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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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Overview of comments received on "draft Guideline on clinical investigation of medicinal products in the treatment of depression"

(EMA/CHMP/185423/2010, Rev.3)

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Line to (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
SG	General comment	0	0	Study population, Exclusion criteria: It is well-documented that many patients are ineligible for antidepressant trials, with negative impact on generalizability of trial results (Zimmerman et al. Psychother Psychosom 2019 PMID: 31096246). Add a specific paragraph highlighting the need for broad study populations and justification for exclusion. Specifically address suicidality and history of suicidal behavior including suicide attempts (see comments on section 2.4.2. below).		Partly accepted. See specific comment on this issue below referring to lines 378-396. Reference to section seems wrong? 4.2.4. instead 2.4.2.
SG	General comment	0	0	Transparency: No mention of pre-registration of trials, and availability of study protocols and SAPs, and clear descriptions of pre-specified vs post hoc analyses. A clear statement on these aspects should be included in the guidance (see comments on section 2.4.3. below).		Reference is made to EMA and ICH guidance in section 3. This is considered sufficient. The transparency requirement is self-evident. No change required.
SG	General comment	0	0	Proportionality: Many trials pose no or minimal additional risk compared to routine clinical care. Safety procedures should reflect this (see specific comments on section 2.4.6. below).		Is section 4.6. meant? See specific comment below.
SG	General comment	0	0	Control conditions, Blinding: It is stated that randomised, double blind, placebo controlled trials are the gold standard to permit adequate evaluation of short-term efficacy but there is no mention of blinding checks. Less than 10% of antidepressant RCTs between 2000-2020 reported blinding assessment (Lin et al., EClinMed 2022 PMID: 35812993). This should be specifically discussed (see comments on section 2.4.3. below).		Accepted. See specific comment on this issue below. Reference to section wrong. It is assumed that section 4.3.2. is meant instead of section 2.4.3.
SG	General comment	0	0	There are a few important aspects of informative clinical trials that are not or only briefly mentioned in this guidance, but may be particularly important for depression and other mental health areas. The guideline could be strengthened by aligning messaging with the WHO's guidance for best practices for clinical trials and the Guidance for Good Randomized Clinical Trials produced by the Good Clinical Trials Collaborative, specifically with regard to transpareny, proportionality, and involvement of potential participants and relevant stakeholders (see comments in section 2.2. below).		Reference is made to EMA and ICH guidance in section 3. This is considered sufficient. No change required. Reference to section 2.2. is misleading and it is assumed that section 3. is meant.
H. Lundbeck A/S	General comment	0	0	H. Lundbeck A/S appreciates the EMA's ongoing efforts to provide sponsors with more clarity on existing guidelines, whilst reflecting current scientific knowledge and practice in research. We appreciate the opportunity to comment and look forward to a continued dialogue with the Agency and other stakeholders on these important matters		The comment is acknowledged and input appreciated.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	General comment	0	0	The International Society for CNS Clinical Trials and Methodology (ISCTM), https://isctm.org/, welcomes the opportunity to respond to the EMA request for comment regarding the Guideline on clinical investigation of medicinal products in the treatment of depression. The ISCTM offers these comments for consideration based on experience and expertise in human CNS research. The ISCTM is an independent organization focused on advancing the development of improved treatments for CNS disorders. No member of this Working Group, comprising scientists, clinicians, trialists, statisticians and drug developers from both industry and academia, received compensation for comments provided. Comments represent individual opinions and not that of the institution, agency, or company affiliation of group members. The ISCTM formed a group, led by Amir Inamdar and Dong-Jing Fu, to review and provide comments on behalf of the Society. The authors (in alphabetical order) of the comments provided below are: Scott Aaronson, MD, Sheppard Pratt Health System Larry Alphs, MD, PhD, Larry Alphs Consulting Corine de Boer, MD, PhD, Tulip Medical Consulting Franco De Crescenzo, MD, Boehringer Ingelheim Pharmaceuticals Franco Di Cesare, MD, Leoben Research AURORA Sonya Eremenco, MA, Critical Path Institute Brisa Fernandes, MD, PhD, The University of Texas Health Science Center at Houston Dong-Jing Fu, MD, PhD, Janssen Research & Development George Garibaldi, MD, Noema Pharma Nanco Hefting, PharmD, H. Lundbeck AS Amir Inamdar, MBBS, DNB (Psych), MFPM, Cybin Ni Khin, MD, Neurocrine Biosciences Colette Kosik- Gonzalez, MA, Janssen Research & Development William Lenderking, PhD, Evidera Antony Loebel, MD, Independent Tom Macek, PharmD, PhD, Novartis Pharmaceuticals Atul Mahableshwarkar, MD, Independent Ronald Marcus, MD, Karuna Therapeutics Annalisa Marotto, PharmD, Boehringer Ingelheim International GmbH Felix Menne, PhD, ki:elements GmbH Eamon O'Loinsigh, PhD, MTOPRA, EOLAS Regulatory Consulting William Z. Potter, MD, PhD, Independent Jill Rasmussen, MD, psi-napse Claire Roberts, PhD, Beckley Psytech Ltd Joshua Siegel, PhD, Sumitomo Pharma America Leif Simmatis, PhD, University of Toronto Adam Simmons, MPH, Premier Research Stephanie Sommer, PhD, Boehringer Ingelheim International GmbH Louisa Steinberg, MD, PhD, ICON Plc Michele Veldsman, PhD, Cambridge Cognition Qing Wang, PhD, Neumarker Wenqiong Xue, PhD, Boehringer Ingelheim Pharmaceuticals Christian Yavorsky, PhD, Valis Bioscience Silvia Zaragoza Domingo, PhD, Neuropsynchro		The comment is acknowledged and input appreciated. Of note, some stakeholders mentioned in the list provided separate comments,e.g. Boehringer Ingelheim International GmbH and Lundbeck. So there are some redundancies.
EFPIA	General comment	0	0	The update to the clinical guideline for depression is welcomed and appears to reflect recent advances in understanding in this therapeutic area. However, the guideline frequently references existing uncertainties in the context of recent developments which may evolve further in the next few years and quite quickly lead to this guideline becoming outdated in some areas. Given this, it would be helpful for the EMA to consider how to provide further updates to medicine developers in this therapeutic area once rev 3 is finalised. Perhaps considering a rapid update alongside the current guidance format may be useful.		The comment is acknowledged. There is a SOP for drafting and updating guidelines at EMA. Adhoc new developments are rather highlighted by postion papers and are incorporated in the guidelines in due time if required.
EFPIA	General comment	0	0	The revision 2 guidance (section 4.1.1) explicitly calls out that "Three-arm trials including both a placebo and an active control are recommended." This is not present in the draft revision 3. Noting about one-third to two-third of the trials, in which an active control is used as a third arm, the effect of the active control could not be distinguished from that of placebo, the absence of active control/reference is welcomed in order to expedite trial conduct and reduce the risk of generation of ambiguous data, but please confirm the draft revision reflects EMA's current attitude.		It is confirmed that the draft revision reflects current EMA attidtude. No explicit requirement for three-arm trials including placebo and acitve comparator versus test product for licensing. See also comment on ISCTM input on this issue.
EFPIA	General comment	0	0	The term placebo effect is used within the document. Placebo effect is a causal statement which cannot be assessed in clinical trials for new medicines. We would propose to replace 'placebo effect' with 'placebo response' throughout the document.		Accepted. 'placebo effect' was replaced with 'placebo response'
EFPIA	General comment	0	0	With the advent of precision psychiatry approaches (e.g. combined EEG/wearable/psychometric profiling) intending to identify subpopulations that may respond better to specific agents, please elaborate on EMA's attitudes to such technologies and expectations for supportive information.		Validation is needed before recommendations on precision medicine approaches can be made. No change required.
EFPIA	General comment	0	0	Please elaborate on EMA's current expectations with regards to anhedonia in depression, notably preferred endpoints and population selection.		Anhedonia is no specifier according to DSM 5 but an inherent symptom of depression. No change required.
EFPIA	General comment	0	0	Given the specific attributes associated with post-partum depression and widespread use of the Edinburgh Postnatal Depression Scale (EPDS) as a peripartum screener for depressive symptoms, consider a recommendation for cut-off scores for inclusion based on EPDS in addition to more general depression assessments.		Partly accepted. The EPDS is a validated screening tool for PPD widely used to assess the likelihood of clinical depression and recently recommended by the American College of Obstetricians and Gynecologists. Gerbasi ME, Eldar-Lissai A, Acaster S, Fridman M, Bonthapally V, Hodgkins P, Kanes SJ, Meltzer-Brody S. Associations between commonly used patient-reported outcome tools in postpartum depression clinical practice and the Hamilton Rating Scale for Depression. Arch Womens Ment Health. 2020 Oct;23(5):727-735. The follwing sentence was added: T**he Edinburgh Postnatal Depression Scale (EDPS) is an example of a patient-reported screening instrument that can be used in addition to the usual depression assessments.** See Section on postpartum depression in 4.4.3.
EFPIA	General comment	0	0	Noting current data on psychedelic agents (4.3.2.4) also suggests rapid action and that these and other agents in development do not follow a classic chronic dosing paradigm, consider expanding the foreseeable treatment situations to include single course or single dose-intermittent treatments to allow elaboration of expectations in these settings.		Partly accepted. A sentence was added in section 4.2. Rapid acting antidepressants including psychedelics might not follow a classic chronic dosing paradigm, so single course treatments or single- dose intermittent treatments should be justified.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	99	100	Non compliance is a concern with existing therapies	Despite many approved antidepressants there is a need for new medicinal products with better efficacy (e.g. faster onset of action, improved compliance, higher rates of response and remission)	Improved compliance although connected does not necessarily improve efficacy of a medicinal product. Not accepted.

