17 January 2013
EMA/CHMP/57220/2012
Committee for Medicinal Products for Human Use (CHMP)

# Overview of comments received on 'Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia' (EMA/CHMP/40072/2010 Rev.1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | H. Lundbeck A/S |
| 2 | Astra Zeneca |
| 3 | International Society for CNS Clinical Trials and Methodology |
| 4 | F.Hoffman-la Roche |
| 5 | Professor Alessandro Serretti, University of Bologna, Italy |
| 6 | EFPIA |
| 7 | Pfizer Inc. |

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# 1. General comments – overview

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
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| H. Lundbeck A/S | H. Lundbeck A/S welcomes the revision of the guideline on schizophrenia to take into account the scientific advances made over the recent years in this area. We appreciate the opportunity to review the draft guideline and provide comments.<br><br>The guideline discusses new areas for development within schizophrenia and thus introduces new opportunities for innovative treatments to address e.g. negative symptoms of schizophrenia, cognitive impairment, insufficient/inadequate response to treatment and treatment resistance.<br><br>There are, though, a number of issues for consideration that we are addressing below. | |
| 1 | Study design for long term trials<br><br>The guideline proposes under section 4.4.4 a number of different study design options to show maintenance of effect in schizophrenia. It is appreciated that the guidance allows such flexibility. There are though some issues in this section of the guidance that Lundbeck would encourage to be elaborated on.<br><br>The guidance proposes trial designs where patients are allocated to relatively long periods of placebo treatment. However, the use of placebo in schizophrenia is problematic from an ethical point of view, which is recognised by the guideline. And this is particularly true in the case of long term studies. Thus, alternative designs are warranted to address this issue while ensuring, to a satisfactory extent, the interpretability of the long-term data.<br><br>Also the guidance describes that in long-term, parallel-group trials using an active comparator, the assay sensitivity should be fully "substantiated". However, no guidance is given on how this can be | Comments acknowledged, no text amendments needed.<br><br>Maintenance of effect can be studied through 3 different designs where the 6 months RWD may offer the shortest duration of placebo exposure to the individual patient. It is left to the companies to make their own choice with respect to the proposed designs. |

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| | achieved. | |
| 1 | In this context, Lundbeck encourages the inclusion of additional designs of long-term trials where the maintenance of effect is supported by showing non-inferiority to an established treatment with the inclusion of a short-term placebo arm to provide assay sensitivity similar to the recommended design for registration trials for acute mania in the framework of bipolar disorder. Such an approach would help documenting assay sensitivity while alleviating ethical concerns of long-term placebo use in schizophrenia patients. | Referred is to the RWD for this purpose. |
| 1 | Another alternative long-term trial design without a placebo arm would be an active controlled relapse-prevention trial where the maintenance of effect is supported by showing non-inferiority to an active treatment. | Referred is to the RWD. |
| 1 | For these potential design options, guidance would be needed on the appropriate non-inferiority margin to be used. | Because of the difficulty in establishing the non-inferiority margin, the placebo control is recommended and preferred. |
| 1 | Patient population/segmentation<br><br>The guideline addresses in general the strategy for showing efficacy in the general schizophrenia population and some guidance for specific symptoms. However it seems that strategies for segmentation of the population that could be developed have no mention in the “4.4.3.2 Study population” section or elsewhere in the guideline.<br><br>Segmentation strategies (e.g. based on genomics, electrophysiology or symptomatology) could be useful in determining a segment of the population more likely to respond or less likely to have adverse events. Therefore the guideline should open the discussion for potential opportunities in this area. | Comments well taken and text adjusted where necessary.<br><br>In anticipation of DSM 5, no segmentation of patient populations has been foreseen. These will be probably dropped. For the use of biomarkers, see further. |
| | Also, the guideline recommends including at least 20% of patients | Data on the specific patient population provide insight in |

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| | with disease history of less than 5 years. However it is not clear whether this is a requirement and if so, it is not clear what would be the rationale for this proportion and how this would have to be implemented in practice on a development programme, i.e. whether the 20% proportion has to be implemented at a clinical programme level, at a clinical study level, or stratified within a study.<br><br>Based on previous approvals of medicines in schizophrenia, the general path appears to include a patient population enriched with severe symptomatology (so-called acute patients) for registration trials and address other segments (e.g. stable, non-acute patients) in separate trials. It would be problematic to stratify patients according to disease phases (acute, chronic) as generally accepted definitions and diagnostic tools to separate those do not exist.<br><br>The recommendation to include a pre-specified proportion of patients with a disease history of less than 5 years raises another issue that is how to define disease on-set. As with the different phases of the disease, a generally accepted, operationalized definition is lacking. | early treatment and e.g. disease progression to build experience for potential future claims. It is recommended to stratify in the main clinical studies and allow subgroup analysis (text amended).<br><br>Only a statement (ref) has been made with respect to symptom severity in acute/chronic patients and potential treatment effect. Inclusion of either population is up to the company. The definition is clarified towards, within 5 years after diagnosis. |
| 1 | Assessment tools<br><br>The necessity to use valid and reliable assessment tools is highlighted repeatedly in the guidance. It would be helpful to give a general opinion on what determines a valid and reliable assessment tool. | It appears unnecessary to explicitly mention validity and reliability requirements for instruments as they apply to regular methodological procedures/rules. Redundancy has been taken out of the text. |
| 1 | Depressive symptoms of schizophrenia<br><br>The guideline makes reference to development programs for treatment of depressive symptoms of schizophrenia (section 4.2). However, no further guidance on development directions or adequate study methodology on this item is given. | Text amended conform the section on negative symptoms. |
| 1 | Cognitive symptoms<br><br>While there seems to be a correlation between the level of cognitive capacity (performance on a cognitive test battery) and functional | It is considered irrelevant to develop products to improve cognitive function without clinical relevance for the patients in terms of improved functioning. The emphasis should be on the clinical relevance of the outcome for the patient. |

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| | capacity (performance on a functional test), the correlation between changes on these tests appears less robust. Also, linking improvement in cognitive capacity to improvement in real functioning needs further discussion. While there may be improvements in functional capacity, it is unrealistic to expect significant improvements in actual functioning within a time frame of 6 to 12 months. Therefore the requirement to linking cognitive improvement with functional improvement sets a high hurdle for drug candidates. We would welcome realistic and pragmatic guidance to demonstrate that the *"relevance to the patients functioning is clear."* | Unfortunately, no data are available to recommend either scale or instrument. The text in this section is amended in order to clarify the purpose of improved functioning. |
| 1 | Inadequate response/partial response<br><br>The guideline describes a patient group with "insufficient response" based on number of failures and specific symptom domains. However it only deals with this patient group in the framework of augmentation strategy (Section 4.5.4).<br><br>Although we acknowledge the interest in augmentation strategies, we would encourage inclusion of recommendations regarding monotherapy trials in this patient population. This group of patient is largely neglected as target for drug development although it is probably larger than the group of treatment resistant patients. | Whether monotherapy is the correct choice for a patient population with insufficient response to first treatment remains a point of controversy. Dose adjustments, checking on compliance, and switching to another product are still the treatment algorithm. Therefore is has been decided to make a distinction between treatment resistance (well defined) and augmentation therapy. No text amendment needed. |
| Astra Zeneca | The updated draft guidance is welcomed by AstraZeneca (AZ). In particular AZ welcomes the additional guidance that addresses the unmet medical need of a broader range of patients whose psychotic symptoms are not sufficiently controlled by current therapy (Section 4.5.3 Treatment Resistant Schizophrenia; 4.5.4 Pts with Insufficient Response)<br><br>However, AZ requests that the final version of the guideline reflects more closely the reality of clinical practice and current treatment guidelines. In particular, AZ requests that CHMP consider additional patient types and treatment options. | See earlier comment on the treatment insufficiency. |

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| 2 | In addition, AstraZeneca believes it is important to clarify the terminology used in the updated guidance to describe patients who are not sufficiently controlled by current therapy, and consistently apply this throughout – the terms 'treatment resistant', 'lack of satisfactory improvement', 'treatment failure', 'insufficient response', 'insufficient effect' and 'treatment refractory' have all been used within the draft guidance, with no clarity on how to reflect these terms in patient selection through inclusion and exclusion criteria. | Text clarified where considered necessary, in particular treatment failure is explained by insufficient response. |
| International Society for CNS Clinical Trials and Methodology | General comments:<br>1) The phrase "and to follow patients regardless of adherence to protocolled treatment" in Section 4.4.3.7 Statistical considerations, may be read to suggest advice for pragmatic (effectiveness) trials rather than explanatory (efficacy) trials. Our understanding is that this guidance is primarily or entirely intended to apply to explanatory (efficacy) trials, where there is a greater attention to ensuring drug compliance and more rigid experimental control over treatment procedures and the subject population to be included. We believe it is important to carefully distinguish between these general classes of trials in this guidance. We have provided suggested rewrites of lines 374-375 and 383-386 that incorporates both our views on handling missing data as well as distinguishing the class of trial under discussion. | Accepted, for details, see further. |
| 3 | 2) It would be helpful to have the guidance comment on the use of biomarkers to assess safety (for example metabolic safety biomarkers), efficacy, and rapid/slow CYP metabolizer effects with specific reference to schizophrenia, citing other guidance on biomarkers or pharmacogenetics as needed. | Acknowledged. Referred is to the section on Metabolic risk factors. |
| 3 | 3) Reference is made to clinical trial programs for the treatment of the depressive symptoms of schizophrenia (e.g. line 137, 232-233), but no further guidance pertaining to study design, adequate measures, or other methodological requirements are made within the document. Also, the distinction of the depressive symptoms of schizophrenia versus co-morbid affective disorders is not described or | Accepted. An additional section has been incorporated under 4.5. |

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| | defined. Guidance should be given for pursuing claims for the treatment of the depressive symptoms of schizophrenia.<br>Differentiation of depressive symptoms of schizophrenia or other affective disorders and co-morbid affective disorders should be made within the introduction and medical treatment sections of the document. | |
| 3 | 4) The notion of using valid and reliable measurement instruments appears repeatedly in the guidance. It would be very useful for the EMA to have a general guidance on how one determines whether a rating scale, cognitive test battery, or other measurement device is valid and reliable for a given use. That guidance could then be referenced in this and other disease specific guidances. | See earlier comment on the requirements for validity/reliability of instruments/scales. |
| Hoffman-la Roche | *The Company would like to share with the EMA additional comments not transmitted to EFPIA.*<br><br>The guideline should distinguish add-on therapy and combination therapy and better define the differences between these notions. Augmentation therapy suggests that new therapies are augmenting an existing effect provided by current antipsychotics. This is not the case when talking about negative symptoms as there is currently no treatment available for these. | Acknowledged. The text has been amended under 4.5.4. |
| 4 | The section should acknowledge new treatment approaches for patients who have previously responded to antipsychotic treatments (Partial responders or sub optimally controlled positive symptoms) but that may further benefit additional treatment as adjunct.<br>The guideline should better acknowledge that demonstration of effect on negative symptoms has to be demonstrated in an adjunct setting, but that eventually a claim in negative symptoms could be made also as monotherapy as these symptoms also exists in all phases of the disease. | See earlier comments on this issue of insufficient response. |
| 4 | The guideline should better acknowledge that demonstration of effect on negative symptoms has to be demonstrated in an adjunct setting, | Text amended under 4.5.1. |

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| | but that eventually a claim in negative symptoms could be made also as monotherapy as these symptoms also exists in all phases of the disease. | |
| Professor Alessandro Serretti | None | Not applicable. |
| EFPIA | EFPIA welcomes the opportunity to review the draft of the revised guidance on the clinical investigation of medicinal products in the treatment of schizophrenia, which represents an important update to the existing guideline – particularly in relation to the newer treatment paradigms, such as specific disease domains and augmentation therapy.<br><br>On a general level, though we think it is warranted to broaden the scope of the guideline even further to address, new non-dopaminergic compounds and other disorders with psychotic symptoms.<br><br>We would also welcome if the final guidance included further comment on the study of earlier (prodromal) stages of the disease. Disease modification in schizophrenia is an important potential area of study and it would be helpful to have greater clarity on acceptable prodromal criteria (e.g., cognitive impairment, social isolation, idiosyncratic thinking) for use in such studies.<br><br>Furthermore, we would welcome further guidance on strategies for segmentation of the overall schizophrenia population. Several companies are exploring such segmentation strategies (e.g. based on genomics, electrophysiology or symptomatology) with the aim of identifying a segment of the population more likely to respond or less likely to have adverse events. Therefore the guideline should open the discussion for potential opportunities in this area. | Points well taken. Referred is to earlier comments with regard to the incorporation of at least 20% of patients in the main clinical trials to get to understand treatment effects in an early stage of disease. There are insufficient data to support treatment of prodromal phases of the disease at this moment, and it is generally accepted to use DSM classifications for patient inclusion. Therefore prodromal stages or disease progression are beyond the scope of the current document, but may change with DSM 5.<br><br>See earlier comments. The use of biomarkers is mentioned under 4.3.1, and genetic markers included. |
| 6 | The current guidelines do not clearly state whether maintenance of | Accepted. The text is made more explicit. |

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| | effect has to be demonstrated for compounds seeking specific claims on negative symptoms and cognitive functioning. | |
| 6 | For compounds that are being developed for use in the general schizophrenic population where maintenance of effect has to be demonstrated, it is proposed that only shorter term studies are required to obtain a specific claim for negative symptoms and cognitive functioning. Studies evaluating the effect on negative symptoms and cognitive functioning tend to be of a longer duration (i.e. 12 to 24 weeks) than short term studies in a general schizophrenic patient population. In addition maintenance of effect for these specific claims could be supported by subgroup analyses in longer-term studies conducted in the general schizophrenic population. | Accepted. Goes along with the previous question. |
| 6 | For compounds that are being developed for specific claims such as negative symptoms or cognitive functioning and not as a general schizophrenia treatment, it is assumed maintenance of effect would need to be demonstrated in the specific patient population. As Ethic Committee's in Europe rarely allow long term placebo controlled studies to be conducted, it is proposed that maintenance of effect in these specific populations could be demonstrated within a 24 week, placebo-controlled study. | Accepted |
| 6 | Among EFPIA's members there were particularly consistent and significant comments on a few particular areas of the revised guideline. These comments are highlighted in general below and more specific comments are provided in the following section:<br><br>Placebo-Controlled studies: Given that Ethic Committee's in many EU countries do not accept the use of placebo in monotherapy schizophrenia trials, it remains a major challenge for Sponsors to conduct placebo-controlled schizophrenia studies in the EU. In contrast to what was stated in the Concept Paper on the need for revision of the schizophrenia guideline, the issue of 'Generalizability | Not accepted. No formal statement will be given in the guideline. It is emphasized that sufficient EU data should be present in the dossier. |

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| | of data with respect to potential cross cultural differences' is not included in the draft revised guideline. Although the guideline does attempt to address the issue of placebo-control, we would welcome further comment in the guideline about a) the scientific need for placebo-controlled studies, and more importantly, b) a statement on generalizability of data across geographic regions and acceptability of foreign data. Specifically, we would welcome an acceptance that data from well-designed and ethically conducted pivotal placebo-controlled studies can be obtained from outside the European Union and that this data can be extrapolated to the EU population. | |
| 6 | Patient Population: The guideline recommends including at least 20% of patients with disease history of less than 5 years. However it is not clear whether this is a requirement and if so, it is not clear what would be the rationale for this proportion and how this would have to be implemented in practice in a development programme, i.e. whether the 20% proportion has to be implemented at a clinical programme level, at a clinical study level, or stratified within a study. Based on previous approvals, the general path appears to include a patient population enriched with severe symptomatology (so-called acute patients) for registration trials and address other segments (e.g. stable, none-acute patients) in separate trials. However, it will be problematic to stratify patients according to disease phases (acute, chronic) as generally accepted definitions and diagnostic tools to separate those strata do not exist.<br>The recommendation to include a pre-specified proportion of patients with a disease history less than 5 years raises another issue, that is how to define disease on-set. As with the different phases of the disease, a generally accepted, operationalized definition is lacking. | See earlier comment. |
| 6 | Assessment of Cognition: Several companies have raised concerns regarding the apparent requirement to test cognitive function for the purpose of safety data collection. Documenting lack of adverse effects on cognitive function is possible on the basis of adverse event reporting or as part of the standard assessment scales, such as the PANSS, thus allowing this requirement to be conducted in a | Point well taken. It is left to the companies whether formal test batteries are used for safety assessment purposes. The guideline does not want to be too specific here. Claims on basis of the safety profile are not foreseen up front. |

