trial: Clarifications are needed for "an extension study for 6 months" (Line 98), as an alternative to a randomized withdrawal design.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
86-87, 102,103 and general comment		Comment: The Guideline (henceforth "Guideline") should avoid using the phrase "major depression" unless this is first identified as meaning "Major Depressive Disorder". Similarly, because major depressive episodes can occur in the context of conditions other than Major Depressive Disorder (MDD), the Guideline should be clearer that MDD is meant, rather than major depressive episodes per se. Proposed changes: (line 86-87) Change "…products for acute and long-term treatment of major depression. Its main focus is on unipolar major depressive episodes." To "…products for acute and long-term treatment of Major Depressive Disorder (MDD, "major depression"). Its main focus is on major depressive episodes that occur in the context of MDD." Line 89: Change "…improved safety profile in patients with major depressive episodes." To "…improved safety profile in patients with MDD." Line 103: remove "particularly" Line 103: change "major depressive episodes" to "MDD".	
110		Comment: As noted in the Guideline, despite multiple available treatments for MDD it remains a leading cause of global disease burden. Paradoxically, a number of major pharmaceutical companies have made the business decision to cease development of MDD drug candidates. Higher upfront regulatory requirements serve to delay time to market of a potential agent or, alternatively, require greater at-risk	

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		investment. Such constraints deter investment in treatments for MDD. While we acknowledge that patient safety is the absolute priority, we encourage the EMA to consider mechanisms allowing registration based on trials in MDD subpopulations (e.g., maintenance effects in populations with Partial Response)	
125-129		Since recurrence trials are, by definition, long-very long in duration, there is less likelihood they to be conducted, especially prior to approval. On the other hand, tachyphylaxis is more gradual process, may be more rapidly followed and is also a clinically relevant and much understudied outcome. Proposed change: Please consider adding information on tachyphylaxis to the desirable data relevant to long-term treatment and strengthening the statement in line 127 with:	
126-129		"pharmaceutical companies should not restrict their development...but should also provide clinical trial data for a possible additional claim of recurrence prevention, reduced tachyphylaxis, or both"	
138-165		Comment: A definition of Partial Response is not provided. It is not clear if this population is intended to be similar to TRD Proposed Change: Please define Partial Response.	
145-151		Comment: The listing of treatments in these sequences omits augmentation with stimulants, which might also have	

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		mechanistic implications for certain forms of TRD. Similarly, it is unclear why the third-line use of MAO-Is is not mentioned. Proposed change: Please add third-line use of MAO-Is and augmentation with stimulants after multiple treatment failures on antidepressant monotherapy to this section.	
151-152		Comment: ECT is mentioned as a "first line" option for TRD. This is subject to misinterpretation: by definition, TRD had multiple (usually 2 or more) treatment failures, and ECT is generally reserved as last/second-to-last option. Proposed change: Please strike "first line" before option to avoid the impression that ECT should be the immediate go-to treatment for TRD.	
155-157		Comment: "fail to induce a clinically meaningful effect" is useful language. However, this can include partial response, as well as "non-response". "Non-response" is too absolute to use here and is confusing. Proposed change: line 155- delete "non-response" or change to "partial response but clinically insignificant"; line 156 and 157—change "non-response" to "inadequate response" or "clinically insignificant response" or "lack of clinically meaningful response"	
159-163		Comment: The Guideline acknowledges that the proposed definitions of TRD and Partial Response have not been prospectively validated and, in fact, there is discordant data (eg., STAR*D). ISCTM believes that lack of validated	

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		definitions represents a major methodological difficulty and recommends that the agency considers regulatory support for the development of such parameters. In the meantime, for the purpose of this Guideline, ISCTM suggests using description of the TRD and Partial response categories without referring to them as definitions, and offers its active support of efforts that attempt to reach clinical consensus on these definitions. Proposed change (if any): Add a statement on the current view of EMA's position on the status of actual definitions for TRD and partial response (e.g., in development, under consideration) and how applicants should approach the agency if they want to pursue an indication in TRD or for treatment of partial response before definitions are fully agreed upon by EMA	
166-179		Comment: The sentence in line 171-172, in Section 2, on Scope, should also refer to the safety evaluation requirements in 4.6 Proposed change: Add and refer to the safety evaluation requirements in 4.6	
206-207		Change "depression" to "Major Depressive Disorder"	
230		Comment: For clarification, it would be useful to address potential ambiguity in the sentence. "Three-arm trials including both a placebo and an active control are recommended", but not required.	