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Certara	Specific comment	109	109	Instead of 'repurposing' suggest 'using recent clinical (or therapeutic) development'.		Accepted.
EFPIA	Specific comment	111	111	Editorial comment: Major Depressive Disorder written out in full again, whereas already defined earlier in the guideline.	… of patients with MDD experience residual symptoms with first line standard	Editorial comment accepted. Full term replaced by MDD.
Certara	Specific comment	122	122	Instead of 'psychedelic associated psychotherapy' suggest using 'psychedelic assisted psychotherapy'.		Not accepted. Suggestion to delete here ~~and the new paradigm of psychedelic associated psychotherapy in the field of MDD~~ See rewording lines 179-180: **Psychological support /Psychotherapy** ~~Psychedelic-assisted psychotherapy~~ **in conjunction with the use of psychedelics** faces several challenges mainly related to standardisation, training, monitoring and safety that need to be addressed in specific study designs (section 4.3.2.4.). Reference is also made to update in lines 554-562 in section 4.3.2.4. Psychedelics.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	126	126	Sex seems to be the more appropriate term - the following reference from the Council of Europe describes different definitions of sex Vs gender from WHO, etc: https://www.coe.int/en/web/gender-matters/sex-and-gender#17. The term gender should be replaced throughout the guideline with "sex" as at present the terms are used interchangeably. Finally, this bullet point should be revised as there is no section on drug metabolism differences (Section 4.5.3 discusses sex-relates to differential 5-HT-related responses in animal models, and discusses higher prevalence of MDD in women combined with sex-related differences in suicide attempts Vs completed suicide - so no recommendations regarding sex-related differences in drug metabolism. So suggest changing this bullet to match the title of 4.5.3.)	Sex-related differences and considerations in MDD	Accepted. See also section 4.5.3.
EFPIA	Specific comment	127	128	Comment/rationale: Providing examples of the instruments/scales would help the sponsors e.g., C-SSRS scale.	The need to monitor the degree of suicidal thoughts and behaviour and their change (improvement or worsening) with antidepressant therapy by use of validated instruments is confirmed (e.g. C-SSRS scale, SIBAT, Sheehan-STS).	Not acccepted here. Examples for rating scales are mentioned in section 4.6.1.3. The reference to this section is added.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	132	136	Line 137 cites WHO Depression FACT Sheet, 2023, but it is not clear if this is the source of the information in the preceding sentences.	Please add citation to reference the source of these figures.	Accepted. A more general refence to WHO web pages is added with access date.
Boehringer Ingelheim International GmbH	Specific comment	136	139	There is a large body of literature pointing towards the fact that patients with MDD frequently also suffer from other comorbidities, most notably from anxiety disorders. This fact is also reflected in clinical treatment guidelines, such as the 2022 NICE treatment guideline for adult MDD.	More than 700 000 people die due to suicide every year (World Health Organization, Depression Fact Sheet, 2023). Depression freequently occurs with comorbid psychiatric disorders. For preschool children MDD is very rare (point prevalence is thought to be 0.5%), in adolescents the prevalence is estimated to be approximately 8%.	Accepted. See also ISCTM comment below.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	136	139	MDD is not the only cause of suicide. For example, in Canada, StatCan estimated in 2017 that ~60% of suicides were secondary to depression. There is a large body of literature pointing towards the fact that patients with MDD frequently also suffer from other comorbidities, most notably from anxiety disorders. This fact is also reflected in clinical treatment guidelines, such as the 2022 NICE treatment guideline for adult MDD.	More than 700 000 people die due to suicide every year (World Health Organization, Depression Fact Sheet, 2023), and MDD is a leading precipitating factor for suicide. Depression frequently occurs with comorbid psychiatric disorders. For preschool children MDD is very rare (point prevalence is thought to be 0.5%), in adolescents the prevalence is estimated to be approximately 8%.	Accepted. See also BI comment above.
EFPIA	Specific comment	166	166	Editorial comment: The text references recent approval of a treatment for TRD. Inclusion of time references may rapidly become outdated and may cause confusion. Propose to remove the word 'recent'	treatment for TRD in an add-on setting with conventional….	Partly accepted. Recent was deleted: The ~~recent~~ approval of a treatment for TRD in an add-on setting with conventional SSRIs or SNRIs after at least two treatment failures has resulted in adjunctive treatment trials being considered a valid approach for TRD (section 4.4.1.).
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	172	172	Period needed after the word "guideline" to separate end of sentence from next one starting with Notwithstanding.	guideline. Notwithstanding the availability of many compounds with established efficacy and safety there	Editorial comment accepted. See same EFPIA comment.
EFPIA	Specific comment	172	172	Typographical comment: Include full stop and space after "guidelineNotwithstanding"	….guideline. Notwithstanding the availability of many compounds with established efficacy and safety there	Editorial comment accepted. See same ISCTM comment.
Certara	Specific comment	179	179	In addition to depression suggest adding post-traumatic stress disorder (PTSD) and anxiety		Not accepted since this guideline focusses on MDD. **MDD** is used instead of depression.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	194	196	"like" is very conversational in tone - same comment for line 202	Specific methodological issues as well as efficacy and safety issues regarding special populations including children and adolescents, young adults and older people have been addressed	Editorial comment accepted. Also for line 202.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	197	200	Although something is mentioned in the Executive summary, the scope section does not state clearly the scope of the guidance regarding non-unipolar depression i.e. in BP-I/II	State clearly to what extent this guide includes recommendations for clinical trials non-unipolar as in BPI/II. No text is proposed because the intentions are not clearly defined. Perhaps include the text or similar from section 4.2.5, Extrapolations, lines 402-404: "a major depressive episode may also occur in the framework of bipolar and related disorders. In general the development of a product in this patient group will be the same as for unipolar depression."	Accepted. The following wording is included: **Since there is a separate Guideline for bipolar disorder bipolar depression is not in the scope of this guideline (see section 4.2.5).** **And in section 4.2.5 line 403/404 was removed.**

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Boehringer Ingelheim International GmbH	Specific comment	201	203	Given the high prevalence of psychiatric comorbidities, it may prove challenging to conduct clinical trials supporting the development of novel antidepressants in patients with MDD who do present with any psychiatric comorbidity. Given that such an "MDD only" populations does not appear to reflect the real-world clinical setting, a more achievable target could be to aim for developing novel antidepressants in patients where MDD is in the primary focus of treatment. Furthermore, the 2018 FDA draft MDD guidance recommends to not exclude such patients. Hence, allowing for such comorbidities would also allow more easily to perform global clinical trials meeting needs of other stakeholders, such as the FDA as well.	Symptoms of major depressive epidsodes occuring in comorbidity with psychiatric disorders are within scope of this guideline as long as depression is the primary focus of treatment. Symptoms of major depressive episodes occurring in comorbidity with somatic disorders like Parkinson's disease, Alzheimer's disease, cerebrovascular disorders, cancer and chronic pain syndromes are not in the focus of this guideline.	Not accepted. The diagnostic criteria in DSM-5 exclude comorbidities that can form alternative explanations for mood disturbances. If a claim in depression associated with for instance Parkinson is pursued the compound should be studies in that population. The wording is kept. See same ISCTM comment below.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	201	203	Given the high prevalence of psychiatric comorbidities, it may prove challenging to conduct clinical trials supporting the development of novel antidepressants in patients with MDD who do present with any psychiatric comorbidity. Given that such an "MDD only" populations does not appear to reflect the real-world clinical setting, a more achievable target could be to aim for developing novel antidepressants in patients where MDD is in the primary focus of treatment. Furthermore, the 2018 FDA draft MDD guidance recommends to not exclude such patients. Hence, allowing for such comorbidities would also allow more easily to perform global clinical trials meeting needs of other stakeholders, such as the FDA as well.	Symptoms of major depressive episodes occurring in comorbidity with psychiatric disorders are within scope of this guideline as long as depression is the primary focus of treatment. Symptoms of major depressive episodes occurring in comorbidity with somatic disorders like Parkinson's disease, Alzheimer's disease, cerebrovascular disorders, cancer and chronic pain syndromes are not in the focus of this guideline.	Not accepted. The diagnostic criteria in DSM-5 exclude comorbidities that can form alternative explanations for mood disturbances. If a claim in depression associated with for instance Parkinson is pursued the compound should be studied in that population. The wording is kept. See same Boehringer Ingelheim comment above.
SG	Specific comment	205	218	There are a few important aspects of informative clinical trials in mental health that are not or only briefly mentioned in this guidance, but may be particularly important for depression and other mental health areas (e.g. transparency, proportionality, and involvement of the public). Here, references to more in depth general guidance from WHO and GCTC would be helpful.	Add the following text to line 218: „General guidance, including on transparency, proportionality, and involvement of potential participants and relevant stakeholders can be found in WHO's guidance for best practices for clinical trials (https://cdn.who.int/media/docs/defaultsource/research-for-health/2023-07_whoguidance-for-best-practices-for-clinicaltrials_draft-for-public-consultation.pdf) and the guidance from the multi stakeholder initiative Good Clinical Trials Collaborative GCTC (https://www.goodtrials.org/guidance)	Reference is made to EMA and ICH guidance in section 3. This is considered sufficient. No change required. See general comment made on this issue above.