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| | pragmatic way. However the guideline seems to ask for specific cognitive assessments to be added to all studies. If comprehensive batteries such as MATRICS (or MCCB) would be required to generate this data, or if detailed analyses by patient were required (i.e., “clinically relevant change”), even when there is no hypothesis of potential differences between treatment arms , this would mean a very substantial burden on the feasibility of running any studies in schizophrenia in the future. Hence we would recommend that the revised guideline provides a pragmatic way to generate the necessary data on cognitive function. Intensive assessment of cognitive functioning should be limited to cases in which there is a reasonable safety signal of cognitive worsening, or when there is an intention to study cognition specifically. | |
| 6 | Paediatrics: We endorse the CHMPs view that studies in children under the age of 13 are not necessary. Further we recommend conducting the adolescent trials only after efficacy is established in adults. However, it would be useful if guidance could be provided on the extent to which data could be extrapolated from adults to adolescents, if at all, e.g. due to the difficulties in conducting paediatric studies, it is often necessary to use smaller sample sizes and shorter studies. We would also welcome a comment on adolescent studies in different settings, e.g. monotherapy, augmentation, treatment of specific domains as the medical need may well be different from adults. E.g. while the effect of the new therapies may be studied on specific symptoms/domains in the adult program, the paediatric Clinical trials addressing combination therapies could be done in a partial responder population, irrespective of whether their symptoms are primarily positive, or negative in nature. | It is now stated in the guideline (4.6.1.) that extrapolation from adults to adolescents is possible for maintenance of effect data under certain circumstances as of 15 years of age. Further post-marketing long-term safety studies are recommended. Trials in adolescents are part of the PIP’s, and include in general the targeted indications for adults, except when explicitly stated otherwise by companies. In that case waivers may be granted by PDCO/CHMP. |
| 6 | Safety and Mechanism of action: The guideline provides strong recommendation on the need for monitoring and labeling of risks commonly associated with current antipsychotics, such as increased | No text amendment needed. The comment is reflected under the Safety evaluation 4.7, Special efforts etc., if relevant |

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| | prolactin, tardive dyskinesia's, neuroleptic malignant syndrome, and endocrinological adverse events. However, many companies commented that these risks are thought to be related to the dopaminergic effects of common antipsychotics, and hence, the guideline should acknowledge that intensive monitoring and certainly class labeling may not be appropriate for compounds with a different mechanism of action. | |
| 6 | Pseudo specificity and Specific claims: The draft guideline does not comment on how to address specific claims for negative, cognitive, nor affective symptoms with regards to managing pseudo specificity and the ethical problem posed by taking patients off of a treatment on which they are symptomatically stable. It would be helpful to have guidance on what type of study design would be acceptable to regulators to address specific domain effects in a monotherapy study. Options might include:<br><br>1. Switch design: Study patients who have stable positive symptoms with persistent, predominant symptoms in the domain of interest with a monotherapy<br>2. Re-randomized design: Stabilize acutely symptomatic patients with a design that has 2 stages, such as 6 weeks of treatment to a randomized assignment and then re-randomize responders based on predefined criteria to the active treatment or active control for an additional 6 weeks<br>3. Continuation design: Stabilize acutely symptomatic patients with a 2 stage design where patients who respond based on predefined criteria after 6 weeks continue on their original treatment assignment through 12 weeks and use the ratings at 6 weeks in responders in comparison to 12 weeks for the domain-specific comparison | It is beyond the scope of the guideline to explicitly state how claims should be obtained, whether true or in the domain of pseudo specificity. This is up to final assessment. The guideline neither wants to be too directive in recommending designs for the different claims. General strategies are provided, and it is up to the company's choice how to proceed in a given case, provided the steps taken are plausible and justified. The latter depends on the compound, the population, and the study objectives. No amendments needed. |

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| | 4. Acute design: Study patients with acute symptoms and look at domain-specific effects. | |
| Pfizer Inc. | The guideline should include mention of the nicotinic receptor as a target for the treatment of schizophrenia.<br><br>Additionally, the draft guideline does not comment on how to address specific claims for negative, cognitive, nor affective symptoms with regards to managing pseudo specificity and the ethical problem posed by taking patients off of a treatment on which they are symptomatically stable. It would be helpful to have guidance on what type of study design would be acceptable to regulators to address specific domain effects in a monotherapy. Options might include:<br><br>1. Switch design: Study patients who have stable positive symptoms with persistent, predominant symptoms in the domain of interest with a monotherapy<br>2. Re-randomized design: Stabilize acutely symptomatic patients with a design that has 2 stages, such as 6 weeks of treatment to a randomized assignment and then re-randomize responders based on predefined criteria to the active treatment or active control for an additional 6 weeks<br>3. Continuation design: Stabilize acutely symptomatic patients with a 2 stage design where patients who respond based on predefined criteria after 6 weeks continue on their original treatment assignment through 12 weeks and use the ratings at 6 weeks in responders in comparison to 12 weeks for the domain-specific comparison<br>4. Acute design: Study patients with acute symptoms and look at domain-specific effects<br><br>Further clarity is also requested regarding the use of an active comparator that is utilized in clinical practice but not approved by the EMA or a competent authority for use. To facilitate development in the EU and globally, we propose that comparator(s) should be | Partially accepted. The guideline mentions the target for cholinergic mediated products.<br><br>Not accepted. The guideline allows flexibility in the design. It is not the intention of the guideline to be too prescriptive. Guidance is provided for monotherapy and add-on trial designs.<br><br>Not accepted. Comparators are considered licensed products, or standard of care procedures, if relevant. The guideline does not have the intention to be too specific for reasons of differences in clinical programs across countries. |

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| | approved, or standard of care, or well defined in established treatment guidelines. | |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| Line 251 | 1 | Comment<br><br>The guideline states that for the assessment of negative symptoms, global assessment of negative symptoms (CGI) should be added. However, as the negative symptoms constitute an integrated subset of the entire complex of schizophrenia symptoms, it may be difficult and less meaningful to make a global assessment of these symptoms alone. | Accepted. Text amended. CGI should be used as secondary measure in all cases, not particular for negative/cognitive symptoms. |
| Line 264-269 | 1 | Comment:<br><br>The draft guideline states: “All pharmacodynamic interactions between the test drug and any other drug that may be prescribed simultaneously in clinical practice should be studied…”<br><br>Is seems unrealistic to require studying interaction with just “any drug” that could potentially be concomitantly prescribed in practice.<br><br>Reference is made to the current guideline, which recommends more realistically that: “Interaction with alcohol, other CNS active drugs and neuro-endocrinological parameters should be studies," which is consistent with other guidelines in the CNS area (e.g. guidelines on depression, GAD, OCD) | Accepted, text amended. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | Furthermore the proposed draft guideline recommends studying interaction with “active illicit substances”, which raises significant concern from an ethical point of view.<br><br>The guideline on drug interaction does not give further clarification on pharmacodynamic interaction as it states: “The interactions may be caused by a large variety of mechanisms. It is therefore not possible to give detailed guidance on pharmacodynamic interaction studies…" and later: "In general, the pharmacodynamic interaction profile of a drug can best be described by using both in vitro studies and in vivo human studies together".<br><br>Proposed change (if any):<br><br>Suggestion to change to “..any other **relevant** drug **class**….” | Accepted. Text deleted. |
| Line 267-268 | 1 | Comment:<br>The sentence on studies in hepatic and/or renal impairment is not about interactions and would rather fit into section 4.3.2 | Accepted. |
| Lines 296-306 | 1 | Comment<br><br>The trend the guideline describes is going towards focus on the use of active comparators as an integral part of the benefit risk evaluation of a new drug. It is recognised that the use of an active comparator provides benefit to both regulator and sponsor in terms on contextualisation of the treatment effect seen in studies and facilitating the interpretation of clinical | Acknowledged. The guideline will not specify the number of active comparator trials. This is left to the companies and dependent on robustness of data. |

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| | | results.<br><br>It is however recognised that this has a significant impact on the size of the studies conducted and the number of patients exposed to study medication. This in practice prolongs the duration of studies thus delaying patients' access to new treatments and overall cost of drug development. This also necessitates study sponsors to increase the number of clinical trial sites thus increasing the variability of the effect in studies and therefore have detrimental effect on the results of studies. Furthermore studies with multiple treatment arms are generally reported to yield higher placebo response rates due to the fact that patients, having less probability of being assigned to placebo, believe they are treated with active treatment which is a relevant factor increasing placebo response in psychiatric diseases.<br><br>Therefore it may be highly informative in a development programme to have studies that focus uniquely on "absolute effect" of the test drug as compared to placebo, i.e. two-arm, placebo controlled studies. This design optimises the variability conditions (limited clinical sites) and the placebo response factor.<br><br>Proposed change (if any):<br>It is proposed that the guideline specifies a minimal requirement of the number of confirmatory studies that include an active comparator, e.g. "at least one confirmatory trial should include an active comparator." | |

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| Lines 305-306 | 1 | Comment:<br><br>The guideline recommends that "alternatively, a two-arm study of test and active comparator would be acceptable provided superiority of the test product over an appropriately justified active comparator was demonstrated."<br><br>It would be helpful if clarification is provided on the implications on product information if the superiority to an active comparator is demonstrated. Would this warrant a "superiority label claim"? | Not accepted. An additional claim is not foreseen, since merely simple methodological rules to demonstrate efficacy are applicable (superiority or non-inferiority). |
| Line 307 and study population: | 1 | Comment:<br><br>Recommendation on potential segmentation strategies for patient population (e.g. based on genomics, electrophysiology or symptomatology) could be useful in determining a segment of the population more likely to respond or less likely to have adverse events (See general comments section). | Not accepted. A segmentation strategy is not foreseen because of the change in DSM5. The use of genomics as biomarker is incorporated under 4.3. |
| Line 359 | 1 | Comment:<br>“End measurement” may be interpreted in different ways when considering early patient withdrawal from study. To avoid misunderstanding the guideline should elaborate further on this or include a reference to section 4.4.3.7 | Accepted, text amended. |
| Line 364-366 | 1 | Comment:<br><br>The draft guideline introduces 30% reduction on the total PANSS compared to baseline as a generally | Accepted. A more flexible approach is taken, and the text amended. |

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| | | clinically relevant definition of response.<br><br>However no consensus is reached yet as to what response rate is considered clinically relevant and a range of values, from 20% up to 50%, are used in the literature. Furthermore the clinical relevance of the percentage reduction may depend on baseline characteristics and severity of the patients, e.g. 20% reduction in chronic patients may be considered clinically relevant.<br><br>The guideline should allow for flexibility in this area and take a case by case approach based on adequate justification of the choice of the response definition. | |
| Line 397-401 | 1 | Comment:<br><br>The guideline provides different scenarios for long-term studies: “A parallel trial using active comparator is the first possibility. When the objective is to show non-inferiority, the active control should be a product with a well documented efficacy in the maintenance of treatment effect in schizophrenia. Due to the natural course of the disease, the duration of such a trial should be 12 months and the assay sensitivity should be fully substantiated.”<br><br>It would be helpful to have clarification on how to assure assay sensitivity in the proposed design, without using placebo. Reference is also made to general comments section of this document that includes potential alternative designs. | See response to earlier comments in the general comments section. |

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| Line 399-400 | 1 | Comment:<br><br>The guidance states that an appropriate active control, in the case of a parallel trial design, should be a product with a “well documented efficacy in the maintenance of treatment effect in schizophrenia”. However, it is not clear what actually constitutes a “well documented efficacy in the maintenance of treatment effect in schizophrenia”. | Accepted, text amended. |
| Line 423-424 | 1 | Comment:<br><br>The guideline states: “In parallel and randomised withdrawal studies, the proportion of patients with exacerbations at pre-specified time points should be analysed”. However, this cannot be done in a meaningful way as patients with exacerbations are withdrawn from treatment.<br><br>It would be useful the have this issue elaborated on. | Not accepted. There should be regular assessment of proportion of patients with exacerbations. |
| Line 425-426 | 1 | Comment:<br><br>The draft guideline states that: “In some cases, if the dose-response data from short term trials is insufficient, dose finding for long-term treatment using multiple doses of the investigational product may be required."<br><br>It is not clear in which cases such approach may be warranted as generally dose-response data is | Accepted, and text amended, i.e. deleted. Dose finding, if inappropriate is up to the company’s risk. |

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| | | generated in short term trials. Long-term trials of multiple doses would increase the burden for drug development as well as the unnecessary exposure of patients to investigational drugs.<br><br>It should also be noted that there are no substantial evidence to support that there is a difference between effective doses in long-term as compared to those in short-term trials. | |
| Line 444-445 | 1 | Comment:<br><br>It is stated that “responder rates should be provided as well, and functional improvement as key secondary outcome is recommended”. It is unclear what is meant by “key secondary outcome” and whether both responder rates and functional improvement should be included as key secondary outcomes. | Accepted. Text amended for clarification. For a claim on negative symptoms, the clinical relevance should be clear. This should be expressed in (pre-defined) responder rates and improved functioning, both as the main secondary outcome measures. |
| Line 446-455 | 1 | Comment:<br><br>We would suggest to re-title this section as “Efficacy on cognitive impairment” to better reflect the content.<br><br>In addition, we would welcome some clarification of the section and provision of definitions of terms used, e.g. what is meant by “cognitive functioning”; what is a “relatively younger patient population”; what would be “the cognitive functioning scale”; how should “relevance to patient functioning” be investigated. | Partially accepted, text structured for clarity, and amended accepting the MATRICS battery and others. |
| 449-451 | 1 | Comment: | Inconclusive. Without sufficient data to refer to, these comments can not be solved at the time of drafting the |

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| | | As regards, the adequate patient population to be included in studies to demonstrate effect on cognition, it is accepted that a younger population may show better response to a pro-cognitive drug. However, it would be useful to have clarification about the impact on subsequent product information claims, e.g. would evidence generated in such a younger population be generalised to claim efficacy on “cognitive symptoms of schizophrenia”? | guideline. |
| 454-455 | 1 | Comment:<br><br>It needs to be acknowledged that the link between cognitive improvement and actual improvement of functioning is generally loose with functional improvement needing longer duration - reference is made to our comment in “general comments” section. Therefore the requirement to linking cognitive improvement with functional improvement sets a high hurdle for drug candidates.<br><br>We would welcome realistic and pragmatic guidance to demonstrate that the *“relevance to the patients functioning is clear.”* | Accepted. See also earlier response to the same topic. Emphasis is put on the clinical relevance of the observed effect. |
| Line 516 - 541 | 1 | Comment:<br><br>As it is more difficult to find and recruit the younger patients (i.e. below 15), the stratification is acceptable providing no minimal requirement are made.<br><br>As regards the duration of short term studies, the draft guideline mentions that 4-6 weeks (or longer) are | Not accepted. Both age ranges are expected in sufficient numbers to allow benefit/risk and safety evaluation.<br><br>Not accepted. The guideline provides guidance for studies with 4-6 weeks duration dependent on the mode of action of the product and the expected stability of effect. It is therefore |

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| | | required. It would be useful to provide clarification as to why studies longer than 4 weeks in adolescents would be needed. | up to the companies' choice which strategy is chosen in a particular patient population. |
| Line 594-599 | 1 | Comment:<br><br>As regards the evaluation of suicide from a safety perspective, it would be useful that the guideline clarifies to which extent this assessment has to be done, e.g. phase I trials included?<br><br>Additionally, reduction of the number of suicide attempts and the incidence of suicidal ideation should be considered as a valid target for drug development, and as such should be dealt with in the guideline. | Accepted, text amended accordingly.<br><br>Not accepted. In general suicidal patients are excluded from participation in clinical trials. Therefore, the reduction of suicidality can not be an objective, but only part of overall treatment of symptoms. |
| Lines 349 – 356<br>Lines 466 - 471 | 2 | Comment:<br>Section 4.4.3.5 – Screening and Run-In Periods<br>Section 4.5.3 - Trials to study monotherapy in treatment resistant patients<br><br>CHMP are asked to provide greater guidance on studying patients with severe symptomology that have shown a lack of satisfactory improvement to previous treatments – either in a monotherapy or adjunctive treatment setting:<br><br>AZ believes there is a group of patients that remain severely and persistently symptomatic despite failing multiple previous treatments but for whom withdrawal of all current medication is not clinically appropriate or safe. Such patients can abruptly deteriorate even further when medications are removed, even though | Partially accepted. See also response to earlier comments related to this topic. Because of lack of data severity of symptoms has not been defined/specified as in/exclusion criteria. However, the number of treatment failures offers the possibility to treat these difficulty to treat/treatment resistant |