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		Proposed change (if any): "Three-arm trials including both a placebo and an active control are recommended; however, an active control arm is not required. "	
244-249		Comment: Clinical trials to demonstrate maintenance of effect require distinct trial designs and select patient populations different from those of an acute trial. Therefore, maintentance of effect may be viewed as an independent regulatory path for a distinct indication and should not be a requirement for the approval of an acute indication. Proposed change: Provide respective clarification	
242		According to the Guideline, non-inferiority is not an option as the sole basis for demonstrating efficacy (Lines 216-217). It further states "A placebo-controlled extension study is not recommended, as there is a risk, that the results will be ambiguous" (Lines 245-255), and "Special attention is needed to distinguish relapse from withdrawal symptoms, when medication is stopped or tapered off in such a study." (Lines 252-253) Clarifications are needed for whether a placebo arm is required to be included in long-term trials to demonstrate that a "short-term effect can be maintained during the episode" (Line 242)	

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242		Proposed change: text edit from "during the episode" to "during the index episode".	
244-245		Comment: According to the Guideline, "responders to treatment of sufficient duration, with the test product, are (re-)randomised to test product or placebo." (Lines 244-245) Randomising patients with MDD who have been stabilized after achieving responder status in "8 to 12 weeks" (Line 248), to a placebo in the continuation phase raises some methodological concerns that should be considered when designing such studies. Relapse risks are highly sensitive to discontinuation artifacts, and are difficult to interpret without paying special attention "to distinguish(ing) relapse from withdrawal symptoms, when medication is stopped or tapered off in such a study." (Lines 252-253) Please provide specific details regarding acceptable designs (e.g. patient populations, efficacy parameters) for 6-month extension studies and/or long-term randomized studies (see also EMA Guideline on clinical investigation of medicinal products in the treatment of schizophrenia).	
249		Comment: The duration of the randomized phase in relapse prevention studies should be better defined and clearly stated. Proposed change: Change "…usually has duration of up to 6 months" to "…usually has a duration of 6 months."	
276		Comment: "Episodes of Major Depression" should be further clarified to be certain that it is clear to the reader that these	

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		episodes are occurring in the context of MDD, rather than another disorder. Suggested change: Change "Episodes of Major Depression" to "Episodes of Major Depressive Disorder" or "Major Depressive Episodes occurring in the context of Major Depressive Disorder"	
281		Comment: It would be useful for the Guidance to comment on the role of meta-analysis of efficacy in evaluating risk benefit. Views on the role of meta-analyses of efficacy vary; they seem to be valued more highly by EMA than FDA. Also, the statistical methods and choice of studies affect the estimated effect size from a meta-analysis. Proposed change: Add at end of this section—"A meta-analysis of efficacy across the clinical studies can be helpful for assessing the clinical meaningfulness of the effect. The statistical methods to be used and the clinical studies to be included should be agreed to with the regulatory agency, as these may influence the results."	
300-309		Comment: Unfortunately, no universally agreed-upon definitions of remission for MADRS, HAM-D etc. exist. On the other hand, we seem to be resigned to achieve a "good enough" result as the best possible outcome - current criteria for remission all include some residual symptoms. A more ambitious ultimate goal would be to introduce full or complete remission. In the case of the MADRS, complete remission is usually defined as a score at endpoint of <5. Making this difficult outcome a defined, attainable claim-strength label	

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		language (% of patients active vs. placebo) would encourage sponsors to at least consider "treatment to wellness" as an outcome worth striving for. Proposed change: Add the fraction of patients achieving complete (full) remission as a recognized outcome parameter.	
303-304		Comment: According to the Guideline, "responders" are typically selected in an open-label, uncontrolled study (OL-SP for open-label stabilization phase) based on change from baseline, as stated in Lines 303-304 that "a 50% improvement on the usual rating scales is accepted as a clinically relevant response". Given the "optimal duration is not known at the moment, but duration of e.g., 8 to 12 weeks for the first period appears acceptable" (Line 248), this raises methodological concerns about using an "improvement" score in an open-label, uncontrolled design to select a responder sample (especially from those with a high baseline severity score). It is possible that these responder samples consist of a composite of true responders and pseudo-responders, selected under the influence of non-specific design factors and an undesirable regression-to-the-mean bias, a statistical artefact unrelated to treatment effect. Proposed change: Acknowledge design-specific differences of short-term studies to arrive at a sufficient number of responders, and consider the mention of alternative designs that do not pre-select responders prior to start of the long-term study. This could include, for example, short-term	