EFPIA	Specific comment	221	237	Comment/rationale: Under section 4.1 (Clinical Pharmacology studies), it will be helpful to add details under three additional sub-headings as shown in the proposed text.	4.1.4. Safety studies like tQT (section 4.6.1.7), driving and human abuse liability potential assessments 4.1.5. Biopharmaceutical studies including relative BA, BE studies, and assessment of impact of acid reducing agents on the investigational drug e.g., proton pump inhibitor drug and antacids. 4.1.6. ADME studies which include absolute bioavailability and mass balance assessments.	Not accepted since a reference to the relevant guidelines is made.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	226	226	Propose to use correct wording for "magnetic resonance"	"magnet resonance" should be spelled "magnetic resonance"	Editorial comment accepted. However, the section was reworded.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	230	232	Besides what it is mentioned as expected, it can be interesting to collect patient experience under the use of the drug using open methods not addressing specific known/expected domains or concepts as cognition, reaction time or sleep.	Studies on cognition, reaction time and sleep may be helpful to characterize the safety profile of an antidepressant and should be considered based on pharmacological profile/MOA and evolving tolerability profile of the proposed product. Safety profile can also include information based on patient subjective experience of drug use.	Partly accepted. The following was included: **In addition, safety profiling should include studies providing data informing the probability of adverse events to be monitored as described in section 4.6.** See also EFPIA comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	231	231	MOA should be spelled out as "mechanism of action" rather than abbreviated in this line. It is spelled out on lines 233 to 236 and not abbreviated elsewhere in the document.	pharmacological profile / mechanism of action	Accepted. Abbreviation explained and full term replaced by abbreviation later.
EFPIA	Specific comment	231	231	Editorial comment: MOA is not defined in abbreviation list and later in the section 'mechanism of action' is written out in full.	…should be considered based on pharmacological profile/mechanism of action (MOA) and evolving…	Accepted. Abbreviation explained and full term replaced by abbreviation later.
EFPIA	Specific comment	232	232	Provide additional details concerning the link to adverse events listed in section 4.6	…….tolerability profile of the proposed product. In addition, safety profiling should include studies providing data informing the probability of adverse events to be monitored as described in 4.6.	Accepted. See also ISCTM comment above.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	233	234		Suggest EMA add to text that if studies evaluating mechanism of action or novel pathways are positive these data could be included in the SmPC.	Not accepted. No change required. What will be included in the SmPC is in the end a matter of assessment. No need to put this into the Guideline.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	235	237	This mention would promote the use of systems like RdOC to stablish the link between pre-clinical and human studies.	For specific domains, it is expected that appropriate preclinical studies (e.g. in vitro and receptor binding studies) should be able to support the mechanism of action and the positive effects in the domains, and forecast the effect in humans based on accepted theoretical constructs.	Party accepted. Not only for specific domains. It is expected that approriate preclinical studies (e.g. in vitro and receptor binding studies) should be able to support the MOA, potential effective dose and where approriate the positive effects in specific domains, and forecast the effect in humans based on accepted theoretical constructs.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	240	240	There are numerous relevant PK guidelines that should be consulted -such as PK studies, special populations (e.g., renal/hepatic impairment, older patients, drug-drug interactions, bioequivalence studies to bridge between different formulations used through development plan through to commercial product).	…see the relevant guidelines on pharmacokinetic studies in man, including special populations, drug interactions, etc…	Accepted.
EFPIA	Specific comment	241	241	Clarification is sought to highlight that responses include both efficacy and safety.	……exposure and response (including efficacy and safety).	Accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	242	242	Sex and gender are not synonyms and should not be treated as such in this guidance. By adding (gender) in parentheses after sex, the current wording treats it as a synonym. Propose to use modern language to refer to "sex assigned at birth" rather than only "sex".	sex assigned at birth	Partly accepted. Sex and geder are both used separately and gender is no longer in parentheses.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	243	243	In clinical practice patients treated with stimulants (ADHD treatment), antipsychotics (elderly or people with behavioural problems), antiepileptics, or substance users might be the end users. The analysis of concurrent therapies/substance use on targeted subpopulation can guide the pharmacokinetic studies. We also need to consider that Cannabinoids use has become widespread in some countries.	Population PK analyses may be used to investigate pertinent covariates e.g. weight, age, sex (gender), healthy vs patient population, concomitant medications relevant to targeted patient subpopulation, etc. that may influence the pharmacokinetics of the drug.	Partly accepted with slight modification: ...concomitant medications **including those relevant to targeted patient subpopulations**, etc....
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	246	248	In clinical practice patients treated with stimulants (ADHD treatment), antipsychotics (elderly or people with behavioural problems), antiepileptics, or substance users might be the end users. The analysis of concurrent therapies/substance use on targeted subpopulation can guide the pharmacokinetic studies. We also need to consider that Cannabinoids use has widespread in some countries.	In general, the guideline on drug interactions should be followed to investigate possible pharmacokinetic interactions with other drugs and food. Interactions with alcohol and other relevant CNS active compounds relevant to targeted patient subpopulation should be investigated.	Not accepted. Would introduce the concept of targeted subpoulations for interaction studies. Reference to the guideline is sufficient.
EFPIA	Specific comment	247	247	CNS drugs may interact with the investigational agent due to either PK-mediated interactions, and/or PD interactions (e.g., serotonin syndrome exaggeration; decrease the threshold for seizures etc.). Therefore, further clarification is proposed regarding interaction studies.	....Interactions with alcohol and other relevant CNS active compounds should be investigated which may include pharmacokinetic as well as pharmacodynamic interactions.	Accepted.
Certara	Specific comment	249	249	The reference 'CPMP/EWP/560/95/Rev. 1 Corr. 2**' is for the drug interaction guideline, while part of it will be relevant even after the ICH guideline has been finalised and come into force, this will be managed by EMA. At the moment it's listed after RI and HI study requirements which is not correct. We propose to delete the reference.		Accepted. The reference is deleted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	257	258	Dosing is different in different populations - 1st episode, recurrent episodes, TRD elderly. Therefore, flexibility should be mentioned.	The minimum effective dose and the dose which most efficacy is achieved should be established when possible.	Accepted. An additional sentence on rapid acting antidepressants was also added based on EFPIA comment. The minimum effective dose and the dose at which most efficacy is achieved should be established **when possible. Rapid acting antidepressants including psychedelics might not follow a classic chronic dosing paradigm, so single course treatments or single- dose intermittent treatments should be justified.**
H. Lundbeck A/S	Specific comment	260	260	The draft guideline states that a relapse prevention study should be conducted. In view of the near consistent success of this type of studies, it could be considered sufficient for medicinal products with conventional mechanism of action to either waive these trials, or to allow them to be conducted as a post-marketing commitment (similar to the FDA approach)?	".....usually at least two pivotal short-term studies are expected. A relapse prevention study should also be considered (section 4.2.3).	Not accepted. A relapse prevention study is expected prior to approval. The wording is kept. See also similar ISCTM and EFPIA comments
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	260	260	In view of the near consistent success of relapse prevention studies, could it be considered sufficient for medicinal products with conventional mechanism of action to either waive these trials, or to allow them to be conducted as a post-marketing commitment (similar to the FDA approach)?	A relapse prevention study may also be conducted (section 4.2.3.)	Not accepted. A relapse prevention study is a requirement for MAA. The wording is kept. See also EFPIA and Lundbeck comment on this issue.
EFPIA	Specific comment	260	260	The draft guideline states that a relapse prevention study should be conducted. In view of the near consistent success of this type of study, could it be considered sufficient to either waive these trials, or to allow them to be conducted as a post-marketing commitment (similar to the FDA approach)?	".....usually at least two pivotal short-term studies are expected. A relapse prevention study should also be considered (section 4.2.3).	Not accepted. A relapse prevention study is expected prior to approval. The wording is kept. See also Lundbeck and ISCTM comment on this issue.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	261	and elsewhere	Consistency of language throughout	"Depression" --> "MDD"	Editorial comment accepted.
Boehringer Ingelheim International GmbH	Specific comment	267	270	Given that approved antidepressants already demonstrated superiority over placebo, and taking into consideration ethical challenges - especially in the monotherapy setting - with the inclusion of a placebo arm, flexibility would be welcom with regard to the number of trials demonstrating superiority over active drug.	A two-arm trial establishing superiority of the test product over active comparator may be considered acceptable as one or two required pivotal short-term studies to establish an antidepressant effect of the new test product	Not accepted. At least one trial should be placebo controlled. The other could be a superiority trial over active comparator. The wording is now: Hence, randomised, double blind, placebo-controlled trials are the gold standard to permit adequate evaluation of short-term efficacy. **A placebo arm in at least one of the studies is required to evaluate the true effect size of a new antidepressive agent. Additionally**, a two-arm trial establishing superiority of the test product over an active comparator is considered acceptable as one of two required pivotal short-term studies to establish an antidepressant effect of the new test product. **However, it does not necessarily allow claiming better efficacy than the comparator as in absence of a placebo arm it cannot be determined whether the response of the active control may approach that of the putative placebo.** See also ISCTM comment.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	267	270	Comment 1:Given that approved antidepressants already demonstrated superiority over placebo, and taking into consideration ethical challenges - especially in the monotherapy setting - with the inclusion of a placebo arm, flexibility would be welcome with regard to the number of trials demonstrating superiority over active drug. Comment 2: As written text can mean superior efficacy is not better efficacy.	A two-arm trial establishing superiority of the test product over active comparator may be considered acceptable as one or two required pivotal short-term studies to establish an antidepressant effect of the new test product, but does not necessarily allow claiming better efficacy than the comparator. Suggest EMA add text to clarify thinking about a trial demonstrating superiority but not being adequate to claim better efficacy.	See above Boehringer Ingelheim comment: The wording is now: Hence, randomised, double blind, placebo-controlled trials are the gold standard to permit adequate evaluation of short-term efficacy. **A placebo arm in at least one of the studies is required to evaluate the true effect size of a new antidepressive agent. Additionally,** a two-arm trial establishing superiority of the test product over an active comparator is considered acceptable as one of two required pivotal short-term studies to establish an antidepressant effect of the new test product. **However, it does not necessarily allow claiming better efficacy than the comparator as in absence of a placebo arm it cannot be determined whether the response of the active control may approach that of the putative placebo.**
Certara	Specific comment	268	268	Missing word.	...test product over an active comparator...	Accepted. "An" was added.