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| | | they may be minimally effective or only helpful in managing symptoms (i.e. sedating) or a subset of symptoms i.e. positive/negative<br><br>The clinical management of these patients presents a significant challenge both in the real-world and in a clinical trial setting given their fragile state and the complexities of their clinical management. The majority of these patients will have been on multiple adjunctive treatments long-term and neither they nor their physician will feel able to remove these medications safely (Zink et al (2010) *Current Opinion in Psychiatry*, 23: 103-111; Wolff-Menzler wt al. (2010) *Pharmacopsychiatry,* 43: 122-129)<br><br>Section 4.4.3.5 of this draft guideline suggests that for severely ill patients screening, baseline assessment, randomisation and study drug start could all be achieved in a single day. This seems unrealistic for most of these patients who will be on multiple medications and require a period of withdrawal greater than one day.<br><br>In addition, Section 4.5.3 states that if TRS is being studied, then at least one treatment failure should be prospectively shown. However, AZ considers that for severely ill TRS patients, prospective demonstration of treatment failure is not possible for the reasons outlined above. Moreover, prospective demonstration of treatment failure would require a switch to a monotherapy treatment for 4-6 weeks that, in all likelihood, the patient has had no previous response to. Given the level of symptomatology in this severely | patients in either a mono- or add-on therapy setting.<br><br>Accepted. A flexible approach is taken, and the text amended for clarity.<br><br>Not accepted. Treatment resistance and refractory are defined such that treatment failure can be ascertained in the trial design to support the target patient population. |

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| | | ill population, this approach seems both unethical and not feasible.<br><br>Indeed, this is reflected in AZ study feasibility work and feedback from psychiatrists and patients which indicate adequate recruitment of this type of severely ill patient into a prospectively designed trial will be very challenging. This in turn raises the risk that findings from any such study will be biased and not generalizable to the larger population of severely ill patients who are treatment resistant.<br><br>Proposed change (if any):<br><br>AZ therefore seeks more guidance from CHMP on studying a severely ill patient population. In particular:<br>• To consider accepting retrospective assessment of previous treatment failure in certain challenging patient populations e.g. the severely symptomatic TRS – perhaps with a requirement for additional consultation with CHMP Sci Advice Working Party<br>OR<br>• To provide greater detail regarding successful recruitment and management of a severely ill patient population in a prospectively designed clinical trial | See response given above. This proposal is beyond the responsibility of regulatory guidance. |
| Lines 412 - 426 | 2 | Comment:<br><br>Section 4.4.4.1. Efficacy parameters in long term studies | |

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| | | CHMP are asked to provide greater clarity on:<br><br>• Time points for analyzing pre-specified endpoints in RWS (e.g. 1, 3, 6, 9 months)<br><br>• Circumstances in which dose finding would need to be extended into a long term study: clarify what constitutes insufficient dose finding information in short term trials e.g. lack of a dose response relationship? or a lack of establishing a minimal effective dose? | Accepted. Text amended.<br><br>See earlier response. Text deleted. |
| Lines 456 - 481 | 2 | Comment:<br><br>**Section 4.5.3 Trials to study monotherapy in treatment resistant patients**<br><br>The draft guidance defines treatment resistance in schizophrenia as a "lack of satisfactory improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration with adequate affirmation of treatment adherence and abstinence from CNS-active illicit drugs". This appears to be based on a definition used in the historic clozapine trials.<br><br>Guidance is needed from CHMP on what is meant by "lack of satisfactory improvement". Further on in this section, the guidance refers to at least one "treatment failure" being prospectively shown, which implies that by "lack of satisfactory improvement", CHMP mean treatment failure, however failure is not defined. In the field of depression, where there has been much debate | Not accepted. See also earlier response to this issue. There are no data to refer to a generally accepted pre-defined patient population. Therefore, dependent on the objective of studies, treatment failure, which is considered insufficient response should be defined on a case by case basis. A flexible approach should be taken in accordance with the flexible approach with regard to responder definition.<br><br>For the guideline the algorithm for clinical treatment of schizophrenia is taken as starting point. |

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| | | on this topic, clinical trials have employed definitions such as 0-24% improvement from baseline on rating scales for 'no response' / 'treatment failure' and 25-49% improvement for 'partial response'. These cut offs are however considered arbitrary and not reflective of clinical practice. A prescriber would not assign a % improvement to a patient in order to make a treatment decision, they would instead consider whether the patient has experienced adequate or inadequate response, adjusting their treatment accordingly. It's also important to note that tolerability or compliance could drive a decision to switch treatment, even in the presence of some, but inadequate, response. AstraZeneca therefore believe that a monotherapy treatment switch should not only be an option after "treatment failure" or in "treatment resistant patients", but should be an option in the event of any level of inadequate response to prior treatment. This then enables prescribers to individualize treatment without there being an arbitrary cut off for when monotherapy becomes an option.<br><br>In addition, the guidance in this section provides for patients who require an alternative treatment option after receiving two or more different agents. There is however a need for treatment options that are licensed for use in patients who have experienced inadequate response to first-line therapy only. The definition of TRS provided by CHMP in this draft guidance acknowledges that patients must first cycle through initial treatment, with subsequent failure on second line therapy, however no guidance is given on the former situation. | |

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| | | Proposed change (if any):<br><br>AZ therefore seeks guidance on how to study a drug as monotherapy in patients with inadequate response to only one antipsychotic agent, in addition to the updated draft guidance for patients who have received at least two different agents and proposes that CHMP consider modifying the guidance so that:<br>• Section 4.5.3 addresses 'trials to study monotherapy in patients with inadequate response to treatment'<br>• Section 4.5.3 should provide guidance on appropriate study designs to assess efficacy and safety in this population from second line treatment onwards, with TRS being one element of this treatment path. | |
| Lines 482 - 513 | 2 | Comment:<br><br>**4.5.4 Trials to study augmentation / add-on treatment**<br><br>This section of the draft updated guidance refers to augmentation in patients with "insufficient response" and states that patients should not be considered for augmentation/add on therapy when there has been "no change" from baseline as a result of treatment. Guidance is needed from CHMP on what is meant by "insufficient response" and "no change", especially as further on in this section the guidance refers to defining the population in terms of number of "failures".<br>In clinical practice, it is considered rare that a patient | See earlier comment. The text is structured in term of proper definitions. |

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| | | would experience no change (0% response) across any domain following treatment. As stated above, clinical trials in the field of depression have employed definitions such as 0-24% improvement from baseline on rating scales for 'no response' and 25-49% improvement for 'partial response'. These cut offs are however considered arbitrary. In clinical practice, irrespective of the level of response to treatment, if the initial drug is being tolerated, prescribers may opt to augment a patient's treatment due to the potential for synergistic effect, or to provide a longer duration on the background treatment to attempt to elicit a response. AstraZeneca therefore believe that augmentation/add on treatment should be an option in the event of any level of inadequate response to prior treatment.<br>It is noted that the current UK NICE guidance for treatment of schizophrenia acknowledges add-on strategies where there is lack of effective response to antipsychotics alone, however it does not explicitly restrict add-on use based on the level of response to initial treatment.<br><br>Proposed change (if any):<br><br>AstraZeneca therefore propose that CHMP consider modifying the guidance so that:<br>3. Section 4.5.4 addresses 'trials to study augmentation / add on treatment in patients with inadequate response to treatment'<br>4. Section 4.5.4 should provide guidance on appropriate study designs to assess efficacy and safety in this population from second line treatment onwards, | |

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| | | including TRS as one element of this treatment path | |
| 116 | 3 | Comment: Schizophrenia co-morbidities also include autism spectrum disorders. We suggest including this in the list of comorbidities and in the differential diagnosis.<br>Proposed change:<br>Add to line 116: “Schizophrenia may be comorbid with, and require differential diagnosis from, autism spectrum disorders. | Not accepted. The most common co-morbidities are mentioned in the text. |
| 122 | 3 | Comment: A deterioration in functioning is often associated with the schizophrenia prodrome in adolescence.<br>Proposed change:<br>Insert sentence in line 122: “A deterioration in functioning is often associated with the schizophrenia prodrome.” | Accepted. Text amended. |
| 229-237 | 3 | Comment:<br>Here we believe you are trying to make a distinction between symptoms that are a part of the schizophrenia syndrome, and symptoms due to other causes, as well as the need to assess for cognitive worsening due to drug. We suggest language to clarify this.<br>Proposed change: Suggest changing lines 229-233 to read: Depressive symptoms occurring in schizophrenia patients may be a part of the schizophrenia syndrome. However, they may also represent a pre-existing or co-morbid depressive disorder, or may be caused by treatment. In order to support an indication for the treatment of depressive symptoms of schizophrenia, a treatment effect should be shown on depressive symptoms that are clearly a part of the schizophrenia syndrome, rather than depressive symptoms that are due to some other cause. If a | Accepted, but any reference to depression is deleted from the guideline.<br><br>Accepted, changed in the text. |

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| | | treatment is thought to worsen or cause depressive symptoms, this effect should be characterized.<br><br>Proposed change: Rewrite lines 234-237 as follows: Likewise, cognitive deficits in schizophrenic patients may be a part of the schizophrenia syndrome that are present chronically, or may be due to other causes such as transient exacerbations of acute psychotic symptoms, medications (especially anticholinergic agents), depression, or under stimulation of the patient (as a result of hospitalization). In order to support an indication for the treatment of cognitive symptoms of schizophrenia, a treatment effect should be shown on cognitive symptom that are clearly a core part of the syndrome of schizophrenia. The effect of treatment on cognitive function should be documented even if no specific indication is sought, for the purpose of characterizing the safety of the drug product. | |
| 251 | 3 | Comment: While they are commonly used, both the SANS and the PANNS negative symptom subscale have significant limitations. The PANNS does not cover a number of symptoms commonly identified as part of the domain of negative symptoms, such as decreased motivation/interests and diminished speech/communication (Alphs et. al. Psychiatry 2010, 7(7): 26-32).The item content if the SANS, for example, does not entirely match current concepts of core anhedonia symptoms, and the scale is frequently modified by academic experts for use in negative symptom clinical trials, often by removing the Attention subscale (see Freedman et.al., Am J Psychiatry, 2008, 165:1040- 1047, or Goff et. al. Schiz. Res. 2008, 106(2-3):320-327, as examples). Individual items and subscales of the SANS have | Accepted, text amended. Development of new scales is encouraged. |

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| | | anchoring and construct problems (Kirkpatrick et.al. Schiz. Bull. 2011, 37(2):300-305). SANS Anhedonia/Asociality subscale ratings, for example, have been criticized as comprising several potentially separate constructs, or possibly reflecting a social performance deficit, rather than describing a fundamental hedonic deficit (Horan et. Al. Schizophrenia Bulletin, 2006, 32(2): 259-273.) Efforts are underway to improve the assessment of negative symptoms in schizophrenia (Kirkpatrick et.al. Schiz. Bull. 2011, 37(2):300-305; and Alphs et. al. Psychiatry 2010, 7(7): 26-32.) For the five factor model of the PANNS, see Marder,S. et. al. J. Clin. Psych. 1997, 58:538-546.<br><br>Proposed change to lines 249-251: Change "Satisfactory reliability and validity has been demonstrated for the negative symptom subscale of the PANNS and for SANS (Scale for the Assessment of Negative Symptoms)." To "While commonly used to assess negative symptoms, the negative symptom subscale of the PANNS and the SANS (Scale for the Assessment of Negative Symptoms) have significant limitations. Other scales to assess negative symptoms, such as the negative symptom factor derived from the five-factor model of the PANNS , or scales currently under development, may be acceptable." | |
| 253 | 3 | Comment: Mention is made of the use of validated scales for the assessment of cognitive symptoms and depressive symptoms, but no examples of such scales are provided nor methodology for validation is described. Further, there is no comment on the potential appropriateness or preference for instruments to measure depressive symptoms that are specific to schizophrenia patients versus those used in | Partially accepted. The reference to the MATRIC test battery has been made. However, it was decided to delete claims for depressive symptoms in schizophrenia, because of potential interference with negative symptoms and the complexity of being primary or secondary. Therefore, all references regarding depression are deleted form the final guideline. |

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| | | studies of MDD. The ISCTM believes that the Calgary Depression Scale (CDS) is acceptable to use for the assessment of depressive symptoms in schizophrenia (Addington et. al. Schiz. Res. 1992, 6:201-208; Lacon et. al. J. Affective Disord., 2000, 58:107-115). Other depression rating scales may also be acceptable. With respect to cognitive symptoms, a years-long collaboration between academia, industry, and the U.S. government produced the MATRICS Consensus Cognitive Battery (MCCB) for the assessment of cognitive symptoms in schizophrenia (see Kern et. al. Schiz. Res. 2011, 126(1-3):124-131; Keefe et. al. Schiz. Res. 2011, 125 (2-3):161-8 for recent data). The ISCTM believes that the MCCB is an acceptable battery to use to assess cognitive symptoms in schizophrenia. Other cognitive batteries could also be acceptable.<br><br>Proposed change:<br>Add to line 253: “The assessment of cognitive symptoms in schizophrenia is an area of active research. Currently, the MATRICS Consensus Cognitive Battery (MCCB) is acceptable for use in the assessment of cognitive symptoms in schizophrenia. Other cognitive batteries may also prove to be acceptable. Less research has focused on the measurement of depressive symptoms in schizophrenia. While the Calgary Depression Scale(CDS) is acceptable for use in the measurement of depressive symptoms in schizophrenia, more research is needed in this area, and other rating scales may also be acceptable.” | |
| 210 and 329 | 3 | Comment: The term “classical antipsychotics” should be refined to reference pharmacological properties or other distinction (typical/atypical; first/second generation) that would encompass these agents | Accepted. Text amended |

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| | | Proposed change lines 210 and 329: Change the phrase “classical antipsychotics” to “first and second generation antipsychotics”. | |
| 226 | 3 | Comment: In line 226, the term “main symptoms” of schizophrenia should be clarified.<br><br>Proposed change (if any): Change “efficacy on main symptoms has to be demonstrated…” to “efficacy on a broad range of schizophrenia symptoms, as captured by the total score on instruments such as the PANNS or BPRS, has to be demonstrated…” | Accepted. Text amended. |
| 246 | 3 | Comment: There are strengths and weaknesses to the CGI-severity versus the CGI-improvement scales. To alert the reader to this, we suggest the following change.<br><br>Proposed change: Add sentence after line 246: Careful consideration should<br>be given as to whether to include the CGI-severity scale, the CGI improvement scale, or both scales. | Not accepted. Both scales provide different information and should be used. |
| 283-285 | 3 | Comment: It is not clear whether the statement on the lack of suitability of flexible dose designs for determining dose-response relationships refers to short term trials, long-term maintenance trials, or both. This should be clarified. Typically, maintenance trials are not launched until phase 3, with dose in these long and expensive trials being determined using dose response information from the shorter-term (usually 6-week) trials. We believe this is appropriate.<br><br>Proposed change: Prior to the sentence starting “It is strongly…”, insert the following into line 285: “Dose response is typically established in short-term studies, and this information serves as a basis for dose selection in both additional short-term phase 3 studies | Accepted. Text amended. |

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| | | and the longer term maintenance study." | |
| 320-325 | 3 | Comment: In Section 4.4.3.2 Study population, lines 320-325 allude to the important issue that the efficacy and safety of a medication for treatment of schizophrenia may differ in recently diagnosed (last 5 years) vs. more chronic patients. We believe this is meant to distinguish between recently diagnosed (<5 years ago), acutely psychotic patients and acutely psychotic patients diagnosed >5yrs ago. The 5 year cut point, while sometimes used, is to our knowledge not supported, relative to other time points, by any specific data. We do agree that response to antipsychotic medication may vary with duration of illness. We believe, however, that stratification is not appropriate, as no particular cut-off for duration can be prospectively chosen for the variety of mechanisms of new antipsychotics that might be tested. Stratification may also obscure information that could be obtained by comparison to historical trials. Finally, stratification would unduly lengthen the time to complete these trials. We believe that a subgroup or other posthoc analysis is appropriate, and that depending on results of this type of analysis, additional work could be appropriate.<br><br>Proposed change: We suggest the following rewrite of lines 320-325: "In studies of acutely psychotic schizophrenic subjects, some subjects will have been relatively recently diagnosed with schizophrenia and others will have been diagnosed at some more distant time. It is possible that the efficacy and safety of a medication for the treatment of schizophrenia will differ, depending on the length of time since diagnosis.. Therefore, it is recommended that the subjects included in studies of the acute exacerbation of schizophrenia span a range of durations since first | Not accepted. From a clinical perspective it is recommended to be more specific with the cut off point to build data for future guidance. |