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		double-blind studies continuing into a long-term double-blind phase, with or without a cross-over design, but preserving the double-blind. Responders status at week 6, 8 etc. would be prespecified to allow for evaluation of maintenance efficacy.	
312; 316		Comment: Add additional definition to "episode", and add episode duration to the sentence on long-term efficacy Proposed changes: change "during an episode" to "during an index episode" and (line 316) change to "Long-term efficacy trials may be needed to demonstrate the maintenance of efficacy throughout an index episode"	
334-335		Comment: Beyond the GAF, measures of meaningful improvement in social functioning should also be allowed as key secondary endpoints, as long as validated and reliable measures are used and type error is adequately controlled for. Proposed change: Add to line 335: "In addition, a measure of social functioning, such as the Sheehan Disability Scale, may also be considered as a key secondary endpoint"	
354-356		Comment: In our experience, inter-rater reliability kappas are not typically calculated or used to evaluate diagnostic precision. This would impose a significant additional burden on clinical trials, where investigators are typically qualified more generally through past training and experience. Similarly, while it is typical to train and assess investigators who will rate the severity of symptoms on a rating scale, kappas are not typically calculated. Further, this raises a series of questions about how this would be accomplished, and whether	

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		every sponsor would do this differently. More general language is needed for describing the assessment of investigators/raters. Proposed change: Change "Investigators should be properly trained in evaluating the patients. Inter-rater reliability scores (kappa) should be documented for each investigator in advance and if necessary during the study, both with regard to the diagnosis and to rating scales used for efficacy and safety, where relevant." To "Investigators should have documented experience and proper training to diagnose MDD, to rate depression symptom severity, and to assess adverse events."	
359-360		Comment: A pre-planned stratification may be too rigid and too hard to predict; rather, a post-hoc analysis of data should be recommended or even mandated in the event that a prespecified significant number of subjects are treated with adjunctive hypnotic medication during the initial portion of a trial. Proposed change: on line 359 replace "stratification" with "a post hoc analysis".	
374-375		Comment: The utility of examining sleep architecture across all potential antidepressants is uncertain. This should be a suggestion, rather than a recommendation. Proposed change: Change "Studies on cognition, reaction time or sleep architecture are recommended concerning the side effect pattern of the product." To "Studies on cognition, reaction time and sleep may be helpful to characterize safety	

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		profile of an antidepressant and should be considered based on pharmacological profile/MOA and evolving tolerability profile of the proposed product."	
398		Comment: According to the Guideline, "In the regulatory setting TRD is considered, when treatment with at least two different antidepressant agents prescribed in adequate dosages for adequate duration and with adequate affirmation of treatment adherence showed lack of clinically meaningful improvement." (Line 163-165) Under Section 4.4 Specific Claims, " at least one treatment failure should be prospectively shown." (Lines 398-399) Proposed change: Clarifications are needed for a definition of "fail to induce a clinically meaningful effect (non-response)" and/or "treatment failure" (Line 398) to sufficiently identify the treatment resistant patient population described under Section 4.4.1.	
400-408		Comment: The description of trials for TRD contains contradictions. An active comparator is recommended and requested, but a statement in line 408 then reads "…no active comparator can be recommended at present...". This leaves the reader having to speculate what the design recommendation is, thereby making comparison across trials difficult. Proposed change: Clarify this statement, possibly by	

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		specifying to what "comparator" is referring to in the different lines of this statement. Also, consider using defining optimized Standard of Care (SOC) and a comparator in TRD trials.	
410-417		Comment: The Guideline, under Section 4.4.2 "Trials to study augmentation/add-on treatment", states that "Augmentation will be useful in case of insufficient response to monotherapy. Therefore the patient population should consist only of partial responders; patients with TRD (who show no clinically meaningful change from baseline as result of treatment) are not suitable candidates for augmentation since there is no response to augment. Based on clinical treatment algorithms these patients should be switched to an alternative monotherapy instead and therefore should be excluded from augmentation trials" (see 4.4.2, Lines 412-417). Clarifications are needed to define "insufficient response to monotherapy" (Line 412) and "partial responders" (Line 413) to select the target patient population described under Section 4.4.2. A definition of "partial response" is not provided in the Guideline.	
414		Comment: Augmentation is deemed acceptable in populations with Partial Response (implied that these patients have demonstrated some clinically meaningful improvement), but not in TRD. Nonetheless, the available data do suggest that minimal or non-responders can indeed benefit from augmentation. For example, adjunctive aripiprazole was	

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		effective in both partial responders (≥25% but <50% improvement on the MADRS Total score during an 8 week prospective treatment phase) and minimal responders (<25% improvement on the MADRS Total score). Change scores on the MADRS Total score were −7.2 with aripiprazole and −5.4 with placebo in partial responders and −9.4 with aripiprazole and −6.0 with placebo in minimal responders (Thase ME, Trivedi MH, Swanink R, et al. Efficacy of adjunctive aripiprazole in major depressive disorder: a pooled subpopulation analysis (Studies CN138–139 and CN138–163). Presented at the Annual Meeting of the American College of Neuropsychopharmacology; Boca Raton, Florida, USA. 2007.) Proposed change: replace current statement (line 413-415) with "Therefore the patient population can consist of partial responders, non-responders and patients with TRD"	
419		Comment: Should clarify study design description. Proposed change: Change "patients are randomised" to "patients who have had a partial response to standard antidepressant therapy"	
420		Comment: The study design description should be clarified. Proposed change: Change "Trial duration of 4-6 weeks" to "A duration of 4-6 weeks for the randomized phase of the trial…"	
426-427		Comment: Recommendation is made to include an augmentation arm with an atypical antipsychotic as an active control. This places significant burden on the trial design and the trial which, in all practicality, would not be adequately	