Certara	Specific comment	271	272	Sentence seems superfluous as this should occur for any assessment - suggest deleting.		Accepted.
H. Lundbeck A/S	Specific comment	274	276	It is unclear whether multiplicity adjustment for response/remission is needed and whether significance or specific numeric advantages are required. The word 'addressed' appears very broad.	"When an effect is quantified in terms of change from baseline to end of treatment using a validated measurement tool, response and remission rates should also be provided"	Accepted. See EFPIA and ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	274	276	Response and remission are clinically meaningful endpoints at patient level to be included. It is unclear whether multiplicity adjustment for response/remission is needed and whether significance or specific numeric advantages are required. The current 2013 MDD guideline states " In MDD a 50% improvement of a patient on a usual rating scale is accepted as a clinically relevant response. Other definitions of responder may be used, e.g. other grades of response or proportion of patients with full remission. "Criteria for response and remission must be pre-specified and justified in the study protocol." - is there a reason this text is no longer included?	When an effect is quantified in terms of change from baseline to end of treatment using a validated measurement tool, this effect has to be addressed also by supportive analyses as rates of responders and remitters.	Partly accepted. The text is still included. See section 4.3.2.1. A reference is added. **When an effect is quantified in terms of change from baseline to end of treatment using a validated measurement tool, response and remission rates should also be provided (see also section 4.3.2.1.).** See similar Lundbeck and EFPIA comment.
EFPIA	Specific comment	274	275	It is unclear whether multiplicity adjustment for response/remission is needed and whether significance or specific numeric advantages are required. The word 'addressed' is very broad.	When an effect is quantified in terms of change from baseline to end of treatment using a validated measurement tool, response and remission rates should also be provided.	Accepted. See also Lundbeck and ISCTM comment.
EFPIA	Specific comment	280	280	Editorial comment: The sentence on the final benefit risk assessment may be moved to the end of section 4.2 Assessment of Therapeutic Efficacy Propose to move the text in lines 271-272 ("For final benefit-risk assessment the whole data package of a development program will be taken into consideration") to the end of section 4.2 after line 280.	...the estimates of effect size. For final benefit-risk assessment the whole data package of a development program will be taken into consideration.	Not accepted.The sentence was deleted as considered superfluous. See also Certara comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	282	329	This section is very much welcomed, and it is appreciated that there is room for flexibility. However, as currently written it is not entirely clear as guidance to what would be accepted and what not. It is acknowledged that the choice of estimands depends very much on the clinical question and the trial design chosen, but the text may be critically reviewed again and clarified. A suggestion would be to divide up in options for primary estimands by trial design, considerations on supplementary estimands and then expectations regarding sensitivity analyses.	"The scientific question(s) of interest, i.e. what the trial seeks to address, and consequently the target(s) of estimation (estimand) should be clearly specified. Trial planning, design, conduct, analysis, and interpretation must be aligned with the estimand. Reference is made to ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials (EMA/CHMP/ICH/436221/2017). Relevance and (expected) frequency of intercurrent events may differ between different therapeutic settings and consequently influence the definition of a relevant (primary) estimand. Different estimands may be warranted depending on the type of treatment such as monotherapy, add-on treatment or rapid acting antidepressants as well as depending on the therapeutic goal: treatment of acute symptoms in current (index) episode, and long-term efficacy (relapse/recurrence prevention) (see also section 4.2.3.). With a considerable number of alternative treatments available in the MDD setting, relevant intercurrent events to be considered include, but are not limited to, treatment discontinuation and changes in medication such as use of alternative anti-depressants or other medications and changes in background therapy (e.g. psychotherapy, anxiolytic medication, hypnotic medication). In addition, depending on the population selected, death due to committed suicide might require incorporation into the estimand definition. Irrespective of the setting and unless an alternative strategy is duly justified, 'treatment discontinuation' should be handled with a treatment policy strategy addressing the treatment effect regardless of discontinuing treatment. Similarly, a treatment policy strategy is relevant for changes in background therapies, which is equivalent to considering them as part of the treatment regimen of interest. "The use of alternative anti-depressants that are not considered part of the treatment regimen of interest (i.e. therapies that could not be co-administered with the investigational treatment) are not part of the treatment effect of interest (i.e. the effects of the investigational product). A treatment policy strategy would not be appropriate, but a hypothetical strategy, in which alternative medication is assumed not to have been an option, is more relevant. The use of alternative medications generally follows patients' discontinuation from the treatment regimen of interest, and appropriate methods should be used to handle these co-occurring events with different strategies.	Not accepted It is acknowledged that clarity, in particular with respect to handling use of alternative medications, is wished for. However, handling of alternative medication is still part of ongoing discussions: treatment policy strategy and hypothetical strategy have both advantages and disadvantages. The choice to leave it open in the GL was intentionally made. General considerations on relevant estimands are provided that are applicable regardless of chosen design. See also Lundbeck and EFPIA comment
EFPIA	Specific comment	289	292	Propose to clarify and strengthen the wording in the following text:..."treatment of acute symptoms in current (index) episode, maintenance of effect during current episode (relapse prevention) and prevention of new episodes (recurrence prevention) with long-term treatment (see also section 4.2.3.)."	...treatment of acute symptoms in current (index) episode, long-term efficacy (relapse/recurrence prevention) (see also section 4.2.3.). All estimands should be clearly aligned with the scientific question of interest.	Accepted.
Certara	Specific comment	297	297	Extra word. Suggest deleting 'committed'.		Accepted.

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H. Lundbeck A/S	Specific comment	304	310	This new section is very much welcomed, and it is appreciated that there is room for flexibility. However, as currently written it is not entirely clear as guidance to what would be accepted and what not. It is acknowledged that the choice of estimands depends very much on the clinical question and the trial design chosen, it is proposed that the text is critically reviewed and clarified. A suggestion would be to divide up in options for primary estimands by trial design, considerations on supplementary estimands and then expectations regarding sensitivity analyses.	"The use of alternative anti-depressants that are not considered part of the treatment regimen of interest (i.e., therapies that could not be coadministered with the investigational treatment) are not part of the treatment effect of interest (i.e. the effects of the investigational product). A treatment policy strategy would not be appropriate, but a hypothetical strategy, in which alternative medication is assumed not to have been an option, might be more relevant. The use of alternative medications generally follow patients' discontinuation from the treatment regimen of interest, and appropriate methods should be used to handle these co-occuring events with different strategies…"	Not accepted It is acknowledged that clarity, in particular with repsect to handling use of alternative medications, is wished for. However, handling of alternative medication is still part of ongoing discussions: treatment policy strategy and hypothetical strategy have both advantages and disadvantages. The choice to leave it open in the GL was intentionally made. General considerations on relevant estimands are provided that are applicable regardless of chosen design. See also ISCTM and EFPIA comment
EFPIA	Specific comment	304	310	A decision must be made as to whether or not the investigational product on its own is effective and to what extent. If other antidepressants are taken after treatment discontinuation, then the effects of these products should not be included in the assessment of the effects of the investigational product.	The use of alternative anti-depressants that are not considered part of the treatment regimen of interest (i.e. therapies that could not be co-administered with the investigational treatment) are not part of the treatment effect of interest (i.e. the effects of the investigational product). A treatment policy strategy would not be appropriate, but a hypothetical strategy, in which alternative medication is assumed not to have been an option, might be more relevant. Delete the following sentence [Still, the downside of this hypothetical strategy is that a theoretical treatment effect – not existing in the real world - is estimated, as alternative treatments are available in real life. Furthermore,]	Not accepted It is acknowledged that clarity, in particular with repsect to handling use of alternative medications, is wished for. However, handling of alternative medication is still part of ongoing discussions: treatment policy strategy and hypothetical strategy have both advantages and disadvantages. The choice to leave it open in the GL was intentionally made. See also Lundbeck and ISCTM comment
Boehringer Ingelheim International GmbH	Specific comment	331	332	Further guidance on these factors including relevant literature references would be welcome. In particular, interest is in approaches to controlling for nonspecific treatment effects, e.g. conferred by participation in a clinical trial per se, contact with site personnel, lengthy assessments above and beyond a pure placebo response.		The section was rewritten and concentrates now only on placebo response.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	331	338	Placebo effect/response is multi factorial. Different enrichment strategies may be employed with data-driven justifications.	"Multiple factors have been used to explain improvements in response observed in patients treated with placebo. These include changes in brain neurochemical activity, patient and rater expectation bias, and sometimes exaggeration or faking of symptoms at baseline. In clinical trials with an adjunctive treatment design, it may relate to prior treatment compliance. Which of these are most important in the context of any specific study often remains an open question at trial completion. Therefore, sponsors are encouraged to identify and, if possible, manage the specific factors that might affect outcome response in their trial. Documentation of features affecting trial outcomes in the population being studied that go beyond the diagnosis of MDD and how these may relate to improvement on placebo treatment is important for understanding treatment response. Population enrichment strategies that screen out individuals likely to improve on placebo may impair clinical validity. Therefore, the use of enrichment strategies such as "placebo lead in" in Phase 3 studies requires data-based justifications that such enrichment minimizes impact on interpretation of the clinical validity of the results."	Not accepted. Enrichment strategies limit representativeness of population and are not acceptable. Selected population would not be representative of the whole MDD. Furthermore, Placebo Run-In periods (PRI) offer no additional benefit. A systematic review study suggests that the use of PRI periods is common in RCTs of antidepressants, despite offering no apparent benefits to RCT outcomes; given the risks and costs of PRI periods, their practice should be ceased. Scott et al. 2021 https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2785863 See also EFPIA and Lundbeck comment.