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| | | diagnosis of schizophrenia in order to allow for subgroup or other analyses. The inclusion criteria…" | |
| 338-341 | 3 | Comment: The ISCTM believes that pre-registration clinical trials should focus first on clarifying the safety and efficacy of the test drug, with the design providing for clear signal detection, and secondarily on generalizability, which is also clearly important. Thus, we suggest that the emphasis of lines 338-341 should be shifted to reflect this. Regarding benzodiazepine use in trials of acutely exacerbated schizophrenia, it would not be possible to require a "stable dose regimen for some time before starting the trial." We suggest the following rewrite of lines 338-341.<br><br>Proposed change: Co-medications, for example benzodiazepines, should be permitted to the extent that they do not compromise detecting signals of safety and efficacy of the drug candidate. In the interest of generalizability, a rationale for excluding concomitant medications should be provided. It also may be appropriate for the sponsor to place limits on the amount of use of benzodiazepines within a study. | Accepted. A compromise text is incorporated. |
| 366-368 | 3 | Comment: It would be helpful to give a suggestion for alternative criteria for response rates for the sensitivity analyses (lines 366-368).This could be alternative cut points on a broad measure of the symptoms of schizophrenia (e.g., PANSS or BPRS), other presentations of these data, or improvement as measured by an instrument using a single measure of overall symptomatology (CGI-Improvement).<br>Proposed change: Add at end of line 368: " The CGI-I (subjects who are much or very much improved), or alternative measures, or alternative cut points on the PANNS total could be used for this purpose." | Not accepted. The text allows for a flexible approach and does not need to be more prescriptive. |
| 369-390 | 3 | Comment: A slight modification to line 370 is | Accepted. Text amended |

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| | | suggested for clarity.<br>Proposed change: Change line 370 to- “For more complete guidance on statistical principles for clinical trials, please refer to ICH E9 statistical principles for clinical trials.”<br><br>Comment: Line 371-372: The sentence starting “The standard three way trial design…” is unclear.<br>Proposed change: Replace the sentence on line 371-372 with “The standard randomized placebo and active-controlled, parallel group trial design is intended to show superiority of the drug candidate to placebo and to quantify efficacy of the drug candidate compared to a drug known to be effective for the treatment of schizophrenia.”<br><br>Comment: Line 374-5. As stated in our first general comment, we believe the guidance is intended for explanatory (efficacy) trials. The suggested change below clarifies the purpose of following patients regardless of protocol adherence in an explanatory (efficacy) trial.<br>Suggested change: Change …”and to follow patients regardless of adherence to protocolled treatment.” To “…and to follow patients regardless of adherence to protocolled treatment to better understand the impact of missing data.”<br><br>Comment: Lines 382-386—The ISCTM believes that some commonly used analysis techniques and methods for handling missing data sometimes bias results in favour of experimental treatments, sometimes bias results against experimental treatments, and sometimes do neither. Further, sensitivity analyses are important for understanding the robustness of the findings. We suggest the | Accepted. Text amended.<br><br>Accepted. Text amended. |

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| | | following change— Proposed change: Replace lines 382-386 with the following: “Some of the commonly used analysis techniques, such as LOCF and BOCF approaches, have the potential to introduce bias. While easy to implement, these methods have a number of limitations, including over-estimation or under-estimation of treatment effects (and the associated variance) and inconsistency with the course of disease. Sensitivity analyses that evaluate missingness assumptions should be performed to assess the robustness of findings. All of the aforementioned analyses should be prespecified in the protocol. Since the statistical findings might be interpretable in the presence of high dropout rates, the dropout rates in a trial need to be considered when interpreting the efficacy findings.”<br><br>Comment: Line 390: The ISCTM believes that secondary endpoints are necessary to fully characterize the efficacy of treatments for schizophrenia. Further, we believe that presentation of secondary endpoints in the prescribing information, when they have been pre-specified and there has been appropriate control for Type I error, is justified and can provide important information for physicians.<br><br>Proposed change: Add the following sentence at end of line 390: “Prospectively identified secondary endpoints with adequate control for Type I error will be considered for inclusion in the prescribing information on a case by case basis.” | Accepted. Text amended<br><br>Not accepted. The guideline refers to ICH E9 for specific points regarding endpoints. |
| 391-426 | 3 | Comment: The ISCTM appreciates that the EMA allows flexibility in the design of longer term efficacy studies in schizophrenia. Each of the designs presented will address a somewhat different question regarding | Not accepted. It is part of EU regulation that maintenance of effect is demonstrated pre-licencing. |

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| | | maintenance of effect. The long term randomized, parallel group design versus an active control, for example, demonstrates that in the same population where the drug works acutely, it also works over a more extended time. The randomized withdrawal design, demonstrates that, for those stabilized on the medicine, whether there is value in continuing it for a longer time. Depending on the drug candidate, the information derived from one design may be more important than that derived from another. In practice, it is the experience of the ISCTM membership that the FDA expects that a randomized withdrawal design will be used. For the sake of efficiency, it would be helpful for the EMA and FDA to have aligned expectations regarding the study designs for demonstration of maintenance of effect. Further, it would be helpful for the EMA to provide guidance on when, relative to submission of the regulatory package for marketing approval, the EMA expects to have results from the maintenance trial available. It has been the experience of the ISCTM membership that, while it has been acceptable to provide these data to the FDA in the U.S. as a post-approval commitment, they have been required at the time of submission of the marketing application in Europe. We understand that there may be many valid reasons for this difference. We would like to point out that, because these maintenance trials are generally not initiated until well into phase 3 when there is substantial knowledge of the dose response from short term trials, and because maintenance trials require a long time to complete, the net effect is that new medications for the treatment of schizophrenia are likely to appear sooner in the U.S. than in Europe. Where the new medication has a novel mechanism of action or shows evidence of substantial novel benefit to patients, it may be beneficial to patients for the EMA | |

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| | | to align with the U.S. on the required timing for providing maintenance data. With these comments in mind, we propose the following changes to this section--<br>Proposed change: Insert after line 411: “Any of the above designs may be most appropriate for demonstrating maintenance of effect, depending on the particular drug candidate. In general, randomized withdrawal designs are preferred. Data from the maintenance of effect study are generally expected to be provided along with other data in the initial marketing application.<br>However, there may infrequently be circumstances, such as when the expected benefit of the new treatment is large relative to currently marketed products, that these data could be provided at some later time point, if agreed to in advance.” | |
| 398-399 | 3 | Comment: More guidance on non-inferiority margins would be useful. ISCTM member experience has been that these are discussed individually for each development program. That may be appropriate given variability in specific study designs or drug candidates. However, if the EMA has a standard expectation that it repeatedly requires about how non-inferiority margins should be set in long term, active comparator schizophrenia trials, it would be useful to provide that guidance to drug developers. In any case, the noninferiority margin that is chosen should be justified.<br>Proposed change: In line 400, after the sentence ending “…effect in schizophrenia.” Insert the following—“Choice of the specific non-inferiority margin should be justified.” Or “Choice of the specific non-inferiority margin should be agreed to with the EMA, but will usually fall within the range of x to y % for an active-controlled extension study intended to provide evidence of maintenance of effect.” | Not accepted. There are no data to substantiate the ideal non-inferiority margin or trials in schizophrenia because of the large variability still seen across the various trials. |

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| 435 | 3 | Comment: Current research supports amotivation, apathy, and associated behaviours as being the key core negative symptoms of schizophrenia, rather than poverty of speech and flat affect. See for example: Foussias, G and Remington, G. Schizophrenia Bull. 2010 Mar; 36(2): 359-369.<br>Proposed change: Change line 435 to: “Amotivation, apathy, an associated behaviours being present as representative of core negative symptoms.” | Not accepted. The present symptoms are still considered valid for inclusion. Yet other symptoms can be present as well without being specifically mentioned. |
| 439-440 | 3 | Comment: Differentiating between depressive symptoms and negative symptoms can be difficult in schizophrenia. We believe that subjects meeting criteria for Major Depressive Disorder should be excluded from trials of negative symptoms. Use of a depression severity rating scale is unfortunately problematic, because of some overlap in the symptoms of these syndromes. One approach to sorting this out is to consider only those symptoms that are a part of the depressive syndromes and not a part of the negative syndrome when setting additional depression symptom severity exclusion criteria. Further, it may be helpful to do sensitivity analyses to assess the magnitude of the efficacy signal in subjects with and without depressive symptoms.<br>Proposed change: Change line 439 to “Major Depression; significant depressive symptoms that do not overlap with negative symptoms; depression should not be prominent or impairing”. Change line 440 to “Subjects with substantially confounding extra-pyramidal symptoms, depressive symptoms, or cognitive impairment.” | Not accepted. Depression has been taken out of the guideline as separate claim because of the difficulties mentioned by the company. |
| 446-455 | 3 | Comment: We agree that an outcome measure relevant to patient functioning should be included (line 454-455). At this time, we believe there is no consensus on which specific functional outcome measure to recommend for this purpose. Further, we | Not accepted. At present the position is maintained that improvement on the full cognitive test battery in additional to relevant functional improvement should be the basis for a potential claim. |

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| | | agree with the FDA position that demonstration of efficacy on at least one cognitive test and on a functional outcome measure should be sufficient to obtain an indication for improvement of cognitive function in schizophrenia. It is likely that, given the broad nature of cognitive deficits in schizophrenia, improvement in functioning will require improvement on more than one cognitive test. However, at this time it is not known which cognitive tests will need to improve and by how much in order for functioning to improve. The requirement for improvement in functioning assures that the cognitive improvement seen on cognitive testing is meaningful.<br>On line 453, the use of the word “scale” is confusing, as it is associated with clinician administered or self-report rating scales (questionnaires). While rating scales to reliably assess cognition in schizophrenia are under development, currently, the standard is to use a battery of cognitive tests to assess cognition in schizophrenia. Language for cognitive “scale” vs. “battery” should be clarified. Whatever cognitive battery is used, the battery should be well-validated.<br>In general, it would be useful to have further guidance on specific inclusion/exclusion criteria for studies of cognition in schizophrenia. A recent paper (Buchanan, RW et al. The FDA-NIMH-MATRICS guidelines for clinical trial design of cognitive enhancing drugs: What do we know 5 years later? Schizophr Bull. 2010 July 13 (epub ahead of print)) is helpful in this regard. If the EMA has a recommended minimal duration for a cognition trial to qualify as adequate to support an indication, the guidance should say so. It would be important for such a recommendation to be supported by data. Because this area of measurement is somewhat specialized it may be useful to alert readers to the need to address and minimize practice | |

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| | | effects on cognitive tests and for the potential need for age-appropriate norms for these tests.<br>Proposed changes: Line 452-3: Change the sentence to read: “The effect of treatment on cognitive functioning should be demonstrated as the difference between baseline and endpoint on a cognitive battery.”<br><br>Line 453-454:<br>Change the sentence to read: “When a cognitive battery is used, reduction on specific tests in the cognitive battery in the absence of improvement in a measure of patient functioning is not sufficient to obtain an indication for treatment of cognitive symptoms in schizophrenia.” Then add: “Whatever cognitive battery is used to assess cognition, it should be widely regarded as valid and reliable for assessing cognition in schizophrenia clinical trials.” Add after line 455: “A measure relevant to patient functioning should be included as a co-primary endpoint, or as a key secondary endpoint with appropriate controls for type I error. Among the instruments that may serve as potential co-primary or key secondary functional measures are (1) functional capacity measures which simulate activities that are important for community functioning; and (2) interview-based measures of cognition which demonstrate whether a patient experiences a change in cognition or an informant observes a change. New measures of functional capacity as they become available should also be considered. Changes in real-world functioning would not be expected during the course of a clinical trial." | |
| 482-513 -- Section 4.5.4 | 3 | Lines 487-488: Comment- The text describing population selection appears to potentially lead to overlap with Sections 4.5.1 and 4.5.2, which do not currently address monotherapy vs. adjunctive treatment approaches. It is recommended that specific | Accepted. Text amended. |

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| | | examples of the symptom domains be provided.<br>Proposed changes: Line 487-488: “The patient population might include insufficient response to one or more antipsychotics, and the insufficient response might refer mainly to specific symptom domains such as positive symptoms, negative symptoms, cognitive symptoms, or affective symptoms.” | |
| | | Lines 491-494: Comment: the exclusion of treatment refractory patients from augmentation trials seems limiting to potential new mechanisms of action that may have beneficial effects on treatment resistant patients in combination with current therapy. It is conceivable that a new adjunctive treatment could lead to a treatment response in combination with a monotherapy where the monotherapy itself (or the adjunctive treatment itself) has not resulted in any improvement in a treatment refractory patient.<br>Thus, it may be beneficial to attain the inclusion of refractory patients as an option in development of new adjunctive treatments.<br>Proposed change: removal of this criterion | Not accepted. The patient populations are defined such that a clear distinction can be made and trials designed accordingly. The guideline should be read as general guidance, and does not have the intention to be too prescriptive with regard to potential alternative trial designs. |
| | | Lines 495-498: Comment: Clarify whether the demonstration of partial response to an antipsychotic can be by history or must be by open label treatment for a specified duration relevant to the particular domain under study. Since stability of the existing treatment response to background treatment is crucial to determining the additive effects of an adjunctive treatment, it is recommended that the design approach of switching current therapy to an open label treatment not be required. Instead, it is recommended that partial response to an antipsychotic be permitted to be demonstrated by history, with the option of including a prospective observation period to | Not accepted. A prospective trial design to assess insufficient response is preferred for patient selection. |

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| | | verify stability of symptoms.<br>Proposed change: “In the recommended standard short term trial with parallel design for an augmentation indication, patients are randomised to receive active augmentation treatment or placebo in addition to open label standard medication. Partial response to current treatment may be demonstrated by history over a defined period, with the option to include a prospective observation period to demonstrate symptom stability. A list of appropriate baseline standard medications should be defined in the trial protocol.” | Accepted. Text amended. |
| | | Lines 495-500: Comment- The specification of a 4-6weeks trial duration may be too strongly emphasized, since different target symptom domains may respond over varying time periods.<br>Proposed change: “Trial duration of 4-6 weeks is likely to suffice for demonstration of short term efficacy for positive symptoms, although longer durations may be necessary for other domains according to the nature of the test treatment and symptom domains targeted. “ | Not accepted. It is considered a general rule that if the first product is accepted, it should be considered as comparator. No need to be more explicit. |
| | | Lines 501-504: Comment- It is agreed that the inclusion of an active comparator cannot be recommended at this time due to the lack of approved products, however we recommend that a statement be added that if a relevant augmentation treatment is approved in the future, it should be considered for inclusion as a comparator in studies of a new drug candidate<br>Proposed change: Line 509- add the following statement “If a relevant augmentation treatment is approved in the future, however, it should be considered for inclusion as a comparator in studies of a new drug candidate.” | Not accepted. The RWD is mentioned at specific part for the |

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| | | Lines 505-509: Comment- a “randomized withdrawal design” is mentioned, and even seems to be recommended, but the language and intent should be more specifically described. The suggestion on lines 508-509 of including a monotherapy arm of the new compound suggest differences from maintenance of effect approaches for the general schizophrenia indication. Rerandomizing subjects who have responded to a new adjunctive compound to a treatment condition in which the open label standard medication is discontinued would introduce many complications in the interpretation of results; for example, it may not be clear to which discontinued medication a return of symptoms should be attributed if the subject was previously stabilized on more than one psychotropic medication. Further, the monotherapy arm of the formerly adjunctive treatment would seem to be asking a new and unintended question about the efficacy as monotherapy of the proposed adjunctive treatment. It is suggested that discussion of the additional use of a new adjunctive compound as a monotherapy be removed from this section, or that this option be addressed separately with a reference to the appropriate prior sections on monotherapy drug development.<br>Proposed change: Line 506- “In this case responders to a combination treatment of open label standard medication and the new compound are randomised to continue on the new compound or switch to placebo with continuation of the open label standard medication treatment(s) for a duration sufficient to demonstrate differences in maintenance of the treatment effect. “ | specific treatment options and cover the comments made.<br><br>Accepted. Text amended. |

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| | | Line 513: The statement that “Drug interactions should be studied prior to pivotal augmentation studies” should be clarified. The direct study of all potential interactions with the large number of potential background psychotropic treatments is not feasible. It is suggested that guidance on the need for studying drug interactions be provided in this context.<br>Proposed change: Line 513- “Pharmacokinetic or pharmacodynamic drug interactions relevant to the specific characteristics of the new compound should be studied prior to pivotal augmentation studies” | |
| 515-541 | 3 | Comment: The adolescent population is a particularly vulnerable population. Typically, it would not be ethical to expose this population until there is clear evidence of efficacy in adults, reasonable understanding of dose response in adults, and support for a reasonable risk benefit in adult patients. It would be helpful for the EMA to provide guidance on when studies in adolescents are expected to be completed. The ISCTM believes that studies in adolescents should not be required to be completed for the initial application, but can be completed at a later time, given the need for substantial information from the adult population to support these studies, and the desire to bring new treatments to market for adult patients without undue delay.<br>Proposed change: Add after line 541: “Studies in adolescents are not typically required at the time of the initial application for marketing authorization, but the timing should be agreed to with the EMA.” | Not accepted. The PIP’s are leading here. Therefore, it is beyond the scope of the guideline to be prescriptive. The guideline foresees in guidance with regard to acceptance of certain data post-marketing. |
| 542-547 | 3 | Comment: If the EMA has a specific or approximate | Not accepted. The number should be such that dose |