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		powered to show a difference between the active and experimental groups. Recent studies have recruited approximately 800 subjects into prospective treatment to randomize sufficient numbers of patients into the randomization phase for two arms. Requiring a third arm would increase that to 1200 patients. Proposed change: "Therefore a third treatment arm with this atypical antipsychotic as active comparator can be considered for augmentation trials, but is not required."	
462		Comment: Please provide definitions of age ranges for children and adolescents	
476-477		Comment: Consider the addition of prior failure to respond to psychosocial intervention as a qualifier before entering a drug study, especially given for age ranges (young adolescents and children) in whom the benefit of psychopharmacological intervention is subject to debate. This would avoid unnecessary exposure of children and adolescents to drugs, and likely reduce the rate and magnitude of placebo response that is due to the concurrent psychosocial intervention. Proposed change: From "Throughout the trials all subjects should receive psychosocial interventions; this should be standardised if possible." to read: "Throughout the trials all subjects should receive psychosocial	

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		interventions; this should be standardised if possible. If this design is to be employed, subjects should have failed to show meaningful response to the psychosocial intervention (monotherapy) to be employed prior to entering a trial studying pharmacological intervention."	
511-512		Comment: The intent of the following should be stated clearer: "A detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim. Effects on cognition…" Adverse effects on cognition are usually assessed through collection of adverse events in the primary efficacy studies, and by objective behavioural (cognitive) testing in a separate study examining drug effects on cognition and motor behaviour. Adverse cognitive effects of antidepressants are not generally assessed with a "validated rating scale" and we are not aware of a specific scale validated for this use in an MDD population. In addition, the time over which effects on cognition should be observed should be specified (6 months, one year), and variables such as performance at school be discussed. Proposed change: Change "A detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim. Effects on cognition, reaction time, driving and severity of sedation should also be studied." To "Potential detrimental effects on cognition, reaction time, driving and severity of sedation	

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		should be characterized."	
517-522		Comment: Neither the InterSept Scale nor the Columbia-Suicide Severity Rating Scale have been shown to be reliable and validated in young children (<11 years of age) to date. This should be acknowledged and additional guidance offered, including the mentioning of other scales that may have similar validity as InterSept or the C-SSRS.	
531-532		Comment: Please specify the duration for which the effects on growth and sexual maturation should be evaluated, and elaborate on recommended techniques to study growth/failure to thrive.	
542-553		Comment: Additional definition is needed to clearly state whether the comments in this section refer to the study of an antipsychotic (dopamine D2 antagonist or partial agonist) as an antidepressant is meant here or not. Proposed change: Change "Therefore, if antipsychotics are used for augmentation or as treatment option in treatment resistant depressive patients rates of extrapyramidal symptoms should be presented." To "Therefore, if antipsychotics (e.g. dopamine D2 antagonists or partial agonists) are used for augmentation or as a treatment option in treatment resistant depressive patients, EPS should be fully characterized, including, primarily, presentation of rates of extrapyramidal symptoms."	
566-567		Comment: Clarify that dependence refers not only to physiologic dependence, but also to potential for abuse. Proposed change: change both occurrences of "dependence"	

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		to "potential for abuse or physical dependence".	
577-578		Comment: More specific information should be listed on the types of protocols and study designs that would be considered appropriate for the evaluation of long-term effects on learning, growth and development and sexual function. In addition, please elaborate on the acceptable minimal duration for the studies of long-term effects – in both children and in adolescents.	
608		Comment: This section could benefit from acknowledgement of differences between the DSM-IV-TR and ICD-10. As soon as these classifications are also likely to be updated with time, it would be useful to note the position of the Agency in case potential conflicts will arise with current Guidelines. Proposed change: Add the following language: "Agency acknowledges the fact that new classifications of mental disorders might be developed in the future and the Agency will provide additional clarification to sponsors on a case by case basis."	
		References: 1. Thase ME, Trivedi MH, Swanink R, et al. Efficacy of adjunctive aripiprazole in major depressive disorder: a pooled subpopulation analysis (Studies CN138-139 and CN138-163). Presented at the Annual Meeting of the American College of Neuropsychopharmacology; Boca Raton, Florida, USA. 2007	

Please add more rows if needed.