Certara	Specific comment	331	333	The training of investigators may be one consideration for controlling the placebo effect, especially as some external factors depend on the investigator, such as overrating patients at baseline, can contribute to a high placebo response in some trials.	Consider adding one sentence for the training of the investigators on the placebo effect.	Accepted. The following sentence is introduced: **Appropriate training of investigators may help to reduce a high placebo response caused by overrating of patients at baseline.**
Boehringer Ingelheim International GmbH	Specific comment	332	334	Suggest to delete this statement, since it seems to be out of place in the current section.		Accepted.
H. Lundbeck A/S	Specific comment	336	338	It is not clear why enrichment strategies with placebo run-in would not be acceptable for Phase 3 studies. Depending on their implementation, these can be effective in mitigating exaggerated placeboeffects. Suggest deleting Lines 336-338 and/or recommending scientific advice on this topic.	"…for which an indication is sought. Taking into consideration the above, randomised double-blind comparisons versus placebo…"	Not accepted. Placebo-run in with subsequent selction of patients limit generalizability to the target population. See also EFPIA and ISCTM comment
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	336	338	It is not clear why enrichment strategies with placebo run-in would not be acceptable for Phase 3 studies. Depending on their implementation, these can be effective in mitigating exaggerated placebo-effects. Suggest deleting Lines 336-338 and/or recommending scientific advice on this topic.	Suggest deleting Lines 336-338. For such studies, further discussion on the relevant estimand may be required.	Not accepted. See above. See also EFPIA and Lundbeck comment.
EFPIA	Specific comment	336	338	We respectfully disagree with the statement that enrichment strategies with placebo run-in would not be acceptable for Phase 3 studies. With appropriate blinding these strategies can be effective in mitigating exaggerated placebo-response. As acknowledged in the text of the guideline, mitigation of placebo response is important, even more in larger Phase 3 trials than Phase 2 trials. Clinical trials can only provide effects of medicinal products in the sample studied under the conditions of the trial. Therefore, observed effects will never be representative for actual treatment effects in individual patients in clinical practice.	Delete the following sentence [Enrichment strategies with a placebo run-in are only acceptable in phase 2 but not for phase 3 studies, since the clinical validity of the studies may be affected (section 4.3.2). For such studies, further discussion on the relevant estimand may be required.]	Not accepted. A placebo run-in is not conducted in clinical practice. See also ISCTM and Lundbeck comment on this issue.
Boehringer Ingelheim International GmbH	Specific comment	339	343	Suggest to move these paragraphs to Section 4.3, since they seem to be more related with the overall trial methodology than potential control of placebo response.		Accepted. Belongs to study design and the paragraphs were shifted to section 4.3.2.

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Boehringer Ingelheim International GmbH	Specific comment	339	340	This change would be in line with the proposal regarding lines 267-270 where the use of superiority study(ies) to support regulatory approval would be acceptable	randomised double-blind comparisons versus placebo or approved comperator in the whole population are needed to allow adequate evaluation of efficacy	Partly accepted. However, lines 339-344 were moved to section 4.3.2. where it is more appropriate. The sentence reads: Two randomised, double blind, ~~**placebo-**~~ controlled trials are required to allow adequate evaluation of short-term efficacy. **At least one of the trials should be placebo-controlled.** See also EFPIA and ISCTM comment. See also section 4.2.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	339	340	This change would be in line with the proposal regarding lines 267-270 where the use of superiority study(ies) to support regulatory approval would be acceptable	randomised double-blind comparisons versus placebo or approved comparator in the whole population are needed to allow adequate evaluation of efficacy	Section was moved to section 4.3.2. Study design and reworded. Only partly accepted. See also EFPIA and BI comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	343	344	Could risks associated with placebo treatment be managed with careful follow up of patients symptoms and intervention if deterioration in symptom status is observed?	Precautions to minimise the impact of the use of placebo on the potential deterioration of the patients' condition should be taken, e.g., by limiting the duration of the study (section 4.3.2.).	No proposed text. No change required. Of note, sentence was moved to section 4.3.2. Study design
Certara	Specific comment	346	346	Replace 'are occuring' with occur.		Editorial comment accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	350	350	It was unclear whether the 50% was a group-level or individual-level response. Reading further makes it clear that they mean individual. So recommending to remove ambiguity here.	"Usually a response criterion of 50% or more is applied to define individual treatment response…"	Accepted. However the sentence is shifted to 4.2. Assessment of Therapeutic Efficacy.
Boehringer Ingelheim International GmbH	Specific comment	357	358	Even though it is agreed that in some conditions the episodes may be longer than 6 month, such an observation may point towards treatment-resistant depression which is addressed in a different section. To facilitate global harmonsiation it would be beneficial if the agency allow an applicant with a justification in the specific population that such a cut-off could be used. In addition the agency should clearer distinguish whether the recurrence and or relapse is mandatory as the sentences before point to the duration of maintance effect and blow the speicifics of relapse prevention are discussed, which may require trials of other durations.	the 6 months cut-off point has been used for regulatory purposes. In addition, the guideline focuses on showing effect during the index episode and/or prevention of the next episode	Partly accepted. There seems to be a confusion on relapse and recurrence. The whole section has been reworded to make definitions (see there at end of the guideline) clearer. See also ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	357	358	Even so agreed that in some conditions the episodes may be longer than 6 months, however this raises suspicions that they may be treatment-resistant depression which are handled in a different section for good reasons. Not only to get a harmonization world wide based the agency should allow an applicant with a justification in the specific population that such a cut-off could be used. In addition the agency should clearly distinguish whether the recurrence and or relapse is mandatory.	the 6 months cut-off point has been used for regulatory purposes. However in addition, the guideline focuses on showing effect during the index episode and/or prevention of the next episode	Partly accepted. Redundant information in section 4.2.3 that is contained in section 4.3.2. has been deleted and information on response criterion shifted to 4.2. See also Boehringer Ingelheim comment.
H. Lundbeck A/S	Specific comment	359	365	Reference is made to definitions of relapse prevention and recurrence prevention, but these definitions are not provided further in the document. In addition, it is suggested that symptomatic improvement occurs before resolution of pathology. As the pathology of MDD is not clear these suggestions are hypothetical. Furthermore, it is unclear how recurrence prevention should be addressed in terms of clinical trial design.	"…during the index episode and/or prevention of the next episode. Whether long-tern efficacy should be shown prior to authorisation or can be deferred to after authorisation will depend on the type of program and should be discussed with the Agency (section 4.3.2)"	Not accepted. Maintenance of effect is a requirement for approval. The whole section has been revised to provide clearer wording. There is a section on Definitions at the end of the guideline. This has been shifted to the beginning. See also Boehringer Ingelheim and ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	359	363	Comment 1: As noted throughout the document, there is considerable individual variability in disease course. As previously mentioned, the underlying pathophysiology of MDD remains incompletely understood. It is also widely assumed there is considerable individual variability in underlying pathophysiology presenting with overlapping symptoms. As such, lines 359-361 should be reconsidered. Reference is made to definitions of relapse prevention and recurrence prevention, but these are not given. In addition, it is suggested that symptomatic improvement occurs before resolution of pathology. As the pathology of MDD is not clear these suggestions are hypothetical. It is unclear how recurrence prevention should be addressed in terms of clinical trial design. Comment 2: In clinical practice, there is significant variability in the duration of maintenance therapy for patients who have had multiple MDEs and are at high risk of recurrence. Long-term use of medications, in the timeframe of years, is more common than indefinite continuation.	Consider striking lines 359-361; Consider revising "prevention of recurrence is seen in the frame of indefinite continuation" to "long-term continuation"	Partly accepted. Section 4.2.3. has been shortened and restructured. The sentence for long continuation is no longer in. Definitons which are given after the references at the end of the Guidleine have been inserted in the text. The Difinitions section was moved to the begining of the document. See also Lundbeck comment.
Certara	Specific comment	359	363	Suggest this paragraph refers to the definition section at the end of the guidance.		Accepted. Reference to the Definitions is inserted. Definitions was moved to the beginning of the guideline. However, the whole paragraph has been reworded based on Boehringer Ingelheim, Lundbeck, EFPIA and ISCTM comments.