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| | | number of elderly subjects in mind that would generally be required to satisfy these objectives, it would be helpful to have guidance provided on that specific or approximate number. | recommendations and safety aspects are provided. |
| 564-579 | 3 | Comment: Restlessness is another important nervous system adverse event that should be described, and this section would be an appropriate place to provide guidance on describing it.<br>Proposed change: Add after line 569: “Rates of restlessness should be described.” | Accepted. Text amended. |
| 565-579 | 3 | Comment: The ISCTM believes that it would be useful for patients to have medicines approved that reduce EPS and/or tardive dyskinesia. Including a statement to this effect, as well as commenting on what types of studies could be used to support this indication would be helpful.<br><br>Proposed change: Add after line 579: “It may be possible to obtain an indication for the treatment of medication-induced EPS or tardive dyskinesia. Possible study designs should be justified and discussed with the EMA.” | Not accepted. No need to be more explicit in the guideline than at present where it is stated that comparative data should be obtained. |
| 589-593 | 3 | Comment: Further clarification of the appropriate measures of adverse events affecting cognitive functioning or further guidance on study design for this outcome would be appreciated. We believe cognitive batteries, rather than rating scales, would be used to more fully assess effects of treatment on cognitive functioning. Cognitive and motor safety studies should be randomized and controlled, and may be either parallel group or crossover in design. Because cognition may vary by age, gender, and duration of illness, it is important to carefully consider these | Not accepted. Unintended effects on cognition should be part of regular safety assessments. For claims, refer to 4.5.2. |

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| | | patient characteristics when evaluating cognitive data or designing studies of cognition.<br><br>Proposed change: In line 589, change “validated rating scales” to “an accepted cognitive battery”. In line 590, change “those” to “that”. In line 590, after “… to support an efficacy claim.” Insert “If a cognitive and motor safety study is conducted, it should be randomized and controlled, and may be either a parallel group or crossover design, depending on the subject population.” Add after line 593: “Because cognition may vary by age, gender, and duration of illness, it is important to carefully consider these patient characteristics when evaluating cognitive data or designing studies of cognition.” | |
| | 3 | Comment: It would be useful to provide guidance on the time course over which to measure weight gain or loss, and whether both mean changes and a %body weight cut off measure should be reported (e.g. changes of more than 7% of body weight are typically reported in US regulatory filings). Weight change may occur and not worse, or may slowly worsen over time. We believe it is useful to characterize these changes in both acute controlled studies, longer term controlled studies, and in the long term safety population.<br>Proposed change: Add after line 603: “Change in weight should be described both by population mean and by describing outliers exceeding a 7% change in body weight. The time course of weight change should be described.” | Not accepted. The guideline does not have the intention to be prescriptive. |
| 610 | 3 | Comment: Hematologic abnormalities may appear | Accepted. Text amended |

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| | | quickly after initiating drug, or at sporadic times. If known, the time of appearance of any hematologic abnormalities should be described.<br>Proposed change: Add after line 610" "If known, the time of appearance of any hematologic abnormalities should be described." | |
| 612 | 3 | Comment: Menstrual problems in females should be specifically mentioned<br>here.<br>Proposed change: In line 612, add "menstrual problems in females"<br>after" …sexual functioning,". | Accepted, incorporated. |
| 68-69 | 4 | Comment:<br>Augmentation therapy suggests that new therapies are augmenting an existing effect provided by current antipsychotics. This is not the case when talking about negative symptoms as there are currently no treatment available for these.<br><br>Proposed change:<br>Would suggest talking about "combination therapy" rather than augmentation when talking about "negative symptoms" or "cognition". "Augmentation" could be used for positive symptoms. | Partially accepted. No specific distinction is made regarding type of symptoms, but the possibility of combination therapy is included in the text. |
| 236-237 | 4 | Comment:<br>It would be useful to clarify that documentation on the effect of treatment on cognitive function should not necessarily mean to include a cognitive function rating scale since this would mean a substantial burden on the feasibility of running studies. This effect on cognitive function should be assessed on a case by case basis for compounds with safety signal on | See earlier response to this issue. |

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| | | cognitive worsening. | |
| 238-253 | 4 | Comment:<br>The section should acknowledge that Factor scores of PANSS (positive or Negative) are adequate to capture effect on specific symptoms domains. | Not accepted. Section 4.4.3.6 refers to an overall indication. For the other sections, there are insufficient data to be explicit on outcome measures, although it is obvious. |
| 282-283 | 4 | Comment:<br>"…the dose at which most efficacy is obtained…" – a BEST "dose" should consider safety as well as efficacy | Not accepted, usually the least and most effective dose should be targeted. |
| 328-336 | 4 | Comment:<br>It looks like that SOC treat negative symptoms and no add-on is needed to have a claim for negative.<br><br>The guideline provides no guidance on treatment duration for negative symptoms, or partial responders. | Not accepted, referred is to 4.5.3 and 4.5.4.<br><br>Partially accepted. An estimate of study duration is incorporated. For partial responders, see earlier comments to this topic. |
| 371<br><br>379-380 | 4 | Comment:<br>Need to clarify "The standard three way clinical trial design to show superiority to placebo…"<br><br>Comment:<br>The listed measurements of compliance should be suggested as examples; i.e., does not mean to mandate all three measurements.<br>Would be useful to add how to incorporate "compliance" data into efficacy assessment. | Accepted, text amended.<br><br>Text restructured. |
| 392-394 | 4 | Comment:<br>It should be acknowledged that the three designs | Accepted. Text amended |

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| | | described in this section "to demonstrate that the effect found in the acute phase is maintained", could be used for both monotherapy and combination (augmentation) therapy. | |
| 413-414<br><br><br><br>423-424 | 4 | Comment:<br>Efficacy "variable" should be also dependent on the indication/ patient population.<br><br>Comment:<br>For parallel design studies, the parameter should measure "maintenance" of effect – thus, shouldn't the parameter incorporate initial response to measure its 'maintenance'?<br>In such case, why "time to exacerbation" (from the initial response) cannot be the parameter – indicated in line 423-424. | Accepted. Text amended.<br><br>Not accepted. Proportion of patients refers to the clinical relevance of the observed effect, and related to both designs. |
| 434 | 4 | Comment:<br>Define better what predominant means. Add "low positive symptoms".<br><br>Proposed change:<br>It should be clarified that despite the fact that the patient population corresponds to persistent/predominant negative symptoms, the effect demonstrated (and subsequent claim) will be for all patients with negative symptoms<br><br>Comment:<br>Is demonstration of lack of pseudo specific efficacy of Negative Symptom? Would be useful to add | Not accepted. The negative symptoms should be dominant, but the positive no necessarily low.<br><br>Not accepted. The wording of claims is beyond the scope of the guideline and up to final assessment. |

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| | | recommendation. | |
| 482<br><br><br><br>498 | 4 | Comment:<br>Clarify that “augmentation therapy” corresponds to an effect on positive symptoms and “combination” should be used for negative symptoms. (Line 508 refers to combination)<br><br>In stable patients with remaining positive symptoms 12 weeks should be required.<br>For negative symptoms, 6 months should be required. | Accepted. Text amended.<br><br>Accepted, a flexible approach is taken. Text amended where appropriate. |
| | 4 | Comment:<br>Would be useful to address whether “bridging” approach between adults and adolescents is acceptable in what circumstances, if at all, i.e. the guideline should state about the statistical power and rigorousness of trials between adults and paediatric population.(due to the difficulty of recruiting paediatric patients) | Accepted. Tex restructured. |
| 195-208 | 5 | Comment: the use of placebo can be questioned by many ethical committees in Italy, which frequently do not follow EMA guidelines, even if the effect size is small, a comparison with an active compound is probably better, also from the point of view of informativeness about the efficacy of the new compound | Acknowledged, but not accepted. For all psychiatric disorders, as of date, at least some three arm studies are recommended for the dossier, because of the still relatively large amount of studies that have inconclusive results* . The design/strategy can be such that the number of subject exposed to placebo is smaller than the active compound. Further, the power of the studies does not need to be such that formal statistics can be applied across and between all arms, but that active compounds discriminate from placebo.<br>* Reference: C. Gispen-de Wied *et al*. The placebo arm in clinical |

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| | | | studies for treatment of Psychiatric Disorders: A Regulatory Dilemma. European Neuropsychopharmacology (2012) 22, 804–811. |
| 66-69 | 6 | Comment: We suggest removing the words “children” and “add-on” as they are not used in the respective sections.<br><br>Proposed change: “[...] specific patient groups (~~children and~~ adolescents) are addressed. Attention is focused on alternative treatment options such as ~~add-on and~~ augmentations therapy.” | Not accepted. The change refers to the actual guideline text. |
| 70 | 6 | Comment:<br>The section should acknowledge new treatment approaches for patients who have previously responded to antipsychotic treatments but that may further benefit additional treatment as adjunct. | Not accepted. The text reflects the comments. |
| 88-93 & 95-97 | 6 | Comment:<br>The Medical need for additional treatment for negative symptoms or positive symptoms which could improve functionality should be better acknowledged.<br><br>Many companies are looking into cognition and further recommendations in the final guideline would be appropriate.<br><br>Proposed change:<br>Add *“Current treatment do not specifically address negative symptoms or positive symptoms and some patients could benefit from additional treatments as combination therapy ”* | Not accepted. Reference is made to current treatment options in 1.4.1. |
| 108-125 | 6 | Comment:<br>This section should address the medical need in the | Not accepted. See earlier comments with respect to the topic of partial responders. There are no data to refer to for |

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| | | paediatric population for monotherapy or combination treatment options.<br><br>It should be acknowledged that clinical trials specifically targeting negative symptoms in adolescents are difficult to conduct, due to the evolution of symptoms over time in this population. The guideline should recommend analyzing the effect of the new therapies on specific symptoms in the adult program, whereas paediatric clinical trials addressing combination therapies could be done in a partial responder population, irrespective of their symptomatology. | different objectives in adults and children. |
| 121-122 | 6 | Comment:<br>Line 117 is in contradiction with line 121-122. Indeed, first episode is characterised by high positive symptoms and therefore negative symptoms and cognitive impairment cannot be more prominent “from the beginning”. No reference could be found.<br><br>Proposed change:<br>Either line 121-122 is removed or it should be clarified that “from the beginning” refers to the “prodromal stage”. | Accepted. Text amended.<br><br>The text in line 117 is deleted. |
| 134 | 6 | Comment:<br>“Maintenance of effect to consolidate control of symptoms”. The use of “consolidate” is not clear in this context. We would suggest using “stabilize” instead.<br><br>Proposed change:<br>Maintenance of effect to ~~consolidate~~ *stabilize* control of symptoms [...] | Accepted. Text amended. |
| 140-143 | 6 | Comment: | Not accepted. The change reflects the current guideline text. |

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| | | The literature has not established a consensus that the non-D2 actions of second-generation antipsychotic drugs have special significance for negative symptom effects.<br><br>Proposed change:<br>The second generation or so-called atypical antipsychotic agents show in addition a varying degree of affinity for serotoninergic (notably 5-HT 2A), dopaminergic, muscarinic, cholinergic, α1 adrenergic and histamine H1 receptors~~, which are thought to be involved largely in the negative symptom presentation~~ | |
| 144-145 | 6 | Comment:<br>Glutamatergic approaches are not limited to reduce glutamate release.<br><br>Proposed change:<br>“Recently compounds that modulate glutamate release *or NMDA receptor function* are being studied [...]” | Accepted. Text amended. |
| 146-149 | 6 | Comment:<br>The list of new targets does not include a number of the most promising targets being studied at present. The text should be changed to indicate that the mechanisms given are examples, and that this is not an exhaustive list, e.g. lacking nicotinics, erythropoietin, etc.<br><br>Proposed change:<br>~~Also drugs acting on the GABA (γ-Aminobutyric acid) system, on alpha-2 adrenergic receptors~~ *Other targets including but not limited to the GABA system, alpha-2 adrenergic receptors,* and various serotoninergic and dopaminergic receptors are being studied. | Accepted. Text amended. |

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| 151-154 | 6 | Comment:<br>The guideline should mention that there is still an unmet medical need for negative symptoms as no rigorous trials/programmes (as combination therapy) have demonstrated an effect. The guideline should also better acknowledge the medical need for patients whose psychotic (positive) symptoms are not sufficiently controlled.<br><br>Proposed change:<br>"There are number of patients whose positive and negative symptoms are not sufficiently controlled with one medicinal product. Patients with negative and residual positive symptoms may benefit from combination of antipsychotics with a new class of agent. At present, strategies combining an antipsychotic to another antipsychotic are quite widely used in clinical practice, but there are no data to support the benefit of this practice, nor products currently approved in the EU (European Union) for use in this way at the time of writing of this document." | Not accepted. The guideline reflects the need for treatment of additional symptoms, and provides options for difficult to treat populations. No further specifications are considered at this moment, since there are no data to refer to. See also earlier comments related to this topic. |
| 161 | 6 | Comment:<br>This guideline does not only address "classical antipsychotics" but also new class of agents.<br><br>Proposed change:<br>"This guideline focuses primarily on ~~antipsychotics~~ products […]." | Accepted. Classical has been replaced by 'first- and second generations antipsychotics'. |
| 165-166 | 6 | Comment:<br>The text states that potential changes to DSM-V "might have consequences for the definitions of the disorders as given in this guideline…" | Not accepted. In prospect, it is not possible to anticipate on potential changes. |

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| | | Clarity of the potential consequences for the interpretation of studies initiated under current DSM-IV criteria would be appreciated, realizing that changes in DSM-V for the core definition of schizophrenia will not change significantly. | |
| 191-192 | 6 | Comment:<br>We would suggest adding that these considerations are relevant regardless of type of therapy (e.g., mono- or combination therapy) and specific indications, UNLESS indicated otherwise. | Not accepted. The text is considered sufficiently general. |
| 194-208 | 6 | Comment:<br>We would recommend that the guideline better acknowledges whether or non-placebo trials are acceptable in the paediatric population, due to the difficult recruitment process in this population. | Not accepted. As stated above, the considerations are irrespective of type of study, population etc. |
| 199-203 | 6 | Comment:<br>The trend of increasing placebo response in schizophrenia trials has indeed resulted in reduced effect sizes relative to placebo and, hence, the need for larger trials or more trials. These facts, together with the debate about the use of placebo-control, imply the need for serious consideration to be given to alternative designs which utilise placebo but allow increased signal detection (thereby reducing trial sizes) or designs which minimise patients' exposure to placebo.<br><br>Enrichment designs, where placebo-responders are excluded, offer the possibility of increased signal detection while maintaining inference, which is appropriately generalizable to the patient population of interest. This approach has been used successfully in psychiatric indications such as bipolar disorder and | Partially accepted. Text not amended in this section. Section 4.4.1 describes the enrichment design for exploratory trials. Confirmatory trials should reflect as much as possible the real life situation. |

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| | | depression [1]. Variations to the standard enrichment design are available, which differ in the handling of placebo lead-in responders. For example, placebo lead-in responders may be a priori excluded from primary analysis based on this baseline characteristic, yet maintained in the study to enable secondary analyses. Also, researchers have proposed a parallel sequential design which includes data from both placebo responders and non-responders combined across different study periods [2].<br><br>Proposed change:<br>"Therefore, a placebo control has been considered necessary for internal validation of non-inferiority trials comparing new drugs to an active control and is highly desirable so that the "absolute" effects (both therapeutic and adverse) of a product can be ascertained. *However, given these difficulties, consideration may be given to alternative designs which utilise placebo but allow increased signal detection, such as enrichment designs where placebo lead-in responders may be a priori excluded from primary analysis."* | |
| 201-203 and 294-306 | 6 | Comment:<br>The design requirement for pivotal clinical trials of acute schizophrenia are not clear here or anywhere else in the document. Several designs are described, such as non-inferiority and superiority vs. active control; however none are stated as standard design. Whether superiority vs. placebo is an alternative design is not clear. | Partially accepted. See earlier comments with regard to the use of placebo and active control. However, the guideline provides options for design but is not prescriptive in this respect. |
| 204-206 | 6 | Comment:<br>The definition and expectations around a controlled | Comment acknowledged. The need for placebo controlled studies is apparent. The clinical setting for executing these |