EFPIA	Specific comment	359	363	Reference is made to definitions of relapse prevention and recurrence prevention, but these are not given. In addition, it is suggested that symptomatic improvement occurs before resolution of pathology. As the pathology of MDD is not clear these suggestions are hypothetical. It is unclear how recurrence prevention should be addressed in terms of clinical trial design.	Delete the following text [The definitions of relapse prevention and recurrence prevention assume that symptomatic improvement occurs before resolution of the underlying pathophysiology and that the risk of relapse only decreases as the pathophysiology continues to resolve. In practice, the prevention of relapse is usually seen in the context of short-term treatment (and within the current depressive episode), whilst the prevention of recurrence is seen in the frame of indefinite continuation.]	The whole section 4.2.3. has been modified. See also ISCTM and Boehringer Ingelheim input.
EFPIA	Specific comment	364	365	Proposed change in line with comment above.	Whether long-term efficacy should be shown prior to authorisation or can be deferred to after authorisation will depend on the type of program and should be discussed (section 4.3.2.) Remove the following text [For authorisation it should be shown that a short-term effect can be maintained during the current (index) episode (relapse prevention)]	Not accepted. See comments above.

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H. Lundbeck A/S	Specific comment	366	372	It is not clear which data are expected to be provided for the frequency of episodes to be determined and how the duration of the trial treatment should be established. Furthermore, clarity is needed on how to retrospectively recognize relapse and recurrence in candidate subjects for a trial	Whole section line 366-372 is proposed deleted and replaced with section clarifying the mentioned elements in the comments	Partly accepted. The whole section has been revised. See ISCTM and EFPIA comments.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	366	372	As noted, there is considerable individual variability in underlying pathophysiology and, as a result, high variability with the timeframe of recurrence of MDEs. To study recurrence prevention, long-term data would be required and this would be more realistic in the context of a RWE study. Alternatively, a model would be required in which patients would be selected that have a history of frequent recurrence. However, this would be in conflict with the advice that enrichment strategies should not be used beyond phase II studies.	Consider striking lines 367-368 "Patients in full remission should be randomized to test product or placebo."	No longer applicable since section 4.2.3. has been modified. See also EFPIA comment.
EFPIA	Specific comment	366	372	It is not clear which data are expected to be provided to determine the frequency of episodes and how the duration of the trial treatment should be established. It is also not clear how relapse and recurrence rates would be recognized retrospectively in candidate subjects for a trial.	Delete the following text [Prevention of the next episode(s) or recurrence prevention is a worthwhile treatment goal. It is encouraged to evaluate this in specific studies (section 1.1.). Patients in full remission should be randomized to test product or placebo. Study duration will be dependent on the frequency of episodes in the study population and should be justified accordingly. Recurrence should be prespecified as a depressive episode that fulfils current DSM-5 criteria and a certain degree of severity on a validated rating scale. In non-bipolar patients, definitive comparisons of the test substance should be performed versus a placebo. For prevention in bipolar patients, the relevant guideline should be consulted.]	Partly accepted. See Lundbeck and ISCTM comment. Section 4.2.3. has been modified.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	368	369	How is the 'frequency of episodes in the study population to be determined? Patients are often unreliable reporters of their episode frequency, especially when they are in the midst of an episode and the clinician managing the patient at the time may not be able to document their frequency as a patient may have several different clinicians during their illness. To do this for an entire study population reliably would seem to be a very difficult task. Which data are expected to be provided for the frequency of episodes and how should the duration of the trial treatment be established? How are relapse and recurrence to be recognized retrospectively in candidate subjects for a trial?	Suggest striking this sentence: Study duration will be dependent on the frequency of episodes in the study population and should be justified accordingly	No longer applicable since section 4.2.3. has been modified. See also EFPIA and Lundbeck comment.
SG	Specific comment	378	396	This section lacks a discussion of study population beyond assessment of diagnostic criteria and MDD severity. It is well-documented that many patients are ineligible for antidepressant trials, with negative impact on generalizability of trial results (Zimmerman et al. Psychother Psychosom 2019 PMID: 31096246). It should be stated that exclusion criteria should be focused on participant safety and that unnecessary restrictions should be avoided . For example, suicidality is mentioned under „Specific adverse events to be monitored", however this is not addressed specifically with regard to study population.	Rename this section to „Study population and entry criteria". Add a specific paragraph highlighting the need for broad study populations and justification for exclusion. Specifically address suicidality and history of suicidal behavior including suicide attempts. This may be combined with the statement on out-patients (lines 395-396). Proposed text: „Efforts should be made to include a broad and varied study population that reflects the range of MDD. Entry criteria should avoid unnecessary restrictions and exclusion criteria should be focused on identifying individuals for whom participation would place them at undue risk compared to risk in routine clinical care. Specifically, patients with a history of suicidal ideation and behavior need not be systematically excluded from trials."	Partly accepted. The heading of this section is changed to Study population **and entry criteria** Proposed wording on population partly accepted. See also general comment above. The paragraph reads now: In addition, cut-off scores, based on an appropriate scale may be used as inclusion criteria. **In studies where the main aim is to show an agent is effective at all, i.e. dose-finding phase II studies, a more homogeneous population more sensitive to detect such effect needs consideration.**
EFPIA	Specific comment	378	378	Major Depressive Disorder written out in full again, whereas already defined earlier in the guideline.	MDD should be classified according to an internationally acknowledged….	Editorial comment accepted.
Boehringer Ingelheim International GmbH	Specific comment	382	384	While it is acknowledged that detailed medical history, in particular with regard to depression ,should be documented, patient records may not always be accessible or complete (e.g., for patients residing in countries without centrally recorded electronic healthcare records; especially in case patients have changed their treating physician in the past).	detailed history, e.g., duration of the depression and of the index episode, number of episodes per time interval, previous treatment outcome, should also be documented, if such data can be obtained and when relevant	Not accepted. It is self-evident. No change required. See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	382	384	While it is acknowledged that detailed medical history, in particular with regard to depression ,should be documented, patient records may not always be accessible or complete (e.g., for patients residing in countries without centrally recorded electronic healthcare records; especially in case patients have changed their treating physician in the past).	detailed history, e.g., duration of the depression and of the index episode, number of episodes per time interval, previous treatment outcome, should also be documented, if such data can be obtained and when relevant	Not accepted. It is self-evident. No change required. See Boehringer Ingelheim comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	389	390	Request more clarity or a more specific number of patients with severe depression to include. As written, a sufficient number is open to interpretation and not specific enough.	More details regarding what a sufficient number of patients with severe depression would help set expectations for clinical programs.	Not accepted. No specific recommendation on a specific number of patients can be given. The aim is better explained. The wording reads now: However, **an appropriate** number of patients with severe depression should be included in the clinical development program allowing the **evaluation of a potential effect modification.**
Boehringer Ingelheim International GmbH	Specific comment	393	394	Pivotal trials tend to be conducted in a larger number of countries and with the aim to generate data supporting global registrations. In addition, the current FDA guidance recommends to not unnecessarily restrict the patient population. In addition, the DSM-5 based diagnostic criteria per se do result in a heterogeneous population. The changed wording would allow for some more flexibility in this regard.	While it is highly desirable that the study population is homogeneous with respect to the indication for the dose finding and pivotal studies, it is acknowledged that some heterogeneity may need to be introduced into pivotal trials to allow for generalizability of the results to the clinical setting (section 4.2.2.).	Partly accepted. See SG and ISCTM comment. The paragraph on homogeneous population has been changed and reads now: **In studies where the main aim is to show an agent is effective at all, i.e. dose-finding phase II studies, a more homogeneous population more sensitive to detect such effect needs consideration.**

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	393	394	Pivotal trials tend to be conducted in a larger number of countries and with the aim to generate data supporting global registrations. In addition, the current FDA guidance recommends to not unnecessarily restrict the patient population. In addition, the DSM-5 based diagnostic criteria per se do result in a heterogeneous population. The changed wording would allow for some more flexibility in this regard. Additionally, Phase 3 studies are typically conducted in a broader population than earlier studies, including more countries where treatment approaches and standard-of-care may differ, to achieve enrolment targets and reflect the target population see below comment in 393-394 on "better generalisability of study results". Additionally, both EMA and FDA have specific guidance documents on the need and approaches for extrapolating ex-EU and ex-US clinical trial data to the EU and US populations respectively in line with the ICH E5 guideline in order to overcome country- and ethnicity-related differences.	While it is highly desirable that the study population is homogeneous with respect to the indication for the dose finding and pivotal studies, it is acknowledged that some heterogeneity may need to be introduced into pivotal trials to allow for generalizability of the results to the clinical setting (section 4.2.2.).	Partly accepted. See SG and Boehringer Ingelheim comment. The paragraph on homogeneous population has been changed and reads now: **In studies where the main aim is to show an agent is effective at all, i.e. dose-finding phase II studies, a more homogeneous population more sensitive to detect such effect needs consideration.**
Boehringer Ingelheim International GmbH	Specific comment	395	396	Depending on the patient population to be included and the indication aimed for, some patients may, e.g., be so severely ill or at such high risk of suicide that an out-patient setting would pose too high a risk to patient safety, especially for those patients randomized to placebo.	Though some of the earlier studies may be done in hospitalised patients, the majority of the database should be in out-patients for better generalizability of the study results, unless patient safety considerations render the conduct of trials in out-patients impossible.	Accepted. See also ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	395	396	Depending on the patient population to be included and the indication aimed for, some patients may, e.g., be so severely ill or at such high risk of suicide that an out-patient setting would pose too high a risk to patient safety, especially for those patients randomized to placebo.	Though some of the earlier studies may be done in hospitalised patients, the majority of the database should be in out-patients for better generalizability of the study results, unless patient safety considerations render the conduct of trials in out-patients impossible.	Accepted. See also Boehringer Ingelheim comment.