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| | | setting for studies with a placebo arm requires clarification as to whether this always means inpatient and would that be for the duration of a study or is there agreement that clinical judgment has a role in whether a subject remains hospitalized. | studies is beyond the scope of the guideline and up to the responsibilities of companies and principal investigators. |
| 206-207 | 6 | Comment:<br>It is stated that short and long term placebo-controlled trials are not considered unethical. We consider that the ethical judgment of use of placebo control is an Ethics Committee decision and should not be included in a regulatory guidance.<br><br>The majority of Ethics Committees in European countries do not allow long term monotherapy placebo controlled studies to be conducted in schizophrenic patients.<br><br>Furthermore, in Section 4.4.4 placebo use and study duration are also discussed in relation to study design. Section 4.1.1 should better specify for which long-term trials a placebo arm is essential and for which trials the use of an active comparator is sufficient, in line with Section 4.4.4.<br><br>Proposed change:<br>"Provided these safeguards are in place, the benefits of using a placebo arm will generally override ethical reservations in both short term and certain long term controlled efficacy trials. For long-term trials, the use of a placebo arm is essential for a 6 month randomised withdrawal study and optional for a parallel double-blind extension study, provided the assay sensitivity is fully substantiated." | Accepted. Text amended. |

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| 210 | 6 | Comment:<br>The term “classical antipsychotics” is unclear and not consistent with the use of “typical” in line 138.<br><br>Proposed change:<br>We recommend the consistent use of “typical” or “antipsychotics significantly impacting D2 receptors. | Accepted. Text amended in ‘first and second generation’ antipsychotics. |
| 210-217 | 6 | Comment:<br>We would recommend that this section describes the concern for pseudopsecificity when a drug must show an effect on positive symptoms before having an effect on other domains of schizophrenia.<br><br>In addition, since at the moment no gold standard exists for negative symptoms or for partial responders, we would suggest that placebo controlled trials in a combination setting would be appropriate.<br><br>Finally, the use of endophenotypes (or intermediate phenotypes) in schizophrenia has been expanding over the past few years. Inclusion of patients who express a specific intermediate phenotype can potentially be used to identify patients who are responsive to specific types of symptoms. Therefore, we would suggest that endophenotypes are a viable target for specific claims. | Not accepted. Segmentation is not foreseen in DSM 5. The use of biomarkers, including genetics, is referred to in section 4.3.1. |
| 226-237 | 6 | Comment:<br>We would recommend to specify that first paragraph (226-228) refers to monotherapy and 2 last one (229-237) refers to add-on therapy. | Not accepted. Differentiation is made in the section 4.5.3 and 4.5.4. |
| 226-228 | 6 | Comment:<br>The guidance should allow for the possibility of authorisation of an acute treatment that effectively allows control of symptoms in acutely ill patients to a | Not accepted. There are no data to refer to, to support this strategy. |

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| | | point where treatment can be switched for long-term maintenance. However, an indication for acute treatment of schizophrenia only or an indication for maintenance only should also be allowed. This represents a different paradigm, but may facilitate the availability of novel, and perhaps more selective/targeted treatments.<br><br>Proposed change:<br>We propose adding: *"It is recognised that other indications may be relevant for products that are targeted solely towards stabilising acute symptoms or maintaining long term efficacy."* | |
| 227-228 | 6 | Comment:<br>We would suggest that it should be possible to submit the maintenance of effect claim post approval. | Not accepted. See earlier comments. |
| 231-233 | 6 | Comment:<br>We consider that it would be useful to add recommendations of acceptable ways of "distinguishing between genuine … and secondary effect." | Accepted. See also earlier comments. Text amended. |
| 236-237 | 6 | Comment:<br>Collecting cognitive function data may be a very significant burden for patients and investigators, particularly in patients with acute schizophrenia. Apart from inferring such an effect from unsolicited adverse events analysis, collecting specific data on cognition as routine safety information, even when there is no hypothesis of potential differences between treatment arms, is an unnecessary burden. It should be limited to cases in which there is a reasonable safety signal of cognitive worsening, or when there is an intention to study cognition specifically. | Acknowledged. See earlier response to this topic. |

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| | | Proposed change:<br>We propose adding: "[...] for purposes of safety data collection *if there is a suspected concern of potential cognitive decline or worsening with the test product* this should be measured using validated rating scales *(e.g. as part of the PANSS scale data)."* | |
| 242-244 | 6 | Comment:<br>A reference to the 16-Symptom Negative Symptom Scale (NSA) as an appropriately validated scale for assessment of negative symptoms [3] should be included in line with comments made by EFPIA on the Concept Paper on the need for revision of the note for guidance on clinical investigation of medicinal products in the treatment of schizophrenia.<br><br>Proposed change:<br>"Satisfactory reliability and validity has been demonstrated for the negative symptoms subscale of the PANSS and for SANS (Scale for the Assessment of Negative Symptoms) *as well as for NSA-16 (16-Item Negative Symptom Assessment)*." | Not accepted. No further reference to scales are made, although the development and use of new sales are encouraged. |
| 247-253 | 6 | Comment:<br>We see the advantage of including secondary parameters in order to better characterize the product. However, the choice of the parameters should be with the applicant. We would like to ascertain that the secondary assessments listed are intended as examples and not intended for mandatory inclusion for every schizophrenia trial. | Not accepted. The guideline is clear in this respect. |

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| 256-259 | 6 | Comment:<br>We would appreciate if the revised guidelines could provide guidance on the type of evidence that would be required for a claim to be presented on the basis of a biomarker, i.e. changes in the grey matter observed via serial MRI scans.<br><br>We understand that the primary labeling claims would be based on clinical outcomes, but it could be useful to include results from these biomarkers in another section of the SmPC (section 5.1). | Not accepted. It is beyond the scope of the guideline to anticipate on claims based on biomarkers. There are no data to refer to. |
| 265-269 | 6 | Comment:<br>The current draft guideline suggests actual data should be collected for any potential co-medication. This is not considered to be realistic or necessary.<br><br>The current guideline recommends more realistically that: “Interaction with alcohol, other CNS active drugs and neuro-endocrinological parameters should be studied". This is consistent with other guidelines in the CNS area, e.g. guidelines on depression, GAD, OCD.<br><br>An alternative approach could be to evaluate the risk for potential DDI using existing information e.g. elimination pathways, CYP450 and transporter affinity, and applying PBPK modelling techniques have been recognized to be useful.<br><br>Furthermore the proposed draft guideline recommends studying interaction with “active illicit substances”, which raises significant concern from an ethical point of view and would present feasibility challenges. If this | Accepted. See earlier responses. Text amended. |

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| | | requirement were to be maintained in the final guideline a recommendation on how interaction trials with CNS active illicit substances could be conducted would need to be included and detailed.<br><br>The request of pharmacodynamic interaction studies and “any other drugs that may be prescribed simultaneously” is not clear. First, it is not possible to test all drugs that may be prescribed. Secondly, it is difficult to perform interaction studies with all possible illicit substances. The need for pharmacodynamic studies (as opposed to pharmacokinetic studies) in all cases is unclear and likely not feasible or desirable.<br><br>The guideline on drug interaction does not give further clarification on pharmacodynamic interaction as it states: “The interactions may be caused by a large variety of mechanisms. It is therefore not possible to give detailed guidance on pharmacodynamic interaction studies" and later: "In general, the pharmacodynamic interaction profile of a drug can best be described by using both in vitro studies and in vivo human studies together".<br><br>Proposed change:<br>The potential for drug-drug interactions ~~All pharmacodynamic~~ between the test drug and any other drug *or any other relevant drug class* that may be *routinely* prescribed simultaneously in clinical practice *and for which a rationale for such interaction exists* should be *assessed.* ~~studied, as well as potential pharmacodynamic interactions with alcohol and CNS (Central Nervous System) active illicit substances.~~ | |

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| 267-268 | 6 | Comment:<br>The association between patient's kidney and/or liver function on the PK of a new chemical entity, in general, is predictable from data obtained in otherwise healthy volunteers.<br><br>Proposed change:<br>"If relevant, pharmacokinetic studies in patients *or healthy volunteers* with hepatic and /or renal impairment should be performed." | Accepted. Text amended. |
| 273 | 6 | Comment:<br>"…maximization of the power of the study…" should clearly mention this refers to the statistical power by adding a word "statistical"<br><br>Proposed change:<br>[...] maximization of the *statistical* power of the study [...] | Not accepted. The whole statistical section is revised. |
| 275-277 | 6 | Comment:<br>This section briefly mentions enrichment designs among designs which are not appropriate "to provide confirmatory pivotal evidence of efficacy". As mentioned above (lines 199-203), enrichment designs, where placebo-responders are excluded, offer the possibility of increased signal detection while maintaining inference, which is appropriately generalizable to the patient population of interest.<br><br>Therefore, consideration should be given to allow the use of enrichment designs even in phase 3 trials.<br><br>Proposed change:<br>"~~These design aspects are only acceptable for~~ | Not accepted. Confirmatory trial should reflect the real life situation as much as possible. |

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| | | ~~exploratory trials, and should not be applied to provide confirmatory pivotal evidence of efficacy.~~ *These designs should also be considered appropriate to provide confirmatory pivotal evidence of efficacy.*" | |
| 278 | 6 | Comment:<br>It may be appropriate to reference ICH E4 regarding dose-response estimations and the utility of modelling in this section of the final guideline. | Accepted. Text amended. |
| 285 | 6 | Comment:<br>Although it is preferable to make direct dose comparisons in a single study we recommend that the revised guideline acknowledges that this is not always possible due to limitations on the number of treatment arms that can be used in a single study. Placebo and/or an active control may also be included in the study and hence it may be necessary to compare doses across more than 1 study. | Accepted. No text amendment considered necessary. |
| 294-306 | 6 | Comment:<br>Open label studies with blinded raters are becoming more common, if these are considered a legitimate study design we would suggest that the revised guideline indicate that such a study design may be utilized in a development program. | Not accepted. Open label studies are, at present, not preferred for registration trials. |
| 294-295 | 6 | Comment:<br>Randomised withdrawal trials should also be considered appropriate as confirmatory trials, if blinded and controlled, as well as dichotomisation of patients into early responders and early non-responders, with subsequent separate blinded randomisation to experimental and comparator treatments.<br><br>Proposed change: | Not accepted. The advantage of such approach for acute treatment is unclear. |

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| | | "[…] parallel group trials. *Randomised withdrawal trials could also be considered appropriate as confirmatory trials for acute efficacy, if blinded and controlled."* | |
| 296-304 | 6 | Comment:<br>This implies that all studies in a clinical programme should include an active comparator and placebo. In programmes with multiple studies recruiting the same patient population use of an active and placebo control in each study is not necessary and would lead to a higher number of patients being enrolled in programmes than necessary. Therefore, we would strongly recommend some flexibility in determining how best to utilize active and control arms in a clinical programme involving multiple studies. | Accepted. Text amended. |
| 299-300 | 6 | Comment:<br>Use of a medical product recognised as "gold standard" should be chosen as a suitable active comparator, but what if no gold standard is available from clinical practice e.g. treatment of cognitive deficits in schizophrenia?<br><br>Similar to the statement that active comparators cannot be recommended for augmentation therapy since no such medicines are currently approved for an augmentation indication (lines 502-504), a similar statement should be included in this paragraph for e.g. products developed for negative symptoms on cognitive symptoms. | Accepted. Text amended according to earlier comments. |
| 301-304 | 6 | Comment:<br>This paragraph seems to imply that active comparator studies must either be designed for non-inferiority or superiority. This is not in line with the CHMP reflection paper on active comparators [4], previous advice given for schizophrenia compounds or the text in section | Accepted, but text considered clear in the guideline. |

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| | | 4.4.3.7 in this document, all of which imply that an active comparator may be used in a 3-way study where the primary endpoint is superiority to placebo, but the active comparator is included as a positive reference control to aid the interpretation of the results.<br><br>Proposed change:<br>"*If the primary objective of the study is to demonstrate superiority to placebo,* ~~If the aim of the study is to demonstrate an estimate of non-inferiority o an active comparator~~ then a three-arm study of placebo, test product and active comparator is recommended *in order to quantify the efficacy* (see also section 4.4.3.7)." | |
| 308-312 | 6 | Comment:<br>To reduce placebo response, diagnosis may require more than a psychiatric assessment and SCID e.g., there may be a need for a confirmatory diagnostic assessment either by additional site staff or from an external provider.<br><br>It is current practice in clinical trials for schizophrenia that the diagnosis is also made by PsychD (PhD Psychology). The guideline should not restrict diagnosis to qualified psychiatrists. | Acknowledged, but no text amendment needed.<br><br>Not accepted. In the EU, clinical practice requires a psychiatrist confirmed diagnosis. |
| 307 | 6 | Comment:<br>The section should distinguish acute vs. maintenance therapy. There are inherent risks to the efficacy outcomes if patients in different phases of the disease are included in one study. The inclusion criteria defining patient population in terms of severity of symptoms are not enough. The section should | Not accepted. Maintenance studies are required to demonstrate whether the effect is maintained over time and therefore refer to the same patient population as for the acute studies. |

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| | | distinguish the target population (acutely exacerbated from chronic). The acute exacerbation should be demonstrated not only by symptom severity but also by behavioural and symptomatic indicators of impending relapse. For chronic patients with psychotic symptoms retrospective stability of those symptoms should be demonstrated. | |
| 307 | 6 | Comment:<br>Recommendation on potential segmentation strategies for patient population, e.g. based on genomics, electrophysiology or symptomatology, could be useful in determining a segment of the population more likely to respond or less likely to have adverse events. | Partially accepted. Segmentation will probably dropped in DSM 5. However, use of biomarkers, including genomic markers are covered in 4.3.1. |
| 308-315 | 6 | Comment:<br>It is mentioned that patients should be stratified at entry depending on their longitudinal course of disease. However, most of the short term studies normally conducted would be limited to those with an acute exacerbation. We would recommend that the revised guideline clarifies in this section if efficacy data are required in patients with all 4 types of longitudinal courses (exacerbation, remission, inter-episode residual symptom, and chronically ill). | Comment acknowledged, but not text amendment needed. The guidelines does not ask for all types to be included, but to specify (e.g. exacerbation etc.) |
| 320-324 | 6 | Comment:<br>The phase of the disease, whether acute or chronic, is not necessarily related to the length of disease history. In addition, recommendations to stratify and to have 20% of patients with less than 5 years history may be challenging to implement. Randomisation in clinical trials is frequently stratified by terms of country/site or other terms relevant to the drug under study. Adding another term of stratification for duration of disease may be very difficult to implement and would require | Not accepted. See earlier response to this comment and the justification for including patients with relative short duration of illness. |

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| | | unrealistic block sizes per site. This recommendation should be removed. If kept as such, the nature of the recommendation should be clarified.<br><br>Proposed change:<br>We recommend deleting the following sentence: "~~It is recommended to include at least 20% of patients with a disease history of less than 5 years.~~" | |
| 325-326 | 6 | Comment:<br>It should be noted that the use of cut-off scores, e.g. on the PANSS may lead to rater inflation bias. Rater inflation occurs when, because of pressure to enrol or desire to help patients get into the study, investigators inflate scores before randomisation to meet inclusion criteria. The effect of this bias has been shown to lead to increased placebo-response. While skilful use of blinding procedures can minimise this effect, it can also be eliminated by removal of the rating scale score from the calculus entirely and therefore, the guideline should also allow for an alternative, i.e. to include patients based on their clinical history.<br><br>Proposed change:<br>"The inclusion criteria should define the patient population in terms of severity of symptoms, as well as illness state, i.e. acute exacerbation. Cut-off scores can be based on efficacy measurement scales (e.g. PANSS), although methods other than rating scales (e.g. patients' clinical history) could be used to establish symptom severity, in order to avoid baseline rating inflation." | Not accepted. Baseline ratings are needed to calculate the primary endpoint (baseline-end of treatment). |
| 328-336 | 6 | Comment:<br>In acute efficacy trials, efficacy starts to be evident as | Not accepted. The guideline provides a flexible approach in this respect, based on available data for reference. A shorter |