Boehringer Ingelheim International GmbH	Specific comment	400	401	Rather than categorically requiring all the trials of a classical development program for MDD, the possibiilty to discuss alternative approaches via Scientific Advice would be welcomed. This is proposed particularly in the light of the possibility that future treatment modalities may be able to address certain types of depression without demonstrating relevant efficacy in MDD.	If such specific claims are strived for, the clinical development program should be discussed early in a Scientific Advice / Protocol Assistence.	Partially accepted. However, depressive symptoms are also seen in other psychiatric disorders or other types of depression. If such specific claims are strived for, **specific studies should be conducted.** ~~**additional studies to the classical development program for major depression should be provided.**~~ See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	400	401	Rather than categorically requiring all the trials of a classical development program for MDD, the possibility to discuss alternative approaches via Scientific Advice would be welcomed. This is proposed particularly in the light of the possibility that future treatment modalities may be able to address certain types of depression without demonstrating relevant efficacy in MDD. Additionally this wording on specific claims regarding MDE in other psychiatric disorders contradicts lines 201-203, Scope)	If such specific claims are strived for, the clinical development program should be discussed early in a Scientific Advice / Protocol Assistance.	Partially accepted. However, depressive symptoms are also seen in other psychiatric disorders or other types of depression. If such specific claims are strived for, **specific studies should be conducted.** ~~additional studies to the classical development program for major depression should be provided.~~ See Boehringer Ingelheim comment. However, there is no contradiction to lines 202-203 since the scope refers to the focus of the Guideline and does not cover all kinds of scenarios.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	415	417	This sentence should mention patient-reported outcome measures of depression that are considered acceptable to determine symptomatic improvement, not only the clinician-reported outcome measures listed in this sentence. Suggest to have SMDDS listed, but it may not yet meet the criteria for sensitivity to change. Could propose BDI or QIDS.	Suggest to add other examples of acceptable validated PRO measures of depression to this sentence.	Not accepted. No specific recommendations on certain scales can be included since some may be copyrighted.
Boehringer Ingelheim International GmbH	Specific comment	421	423	Since novel antidepressants should address symptoms that are considered relevant by patients, it could be envisioned that novel assessment tools will be developed based on patient input. Opening the guidance to the potential use of novel assessment tools would therefore be welcome.	In addition, changes in other aspects of the disorder including, but not limited to changes in global assessment (e.g. Clinical Global Impression assessment scale) or in social functioning may be used as a key secondary endpoint as long as the assessment tools are validated.	Accepted. See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	421	423	Since novel antidepressants should address symptoms that are considered relevant by patients, it could be envisioned that novel assessment tools will be developed based on patient input. Opening the guidance to the potential use of novel assessment tools would therefore be welcome.	In addition, changes in other aspects of the disorder including, but not limited to changes in global assessment (e.g. Clinical Global Impression assessment scale) or in social functioning may be used as a key secondary endpoint as long as the assessment tools are validated.	Accepted. See also BI comment.
Boehringer Ingelheim International GmbH	Specific comment	424	426	While it is acknowledged that there may be a need for psychometric analyses for novel assessment tools, for which limited data are avilalble, these may be fulfilled both by data from the clinical studies as well as stand-alone studies. Hence, some flexibility would be warranted. In addition, requiring such analyses for all investigator in a large multinational trial is likely to be unfeasible.	Inter-rater reliability scores (e.g. by using kappa statistics) should be documented fo a group of raters sufficiently sized for such analyses with regard to rating scales used for efficacy, where relevant.	Partly accepted. Text is modified: Investigators **and raters** should be properly trained in evaluating the patient. Inter-rater reliability scores (e.g. by using kappa statistics) should be documented ~~for each investigator~~ **for a group of raters sufficiently sized** ~~in advance and if necessary, during the study, both with regard to the diagnosis and to~~**for such analyses.** See also ISCTM comment on this issue and also broader comment of EFPIA.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	424	427	" Clarify the intent here. As written, this sentence does not make sense. Inter-rater reliability is a measure of agreement among 2 or more investigators - one would not calculate a kappa statistic for each investigator. If the intent is to look at intra-rater reliability, this does not seem feasible before the study starts and likely would not be interpretable during the study. In addition, this is a feasibility issue as currently written because it requires using kappa statistics for each investigator in advance of starting the study. During the conduct of the studies, inevitably there are changes in Site raters (e.g., drop outs, additional raters), making it impossible to have Kappa scores in advance."	Inter-rater reliability scores should be documented for each investigator during the study, with regard to the rating scales used for efficacy, where relevant.	Partly accepted. Text is modified: Investigators **and raters** should be properly trained in evaluating the patient. Inter-rater reliability scores (e.g. by using kappa statistics) should be documented ~~for each investigator~~ **for a group of raters sufficiently sized** ~~in advance and if necessary, during the study, both with regard to the diagnosis and to~~ **for such analyses**. See also Boehringer Ingelheim comment on this issue and broader comment of EFPIA.
EFPIA	Specific comment	424	427	With the widespread application of central rating approaches (site-independent raters, centralised over-read of site ratings, technologies contrasting rater vs patient outcomes etc) please clarify EMA's attitude to implementation of these services and any expectations with regards to use for primary or secondary endpoints. Some commentary on this approach is already noted in section 4.3.2.4 in terms of assessment of psychedelic compounds but has widespread applicability for other agents beyond psychedelics. There is a brief reference in lines 534-536, but the wording could be expanded within lines 424-427.	No specific text proposed	Accepted. The following sentence is introduced: **The use of independent and blinded central raters can be used in particular cases provided that the central rating assessments have been validated (section 4.4.2.4.)**
SG	Specific comment	428	431	Patient-reported outcomes (PROs) are mentioned but no reference is made to involving members of the community (e.g. patients' and relatives' groups) in the planning and conduct of clinical trials. The guideline should therefore include a statement that highlights the importance of this.	Add the following text in line 431: " The perspectives of members of the community (e.g. patients' and relatives' groups) should be included in the planning, execution, and interpretation of trials. The involvement of patients and relevant stakeholders / members of the public (e.g. relatives) should play a key role in refining and prioritizing research questions; assessing RCT acceptability and feasibility; selecting outcomes that are relevant and meaningful to the intended population; developing the RCT design and procedures; optimizing the nature and delivery of information; and encouraging dialogue about access to health interventions that prove effective."	Not accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	428	430	The sentiment of this sentence is greatly appreciated, and minor revisions are proposed. The word "Since" at the beginning should be replaced by "Because" due to the fact that the sentence is about causality and not about time since something occurred. A comma was added after "relevant" to add readability. It would be clearer to refer to the development of new PRO measures not new PROs, because the measures are the tool to assess the outcome and are in need of development.	Because the patients' perspective on the relative importance of symptoms of their disorder is relevant, self-rated symptoms scales can also be used and the development of new patient-reported outcome (PRO) measures is encouraged.	Accepted. See BI comment.
Certara	Specific comment	428	431	Can the agency give some examples of more relevant PRO scales? For example, EQ-5D?		Not accepted. Sponsors should justify their choice of PRO. There are several options.
Boehringer Ingelheim International GmbH	Specific comment	429	430	Suggest to replace. Given that the aim of developing novel antidepressants is to provide treatments to patients that they consider relevant, situations may emerge where the primary or key secondar treatment target could be measured by novel PROs assessing how the patient feels, functions or survives. In addition some endpoints might be only measurable with PRO (e.g., Suicidality).	If such outcomes are to be considered as primary or key secondary endpoints, Scientific Advice is recommended.	Accepted. See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	430	431	Suggest to replace. Given that the aim of developing novel antidepressants is to provide treatments to patients that they consider relevant, situations may emerge where the primary or key secondary treatment target could be measured by novel PROs assessing how the patient feels, functions or survives. In addition some endpoints might be only measurable with PRO (e.g., Suicidality). We strongly request that this sentence be reconsidered and rewritten entirely so that the place of PRO measures in the endpoint hierarchy is not limited in the future to second-place status. Sentences like this in regulatory guidance will make it harder to justify inclusion of PRO measures in clinical trials in which they are greatly needed. The proposed revision is more encouraging of their use to support secondary endpoints, while not completely ruling out other endpoint positioning. Additionally, relevance to mention methods that have been or will be used in a near future, defining its role and views from the agency. Please comment if other PROs (as above for comment to line 423) may be suitable as key secondary endpoints. As written - the use of PROs is relegated to supplementary and relegated to secondary endpoints in clinical trials.	Several suggestions included to replace the current sentence.1) If such outcomes are to be considered as primary or key secondary endpoints, Scientific Advice is recommended. 2)These outcome measures are recommended to support secondary endpoints in clinical trials. The use of adaptive assessment instruments or other methods (Goal Attainment Scaling, Digital Health Technology) can also be considered as fit-for-purpose under a personalized approaches and with exploratory purposes in early stages. Proof of validity should be documented in order to be considered as secondary or primary endpoints.	First proposal is accepted.
Certara	Specific comment	437	437	Can the agency provide guidance on how real world data/evidence should be used in trials for MMD?		Real word data/evidence can only be supportive. This section is about study designs for a standard program. No change required.
SG	Specific comment	438	438	Given that the guidance highlights the importance of placebo-controlled, double blind trials (line 438), it should specifically be mentioned that blinding is not only attempted but its success tested and those results reported. Less than 10% of antidepressant RCTs between 2000-2020 reported blinding assessment (Lin et al., EClinMed 2022 PMID: 35812993). Here, strong guidance by EMA is required.	Add the following text to line 441: "Assessment of success of blinding should be included in all trials and methods predefined in the trial protocol. Blinding success should be reported using suitable statistics that account for correct guesses by chance."	Accepted.