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| | | early as 2 weeks, therefore, 4-6 week trials are generally sufficient for the assessment of acute efficacy regardless of the pharmacology of the compound in study. The risk of not achieving the maximal effect is a risk that can be assessed by the sponsor.<br><br>Proposed change:<br>The preferred design for demonstrating short term efficacy is a 4-6 week clinical trial. This is because efficacy most often starts to be evident as early as 2 weeks ~~so far for classical antipsychotics,~~ and a reasonable stability of effect ~~has been~~ can usually be observed ~~as well as some effect on negative symptoms~~ within a 4-6 weeks timeframe~~, often only after 6 weeks of treatment~~. ~~Shorter study duration (e.g. 4 weeks) could also be considered, especially for drugs with a similar profile to existing antipsychotic drugs, although the latter carries the risk of negative results if maximal therapeutic effect is not obtained after 4 weeks, and is disadvantageous in terms of demonstrating stability of effect.~~ For new compounds ~~with novel mechanism of action, (different from the currently available antipsychotics) and/or~~ targeting other domains such as negative symptoms or cognition, the study duration might need to be adapted accordingly (see section 4.5). | duration of trials is not supported by sufficient data to date. |
| 346-348 | 6 | Comment:<br>It may be more appropriate to only allow those subjects that are receiving standardised psychotherapy, psycho-education, support or counselling before entry as long as frequency does not change during trial. | Acknowledged. The text reflects the comment |

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| 350-356 | 6 | Comment:<br>The guideline should provide guidance with regards to patient stability for studies in negative symptoms and partial responders.<br><br>The rationale for not allowing placebo responders to be excluded from randomization is unclear and we would suggest deleting this sentence. | Accepted, a patient stability should be ensured for 6-12 weeks. Text amended in sections 4.5.1. and 4.5.2<br><br>Partially accepted. Exclusion of placebo responders is accepted for exploratory trials. See also earlier comments to this topic. |
| 364-368 | 6 | Comment:<br>We would suggest that in stable, partially responsive, or treatment refractory patients (add-on therapy) a 20% improvement on the factor score should be sufficient. | Partially accepted. A flexible approach is taken and the text amended. |
| 375-376 | 6 | Comment:<br>The recommendation to follow patients regardless of adherence to protocol treatment seems reasonable for effectiveness studies. However, in the case of pivotal efficacy trials, allowing patients to remain in the study and have efficacy/safety data collected, even when they may not be taking study medication and may be receiving another antipsychotic, would invalidate study results.<br><br>Comment:<br>The draft guideline does not give enough details on the meaning of the “standard three ways trial design to show superiority to placebo”. Need more clarification.<br><br>Comment:<br>The measures to assess the compliance (drug plasma levels, tablet counting and urine screening) should be suggested as examples and not as mandatory measurements. | Not accepted. The reason to emphasize follow up is related to the optimal handling of missing data.<br><br>Accepted. Text amended accordingly.<br><br>Accepted. Text amended by incorporating ‘e.g.’ measurement, etc. |

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| | | Proposed change:<br>"All reasonable steps should be taken to minimise their occurrence and to follow-*up with* patients *who do discontinue in order to obtain a final assessment and document their reason for discontinuation* ~~regardless of adherence to protocolled treatment~~*."* | |
| 380 | 6 | Comment:<br>The guidance recommends the use of drug plasma levels and urine screening as methods to assess compliance with treatment. It would be helpful if the revised guideline could offer some guidance on how plasma levels and/or urine samples can be obtained and measured without unblinding trial subjects and investigators. | Not accepted. The methods mentioned are routine for conduct of clinical trials. |
| 382-386 | 6 | Comment:<br>This section is too vague and should be omitted as it neither provides recommendations nor clearly outlines considerations/concerns for sponsors to consider when planning analyses. E.g. why is it assumed that the bias would be in favour of the experimental treatment? In addition, special features associated with schizophrenia trials in relation to missing data would be a welcomed addition to the guidance. E.g. it would be helpful to indicate if there is a recommended framework for developing sensitivity analyses, in particular, for assessing the impact of departures from the missing-at-random (MAR) assumption.<br>The current language ends with the following statement: "this method of missing data imputation". However, it is not clear to which method the guidance refers and in particular whether it refers to last-observation-carried forward (LOCF) imputation? | Accepted. Text structured and clarified See response to earlier comments. |

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| | | Proposed change:<br>We suggest deleting the entire paragraph and keeping the reference to the CHMP guidance on missing data in confirmatory trials [5]. | |
| 391 | 6 | Comment:<br>The section title should read “Design of Maintenance of Effect Studies” since this section is about specifically such studies. | Not accepted. The long-term trials do not only cover maintenance of effect. |
| 393-394 | 6 | Comment:<br>It should be acknowledged that the three designs described in this section “to demonstrate that the effect found in the acute phase is maintained”, could be used for both monotherapy and combination therapy. | Acknowledged, but taken care of in the different sections (4.5.1 and 4.5.2) |
| 397-411 | 6 | Comment:<br>This section of the guideline seems to be confused about the necessary duration of maintenance of efficacy studies. However, since a duration of 6 months is deemed acceptable for placebo-controlled studies, this duration should apply to all three options. It should be clarified that randomised withdrawal trials may be against placebo or in case of non-inferiority or superiority design to an active control (as per line 422). It should also be clarified what is meant by “substantiating assay sensitivity” for an active comparator study, it is not assumed that a placebo control arm is necessary.<br><br>In addition, the wording in lines 405-407 should be revised as it essentially says that blinding should be preferred to avoid unblinding. | Accepted. See response to previous comment. |

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| | | Proposed change:<br>"Extension studies may provide evidence of maintenance of efficacy as long as they stay double blind. *In general a duration of 6 months is required due to the natural course of the disease.* A parallel trial using active comparator is the first possibility. When the objective is to show non-inferiority, the active control should be a product with a well documented efficacy in the maintenance of treatment effect in schizophrenia. ~~Due to the natural course of the disease, the duration of such a trial should be 12 months and the assay sensitivity should be fully substantiated.~~<br>Another alternative is a randomised withdrawal design study, in which responders to the short-term treatment are included and randomised either to the study medication or to placebo/*active control*. When this design is applied, it may be useful to first stabilise the patients in an open label treatment period of sufficient duration. Blinding patients to the time point of onset of randomised treatment is preferred to avoid *potential biases that may result from* ~~unblinding due to~~ patient awareness of treatment allocation, as this could potentially increase bias in favour of the test product.<br>A third alternative is a two-arm placebo controlled trial ~~with duration of 6 months~~. [...]" | |
| 412 | 6 | Comment:<br>The section title should read "efficacy parameters in Maintenance of Effect Studies" since this section is about specifically such studies. | Not accepted. See earlier comment to this point. |
| 415-417 | 6 | Comment:<br>For parallel design studies, it should be clarified that | |

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| | | the efficacy parameters should measure maintenance of effect. This is indeed clarified in lines 423-424, but it would be clearer to consolidate this.<br><br>Similarly, the proportion of patients with exacerbations should also be included in lines 418-422.<br><br>Comment:<br>It should be taken into account that “the primary efficacy variables to measure maintenance of effect” would not only depend on the design of the study since indication and patient population may have an impact on the efficacy variables.<br><br>Proposed change:<br>“In parallel design studies, the primary efficacy should be measured as the difference between baseline and endpoint on the symptom score, as in the short term studies. Drop out rates which indicate a treatment failure could be included as a key secondary endpoint. *In addition, the proportion of patients with exacerbations at pre-specified time points should be analysed.*<br><br>In a randomised withdrawal design, the primary efficacy measure would be time to exacerbation of symptoms using pre-specified criteria, *and a secondary endpoint should be the proportion of patients with exacerbations at pre-specified time points.* Patients with exacerbations must be clearly distinguished from withdrawals due to other reasons. The duration of the randomised treatment period should be sufficient to ensure that the number of patients with exacerbation | Not accepted. The text is considered clear.<br><br>Acknowledged. No need to be this explicit in the text. |

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| | | (event rate) is sufficient for adequate statistical power for the comparison with active comparator or placebo.<br><br>~~In parallel and randomised withdrawal studies, the proportion of patients with exacerbations at pre-specified time points should be analysed."~~ | |
| 425-426 | 6 | Comment:<br>The draft guideline states that: "In some cases, if the dose-response data from short term trials is insufficient, dose finding for long-term treatment using multiple doses of the investigational product may be required."<br><br>It is not clear in which cases such approach may be warranted as generally dose-response data is generated in short term trials. Also it is not clear whether special consideration is given to dose finding for "maintentance of effect". Long-term trials of multiple doses would increase the burden for drug development as well as the unnecessary exposure of patients to investigational drugs.<br><br>It should also be noted that there are no substantial evidence to support that there is a difference between effective doses in long-term as compared to those in short-term trials. | Accepted. Text amended. See also earlier comments to this issue. |
| 429-440 | 6 | Comment:<br>It should be clarified that despite the fact that the study population has persistent/predominant negative symptoms, the effect demonstrated (and subsequent claim) will be for all patients with negative symptoms.<br><br>Predominant negative symptoms inclusion criteria also | Not accepted. Intended claims are beyond the scope of the guideline. |

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| | | include low positive symptoms, this should be acknowledged.<br><br>Guidance would be welcome on the appropriateness of studying specific domains within the negative symptom construct as potential targets for drug development (e.g. anhedonia, restricted affect or diminished social drive).<br><br>It is understood that trials in negative symptoms should include patients with predominant and persistent negative symptoms. However, the requirement for a stable condition of the illness greater than 6 months seems unnecessary and may best be served by a prospective lead-in period of 3 to 4 weeks to confirm symptom stability and persistence.<br><br>The requirement of flat affect and poverty of speech as inclusion symptoms is too restrictive and should be removed, given that focus may be on other core negative symptoms. The hallmark of negative symptoms is volitional disturbance. Therefore it is unclear why flat effect should be a requirement. We think a patient having mildly constricted affective range, in the absence of depression, in the presence of profound (and primary) avolition, apathy, asociality and anhedonia with shallow content of speech but not necessarily alogia, should still qualify as a negative symptom patient.<br><br>The exclusion of cognitive impairments is not practical since virtually all patients with schizophrenia have cognitive deficits. Specificity of effect for the purposes | Not accepted. Predominant negative symptoms do not necessary go along with low positive symptoms.<br><br>Not accepted. There are no data to refer to for such specification.<br><br>Partially accepted. Stability of symptoms has been covered under 4.5.1.<br><br>Partially accepted. Text amended in the sense avolition is added to the core symptom presentation. |

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| | | of a claim, should rest on whether the drug's benefit is limited to negative symptoms, is seen on both negative symptoms and cognition (i.e. residual schizophrenia symptoms) or cognition alone. We realise that this requirement is inspired by the interconnection of negative symptoms and cognitive deficits but this should be dealt with by using appropriate assessment for each of these 2 aspects of the disease rather than excluding the majority of schizophrenia patients suffering from predominant negative symptoms.<br><br>Guidance on the recommended study duration for efficacy in negative symptoms trials would be valuable.<br><br>As per comment above (lines 249-251), the NSA-16 scale should be added as an appropriately validated scale for assessment of negative symptoms [3]. The PANSS Factor Score could also be included.<br><br>Proposed change:<br>"If an effect on negative symptoms is claimed, specially designed studies in patients with predominant negative symptoms *(for a general claim) or a specific domain of negative symptoms (for a specific claim)* should be conducted. [...] To ensure that patients with negative symptoms, other than related to depressive symptoms or EPS, are studied, the inclusion criteria should encompass:<br>a) Predominant and persistent negative symptoms.<br>~~b) Flat affect and poverty of speech being present as representative of core negative symptoms~~<br>~~c~~b) Stable condition of schizophrenic illness | Accepted. Text amended.<br><br>Not accepted. The guideline text allows for other instruments to be used and does not need to be too prescriptive in this respect. |

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| | | *demonstrated over 3-4 weeks* ~~for longer than 6 months~~, especially of the negative symptoms. [...] Improvement on negative symptoms should be demonstrated through validated scales (e.g. PANSS negative subscale, SANS, *NSA-16, PANSS Factor Score* or other) [...]."<br>[...]<br>e) Subjects with substantially confounding extra-pyramidal symptoms ~~and cognitive impairment~~. | |
| 444-445 | 6 | Comment:<br>The recommendation of functional improvement as key secondary outcome is endorsed. However, functionality is different from functional capacity. The former is highly dependent on socio-economic circumstances and may therefore not be affected in short to medium term by severity of negative symptoms. Functional capacity is less dependent on socio-economic environment and tools already exist to evaluate functional capacity in schizophrenic patients.<br><br>Proposed change:<br>"...and improvement of functional capacity or functioning as key secondary outcome is recommended." | Accepted. Text amended. |
| Section 4.5.2 | 6 | Comment:<br>Clarity is requested on whether studies mentioned in this section would lead to a domain specific claim (as alluded to in Section 4.1.2) or a general cognition claim based on a composite cognitive testing score<br><br>Guidance on the recommended study duration for efficacy on cognitive functioning trials would be valuable. | Not accepted. The type of claim is beyond the scope of the guideline. It is stated that a mere reduction on specific item(s) is not acceptable. In addition, the clinical relevance of the observed effect should be clear.<br><br>Accepted. Text amended. |

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| | | The guideline is unclear on whether subjects selected for such studies should have documented deficits compared to healthy subjects or whether all schizophrenic patients can be recruited in the understanding that all schizophrenic patients actually perform cognitively below their capacity although for some schizophrenic patients this may not be below the norm of the average healthy subject. The latter may be a defendable approach as long as a cognitive improvement is documented over the broad range of cognitive baseline status including those not performing below the norms. The MATRICS group reflected on this in their recent position paper, stating that it is not necessary to set a baseline cut-off score for cognitive deficits for inclusion in studies. However, consideration may be given to the stratification of patients to treatment arms based upon baseline cognitive performance.<br><br>In addition, some elaboration would be helpful regarding the issue of pseudo-specificity. To support a claim for efficacy on cognitive aspects would a concurrent absence of effect on negative symptoms in the tested population have to be shown?<br><br>The statement in lines 454-455 is currently unclear. Is a reduction of specific items or a specific cognitive domain of a larger test battery without beneficial effect on functionality not acceptable or is a reduction on specific items of a larger test battery without showing a significant reduction on the total test battery not acceptable, even in the case where the reduction of | Acknowledged. Since the guideline is not explicit with regard of the use of MATRICS (MCCB), no guidance is provided for baseline inclusion. However, the baseline is specific with regard to the endpoint: difference from baseline.<br><br>Acknowledged. The guideline can not go further than state that a genuine effect on cognitive function is required. |

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| | | specific cognitive domains is associated with a functional improvement?<br><br>The latter should not be the meaning of this guidance. Clinical relevance should be established through the use of appropriate measures, and improvement on measures of functional capacity. It may very well be possible that an improvement on certain cognitive domains e.g. executive functioning, attention... does not lead to an overall improvement of e.g. the MATRICS battery while it may lead to improved functioning.<br>We therefore suggest that an effect on “specific items” of a cognitive test battery may be acceptable if there is rationale based on mechanism of action of the product and if there is a beneficial effect on functionality.<br><br>Finally, it would be helpful if the revised guideline could indicate what tools or batteries may be used e.g. MATRICS and/or CogState and/or BACS for cognition.<br><br>Proposed change - Address above points if possible and add:<br>“Similarly, the effect of treatment on cognitive functioning should also be demonstrated as the difference between baseline and endpoint on the cognitive functioning scale. *Tools such as MATRICS and/or CogState or equivalent could be used, but* whatever tool is used, mere reduction on *the total cognitive test battery or on* specific items *or domains* of a larger test battery *without documented benefit on patient functional capacity or functioning* is not acceptable. ~~The outcome should be such that~~ | |

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| | | ~~relevance to the patients functioning is clear.~~" | |
| 457-459 | 6 | Comment:<br>The guidance states that all products must be registered as a general treatment for schizophrenia before a separate and additional treatment resistant claim could be obtained. This requirement could restrict the development of products for treatment resistant schizophrenia.<br><br>It is agreed that studies in a general population are likely to be conducted during the development of a product for treatment resistant schizophrenia. However due to differing benefit/risk profiles of compounds it may not be appropriate to develop a particular product for the general population but because of less treatment options and a higher unmet medical need, it is possible the same product could have a favorable benefit/risk profile in patients with treatment resistant schizophrenia.<br><br>Proposed change:<br>"Monotherapy in patients with treatment resistant schizophrenia could be a separate ~~but additional~~ claim. This could be granted to compounds with an adequately substantiated general schizophrenia indication. *In this case,* at least one additional trial should be performed to support extension of the indication to treatment resistant patients. *Alternatively a substantive development programme would be required for a stand-alone indication in treatment resistant patients.*" | Partially accepted. In general, an additional claim to the general claim in schizophrenia can be obtained if proven efficacious in this patient population. An exception can be made for those products that, for safety reasons, warrant a second/third line or restricted indication. However, this is part of the assessment and beyond the scope of the guideline. However, text amendment has taken place to address this issue.<br><br>See earlier comment. |
| 460-462 | 6 | Comment:<br>This statement should be clarified to emphasize basic | Accepted. Text amended. |

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| | | scientific principles, i.e. the fact that post hoc analyses and findings are generally not sufficient to obtain the extended indication. However, clearly pre-specified hypotheses and analyses as part of a broad trial, which includes sufficient representation of treatment resistant patients, would represent a confirmatory study of efficacy in this population.<br><br>Proposed change:<br>"Subgroup analyses among treatment resistant patients in trials conducted in a general schizophrenia population are *generally* not sufficient to obtain the extended indication, *except when clearly pre-specified as part of a broad trial including sufficient representation of treatment resistant patients. In any case, analyses among treatment resistant patients* ~~although they~~ could provide useful important supportive data." | |
| 487-490 | 6 | Comment:<br>Reference to number of failures should be avoided in the discussion of augmentation as it is usually related to the definition of treatment resistance. Patients who are candidates for augmentation/add-on treatment may be defined in different ways dependent on their level of response to standard of care and on the domains with residual symptoms, i.e. a patient population for which additional symptom improvement would be clinically relevant.<br><br>Proposed change:<br>"The patient population might include insufficient | Accepted. Text amended according to previous comments. |

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| | | response to one or more antipsychotics, and the insufficient response might refer mainly to specific symptom domains. Therefore it is recommended to define the patient population to be included in the studies in terms of number of failures and domains with insufficient effect." | |
| 491-504 | 6 | Comment: We strongly support the proposed distinction between treatment refractory patients who should be switched and insufficient responders for whom switching is not a recommended option. Hence we endorse the CHMPs position that, at present, placebo-controlled augmentation studies should be acceptable. | Acknowledged. |
| 506-509 | 6 | Comment:<br>We suggest replacing "similar to the general schizophrenia indication" with a reference to section 4.4.4, which deals with maintenance studies.<br><br>Further, the guidance should specify that the standard two arms design (augmentation therapy vs. standard treatment alone) is generally sufficient to establish maintenance of effect for an augmentation indication. It is not clear under which conditions it would be appropriate to consider switching patients from augmentation therapy to monotherapy treatment with the new compound.<br>We also suggest being consistent and use the term "augmentation" rather than "combination" as the two may convey different meanings. Augmentation is used to describe positive symptoms and combination for negative symptoms. Since there are no treatments approved in negative symptoms, an augmentation | Accepted. The lines of text are revised. |

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| | | cannot be obtained in such symptoms.<br><br>Proposed change:<br>"Maintenance of effect of long term augmentation can be demonstrated in a randomised withdrawal design *as described in Section 4.4.4*. ~~similar to the general schizophrenia indication.~~ In this case responders to *augmentation* ~~combination~~ treatment of a known antipsychotic and the new compound are randomised to *continue on* ~~one of the following three treatments:~~ ~~combination~~ *augmentation* therapy~~,~~ *or to receive* monotherapy with a *standard* antipsychotic *alone*~~, and monotherapy new compound (if appropriate).~~ | |
| 515-541 | 6 | Comment:<br>We endorse the CHMPs view that studies in children under the age of 13 are not necessary. Further we recommend conducting the adolescent trials only after efficacy is established in adults.<br><br>We would welcome a comment on adolescent studies in different settings, e.g. monotherapy, augmentation, treatment of specific domains as the medical need may well be different from adults. It should also be acknowledged that clinical trials addressing specifically negative symptoms in adolescents may be difficult to conduct, due to the evolving nature of their symptoms. Hence, while the effect of the new therapies may be studied on specific symptoms/domains in the adult program, the paediatric Clinical trials addressing combination therapies could be done in a partial responder population, irrespective of whether their symptoms are primarily positive, or negative in nature. | Acknowledged. In principle studies in adolescents can follow the strategy of studies in adults. No amendment needed. |

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| | | As it's more difficult to find and recruit the younger patients (i.e. below 15), the stratification is acceptable providing no minimal requirement are made. | Not accepted. The number of patients in each age strata should allow benefit/risk assessment. |
| | | As regards the duration of short term studies, the draft guideline mentions that 4-6 weeks (or longer) are required. It would be useful to provide clarification as to why studies longer than 4 weeks in adolescents would be needed. | See earlier comments. There is no reason to assume that study duration in adults and adolescents would offer different results. |
| | | We suggest that Maintenance of efficacy may be extrapolated from adult data or, if required, that it can be demonstrated in a 6 months study (not 1yr) especially given the difficulty in recruiting and retaining adolescents with schizophrenia in clinical trials. In addition, we would welcome a rationale for the 2 years long-term safety data (vs. '1 year' for adults in general). Particularly, if required, can it be confirmed that the 2-years of safety data in the paediatric population can be provided part of a post-approval commitment? | Text revised. |
| | | It is mentioned that the rating scale should be amended to tailor to the requirements of a paediatric population. Can the revised guideline clarify if any such amendments to a standard rating scale would require formal validation before it can be accepted for evidence of efficacy? | Acknowledged. It can not be made explicit to what extend validity/reliability of tailored scales should be ensured, except that should follow the regular methodological rules for incorporation in clinical trials. No text amendment made. |
| | | In terms of safety monitoring, we suggest that the specific study of adverse events, e.g. prolactin changes should be determined on a case-by-case basis i.e. | |

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| | | limited to compounds known to cause such effects in adults or based on mechanism (such as D2 antagonists. Sexual maturation is particularly difficult to study in the adolescent population, where most patients would be either mature or at the very final stages of maturation when entering studies. We therefore doubt that scientifically interpretable results could be obtained in this age group.<br><br>Proposed change:<br>"~~Studies in adolescents should include sufficient patients of each age range.~~ The age distribution *in adolescent studies* should reflect the target patient population. Stratification of patients into two groups by age, e.g. 13-15 years versus 16-18 years, or by sexual development stage is recommended since the clinical features and incidence of schizophrenia may differ between strata. Separate studies in subgroups are not required. *It is acknowledged that the younger aged (or less sexually mature) strata is likely to be smaller than the older due to the relative difficulties in recruiting patients from the younger age group."*<br>[...]<br>"Efficacy measures should include cognitive and functional outcomes *as secondary endpoints*. Efficacy in acute treatment should be demonstrated in at least one short term trial of 4~~-6~~ weeks duration ~~(or longer)~~. Maintenance of efficacy *may be extrapolated from adult data, but* ~~(6-12 months) and~~ long term safety data (2 years) should be generated as well. Special attention should be given to possible adverse effects *which may impact* ~~on~~ sexual maturation, cognition, endocrine function and other aspects of | |

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| | | development. ~~Undesirable effects relating to changes in prolactin levels should be actively studied (see section 4.7)~~." | |
| 542 | 6 | Comment:<br>Could the revised guideline define elderly? Could elderly be defined as > 55 years of age or > 65 years of age?<br><br>Proposed change:<br>"For the general indication "treatment of schizophrenia" no specifically designed trials in elderly patients *(>65 years)* are necessary." | Accepted. Elderly are considered those >65 years of age. |
| 551-552 | 6 | Comment:<br>Need to clarify what "recovery time" meant.<br>It is assumed that there is no requirement to use "adverse event scales" and this should be clarified.<br><br>Proposed change:<br>"Identified adverse events (AEs), including serious AEs and AEs leading to withdrawal, should be characterised in relation to duration of treatment, dosage, *time to* recovery/*resolution* ~~time~~, age, and other relevant variables. *If using* adverse event scales, *these* should be standardised for use in studies with psychotropic drugs (e.g. UKU scale). " | Accepted. |
| 575-577 | 6 | Comment:<br>Tardive dyskinesia should not automatically be mentioned in the SmPC for new molecules with non-dopamine mechanism of action and no reported cases.<br><br>Proposed change:<br>"The possibility that a test drug might cause tardive dyskinesia cannot be excluded in the typical clinical | Accepted. Text amended. |

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| | | development programme and therefore the possibility should be mentioned in the SmPC *for dopaminergic drugs* even if there are no reported cases." | |
| 586-587 | 6 | Comment:<br>Depression and anxiety symptoms are captured by general scales like PANSS. Implementing specific depression/anxiety scales just for collecting safety signals seems an unnecessary burden.<br><br>Proposed change:<br>"As part of the adverse event data, undesirable psychiatric effects including depression and anxiety should be measured using validated rating scales *(e.g. as part of the PANSS scale data)."* | Not accepted. Sub scores on the PANSS are considered insufficient to capture true depressive/anxiety symptoms. |
| 588-593 | 6 | Comment:<br>It is not clear if all the listed functions (e.g., cognition, reaction time, driving and sedation, as well as learning and memory and school performance in adolescents) should be monitored in each patient study or if a dedicated study in either patients or healthy subjects should be performed | Accepted. A dedicated study with robust data is considered sufficient. Text amended. |
| 588-593 | 6 | Comment:<br>• Cognitive function is captured by general scales like PANSS. If batteries such as MATRICS would be required to fulfil this requirement, or if detailed analyses by patient are required (i.e., "clinically relevant change"), this would mean a very substantial and unnecessary burden on the feasibility of running any study in Schizophrenia.<br>• The second sentence encompasses the first and can be deleted | Accepted. Text amended. |

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| | | • Any reference to assessment on driving should not be included. It would be impractical to assess the effect on driving particularly in patients who do not have a driving licence.<br><br>Proposed change:<br>"*The possibility of* ~~a~~ detrimental effect on cognition and *reaction time, whether via sedation or some other mechanism,* should be monitored using validated rating scales, (e.g. part of the standard PANSS assessment). In the adolescent population specific issues such as memory, learning, school performance, etc. should be studied in relation to both the safety and efficacy perspective." | |
| 594-599 | 6 | Comment:<br>1) Columbia Classification Algorithm is not a scale; C-SSRS is the scale.<br>2) It is unrealistic to collect narratives for all suicidal patients, it would be appreciated if the EU and FDA could align their approach to prospective suicide monitoring.<br><br>Proposed change:<br>"The potential for the test product to precipitate suicidal thoughts and behaviour should be actively measured using ~~validated~~ *widely accepted* rating scales (e.g. InterSePT Scale for Suicidal Thinking, ~~Columbia Classification Algorithm for Suicide Assessment~~ Columbia Suicide severity rating scale [C-SSRS]). Rates of suicidal events (from suicidal ideation to completed suicide) should be presented and narrative summaries of *cases of* suicidal behaviour *or ideation*~~patient statements or behaviours~~ should be | Accepted. Text amended. |

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| | | provided. | |
| 604-608 | 6 | Comment:<br>The section about a “neuroleptic malignant syndrome” is linked to the risk of abrupt withdrawal of treatment with antidopaminergic compounds. There is no evidence that other modes of actions are involved.<br><br>Proposed change:<br>“Neuroleptic malignant syndrome (NMS) has been reported for all *dopaminergic* antipsychotics. Therefore possible cases should be thoroughly investigated and reported. The possibility that a test drug might cause NMS cannot be excluded in a typical clinical development programme. Therefore the possibility should be mentioned in the SmPC *for dopaminergic drugs* ~~for drugs of this class~~ even if there are no reported cases.” | Accepted. Text amended. |
| 611-615 | 6 | Comment:<br>Again this section is only relevant if the mode of action targets dopamine receptors.<br><br>Proposed changes:<br>add a qualifier that<br>“*The assessment of endocrinological events depends on the mode of action and is of particular importance for dopaminergic drugs.* Special attention should be paid to effects on sexual functioning, galactorrhoea, gynaecomastia and weight gain. Investigation of neuro-endocrinological parameters relating to prolactin is necessary. In the adolescent population *adverse* effects *that may impact* ~~on~~ growth and sexual maturation require specific attention and should be closely monitored.” | Not accepted. Endocrinological events do not only depend on the mode of action of dopaminergic drugs, but serotonergic drugs as well. |

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| Editorial comments: 279 | 6 | Comment: The terms “SmPC” and “SPC” are interchangeably used in the draft guideline. For consistency, the official abbreviation (i.e. “SmPC”) should be used. | Acknowledged. Amended. |
| | 6 | References:<br>[1] Post *et a.l*, Journal of Psychiatric Research, 37: 61-73, 2003; Laska et al: Design Issues for the Clinical Evaluation of Psychotropic Drugs: Prien RF, Robinson DS, editors. Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines. New York. Raven. 29-67, 1994<br>[2] Tamura RN, Huang X Clinical Trials, 4: 309-317, 2007: Fava et al: Psychotherapy and Psychosomatics, 72: 115–27, 2003: Fava et al: Erratum. Psychotherapy and Psychosomatics, 73:123, 2004<br>[3] Axelrod BN *et al.* Validation of the 16-item negative symptom assessment, Journal Psychiatric Research., Vol. 21. No 3. ,pp 253-258, 1993<br>[4] Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available EMA (EMA/759784/2010)<br>[5] Guideline on missing data in confirmatory clinical trials (EMA/CPMP/EWP/1776/99 Rev. 1) | |
| Lines 204-206 | 7 | Comment: The definition and expectations around a “controlled setting” for studies with a placebo arm requires clarification as to whether this always means inpatient and would that be for the duration of a study or is there agreement that clinical judgment has a role in whether a subject remains hospitalised. | Not accepted. The text is considered clear and should not be prescriptive on issues that differ worldwide. |
| Lines 265- | 7 | Comment: Due to a feasibility challenge, clarification is | Accepted. Text amended now referring to relevant drugs. |

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| 267 | | needed on the interest in all pharmacodynamic interactions with other drugs used in clinical practice as well as alcohol and CNS active illicit substances to be studied. | |
| Line 278 | 7 | Comment: It may be appropriate to reference ICH E4 "Dose-Response Information to Support Drug Registration" regarding dose-response estimations and the utility of modeling in this section of the final guideline. | Accepted. Text amended. |
| Lines 308-312 | 7 | Comment: To reduce placebo response, diagnosis may require more than a psychiatric assessment and SCID e.g., there may be a need for a confirmatory diagnostic assessment either by additional site staff or from an external provider. | Not accepted. This would unnecessarily increase the burden of trial conductance. |
| Lines 428-445 | 7 | Comment: The draft guidance is not clear on whether positive symptoms must be well controlled for a negative symptom claim (this appears to be assumed). Additionally, the text in this section is not clear on whether it covers monotherapy or augmentation treatment. | Not accepted. The guideline does not want to be too prescriptive here. It is up to the company to design the studies such that the effect on negative symptoms is clear. The patient population is chosen such that that the negative symptoms prevail. |
| Lines 429-430; and Line 434 | 7 | Comment: It is unclear for negative symptoms whether they need to be both predominant and persistent – symptoms may be persistent and clinically relevant but not predominant. | Not accepted. The patient population is described in general terms. There are no data to rely on for more specific recommendations. |
| Lines 431-434 | 7 | Comment: A minimum score is not specified as an inclusion threshold to characterize a study participant as having predominantly negative symptoms. | Not accepted. This is left to the company. See also earlier comments on patient population. |

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| Lines 444-445 | 7 | Comment: We agree that a functional endpoint should not be “required” as a co-primary endpoint for assessing negative symptoms (which is consistent with FDA’s past position). | Acknowledged. |
| Lines 452-455 | 7 | Cognitive symptoms: Clarity is requested regarding the feasibility of obtaining a domain specific claim based on pre-specification of a domain-specific effect, in addition to a cognition claim based on a composite cognitive testing score. | Not accepted. There are no data to rely on. Therefore, at present it is recommended to demonstrate an overall effect based on a test battery of choice. For further specification, scientific advice is recommended. |
| Lines 466-469 | 7 | Comment: The use of the term “treatment resistance” draws from the standard for treatment-resistant depression, with 2 prior unsuccessful trials of adequate dose and duration required. The text, however, is unclear on whether the prior trials need to be during the current episode. | Acknowledged. No need for amendment. The text allows for the current or previous episodes. |
| Lines 531-532 | 7 | Comment: Prodromal treatment and prevention of progression to full schizophrenia are noted as not sufficiently investigated to be applicable at this time for pediatrics. With regards to adults, it would be helpful for the final guidance to be more explicit on whether this also applies to adult studies in early stages of the disease. Disease modification in schizophrenia is an important potential area of study and it would be helpful to have greater clarity on acceptable prodromal criteria (e.g., cognitive impairment, social isolation, idiosyncratic thinking). | Not accepted. Treatment of prodrome is beyond the scope of the present guideline (see earlier statements) because of insufficient data to support a proper patient population. |
| Lines 589-591 | 7 | Comment: Greater clarity is needed on the requirements for prospective safety assessment (e.g., | Accepted. See also earlier comments. Cognitive impairment as part of the safety aspects of psychotropic drugs should be |

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| | | is cognition now to be consistently measured or just when it is also an efficacy endpoint in a study?). In addition, clarity is requested on whether it will suffice for the prospective assessment of cognitive impairment as an adverse event to be done in a single study and not be repeated across the studies in a filing. | assessed with specific scales is relevant. For claims, refer to 4.5.2. |