H. Lundbeck A/S	Specific comment	442	445	The guidance text mentions issues associated with placebo run-in periods and that the population in a clinical trial with a placebo run-in is different from a trial without placebo run-in. Furthermore, it is not clear why it would be (more) different from clinical practice if all patients would be randomized There are study designs where placebo lead-in periods are used for reasons other than subject inclusion - this guidance should differentiate between these two uses and provide guidance on each.	"Use of a placebo run-in period in phase 2 and phase 3 trials (single- or double-blind) and potential subsequent patient selection should be discussed in Scientific Advice prior to the conduct of the trial(s). Generalizability of the results to the population treated in clinical practice should be considered. With respect to placebo response reference is made to section 4.2.2."	Not accepted. See also ISCTM and EFPIA comment on placebo run-in.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	442	442	The dismissal of placebo run-in in this document as an acceptable enrichment strategy in phase 2 (but not phase 3) makes this statement unclear.	Please comment or affirm if a phase 2 study that utilizes a placebo run-in (336 - 338) would be acceptable for this purpose.	Accepted. It is confirmed that this refers to confirmatory phase 3 studies.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	442	446	The rationale that this enrichment strategy is problematic to the generalisability in clinical practice is irrelevant to the context of a clinical trial. A clinical trial does not mirror clinical practice or may not correspond to the target population. As written - this negates an enrichment strategy that could be based on a double-blind enrichment strategy (such as sequential parallel design, Fava) would be considered problematic or possibly unacceptable. In addition - based on the rationale given for why a placebo enrichment run-in (even if single blind) would be excluded by this statement. Why would the population in a clinical trial with placebo run-in be different from a trial without placebo run-in and why would it be (more) different from clinical practice if all patients would be randomized?	Strike or clarify	Not accepted. In clinical practice there is ususally no placebo run-in. Questioning validity of clinical trials for practice in genetral, this would invalidate the whole approval process based on such trials. Morover, SPD designs by FAVA are also not acceptable (see Benda 2020; https://onlinelibrary.wiley.com/doi/full/10.1002/pst.1992). In short, they either are biased for the overall population or inefficient. Consequently they are not acceptable for pivotal trials. See also Lundbeck and EFPIA comment.
EFPIA	Specific comment	442	445	The guidance text describes issues associated with placebo lead-in periods when used to select subjects for a subsequent randomised period. There are study designs where placebo lead-in periods are used for reasons other than subject inclusion - this guidance should differentiate between these two uses and provide guidance on each.	Use of a placebo run-in period (single- or double-blind) and potential subsequent patient selection should be discussed in Scientific Advice prior to the conduct of the trial(s). Generalisability of the results to the population treated in clinical practice should be considered. With respect to placebo response reference is made to section 4.2.2.	Not accepted. Enrichment is not accepted (see above) and suggesting scientific advice will not change that. Placeb-run in do usually not happen in practice and in clinical trials they usually result in patients beeing excluded (even if no criteria are specifiefd for this). See also Lundbeck and ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	447	448	Randomization would likely provide equitable distribution between treatment and placebo groups with the use of anxiolytic or hypnotic medication use in combination with study drug treatment. An apriori subgroup analysis of the use of anxiolytic or hypnotic medications or no use of these medications can be performed at study completion after database lock. However, if treatment effect in these subgroups is expected to be different or considered as important (e.g., labelling) then stratification should be considered.	Request modification of the proposed stratification language on lines 447-448 (see comments).	Accepted. The following wording is included: If a constant anxiolytic or hypnotic medication cannot be avoided, **a corresponding subgroup analysis should be pre-specified to assess consistency of the treatment effect in each relevant subgroup. Stratifying randomization by use of anxiolytic or hypnotoc medication in combination with study treatment should be considered, in particular, if this subgroup is considered of special relevance.** ~~stratified randomization may be useful to help assess consistency of the treatment effect in each relevant subgroup.~~
Boehringer Ingelheim International GmbH	Specific comment	449	452	While true standardized psychotherapy may not be implementable in the context of a clinical trial, other means of psychosocial interventions might be both feasible and beneficial.	A trial-specific, standardised psychosocial support (e.g., psycho-education, motivational support or counselling) may be given as supplementary treatment, though it may enhance the response in both treatment groups, but it should be prospectively defined in the protocol. It should be documented in detail and its influence on treatment effect should be analysed.	Not accepted. Adapted to wording in section 4.3.2.4. Psychedelics. A trial-specific, standardised psychotherapy**/psychological support,** (psycho-education, **motivational** support or counselling) may be given as supplementary treatment, though it may enhance the response in both treatment groups, but it should be prospectively defined in the protocol. See also ISCTM comment
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	449	452	While true standardized psychotherapy may not be implementable in the context of a clinical trial, other means of psychosocial interventions might be both feasible and beneficial. It will be difficult to assess influence of standardised psychotherapy/psychosocial support on tx effect unless you have sub-groups of patients (e.g., at a site- or country-level) that receive and do not receive psychosocial support - if all subjects receive this then how can you analyse influence on treatment effect?	A trial-specific, standardised, psychosocial support (e.g., psycho-education, motivational support or counselling) may be given as supplementary treatment, though it may enhance the response in both treatment groups, but it should be prospectively defined in the protocol. It should be documented in detail and its influence on treatment effect should be analysed.	Partly accepted. Adapted to wording in section 4.3.2.4. Psychedelics. A trial-specific, standardised psychotherapy**/psychological suppor**t, (psycho-education, **motivational** support or counselling) may be given as supplementary treatment, though it may enhance the response in both treatment groups, but it should be prospectively defined in the protocol. See aso BI comment
Boehringer Ingelheim International GmbH	Specific comment	454	465	As section 4.2.3 covers three phases including the acute phase, the continuation phase and the maintenance phase, it's a bit confusing in terms of the objectives of short-term and long-term trials, suggest to clarify	short-term trials for acute effect; long-term trials for relapse prevention	Partly accepted. Wording was clarified in section 4.2.3.
Certara	Specific comment	457	458	How does the agency look at interventions where the pharmacodynamic effect far outlasts the PK profile, i.e., in treatment interventions affecting neuronal plasticity)?		The introductory sentence reads: Depending on the mechanism of action, pivotal trials should be long-enough to demonstrate a treatment effect. No change required.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	496	497	As recognised elsewhere in the guidance, alternative comparators may be applicable for psychedelics. Suggest to include wording to indicate one placebo-controlled trial may be sufficient when combined with trials utilising other comparators.	"At least one double blind, randomised, parallel group, placebo controlled clinical trial is required.	Partly accepted. Changed to: **At least one ~~Double~~ of the pivotal trials should be double** blind, randomised, parallel group, placebo-controlled ~~clinical trials are required~~, as is the case with conventional antidepressants.
EFPIA	Specific comment	504	504	The sentence seems to be missing two words.	…where the rapid acting antidepressant is administered alone in patients initiating therapy or replacing a conventional antidepressant….	Editorial comment accepted.

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Boehringer Ingelheim International GmbH	Specific comment	508	509	The 3 described scenarios may need different durations especially b) that would be replaced with an already aproved AD and testing durability again would mainly rrepeat the testing that was already completed for the approved drug.	In any case durability of effect beyond the initial treatment response should be characterized, dependent on the chosen treatment situations mentioned before.	Accepted.
Psychedelic Access and Research European Alliance	Specific comment	513	518		513 psychedelics including dissociative anaesthetics (e.g. ketamine, esketamine) and entactogens (e.g. 514 MDMA). Psychedelics alter perception, mood and affect numerous cognitive processes 515 via different mechanisms of action; those relevant in the context of therapeutic use remain to be definitively established. 516 They can however also acutely induce anxiety and other psychiatric adverse events including suicidal ideation 517 and behaviour (section 4.6.1.). These as well as cardiovascular effects (particularly for MDMA) require careful monitoring and 518 further investigations.	Accepted. See also Certara comment
Certara	Specific comment	516	517	This statement is not fully supported by research, in fact, the opposite may be true. It is suggested the sentence is revised.	In some studies, psychedelics have been associated with increased anxiety and other psychiatric adverse events including suicidal ideation and behaviour.	Not accepted. Induce is replaced by **acutely induce** See comment by Psychedelic Access and Research European Allicance
Psychedelic Access and Research European Alliance	Specific comment	520	520		antidepressants, to establish a positive benefit/risk ratio	Editorial comment accepted. benefit/risk **ratio**
Psychedelic Access and Research European Alliance	Specific comment	521	522		521 term trials are needed, as well as trials to determine the maintenance of effect, optimal psychological support and the impact of these treatments on recovery and functioning over time. Moreover, rigorous application of real-world evidence and digital health technologies can supplement traditional confirmatory trials.Due to the high unmet medical needs , it is recommended to start development in a more	Partly accepted. The sentence reads now: As with all other antidepressants, to establish a positive benefit/risk **ratio** randomized, double-blind placebo-controlled short-term trials are needed, as well as **extended or long-term** trials to determine the maintenance of effect, o**ptimal psychological support and the impact of these treatments on recovery and functioning over time.** Real-world evidence difficult to interpret for regulatory purposes,e.g. indigenous communities. Digital health technologies too unspecific.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	521	523	To date the safety profile of psychedelics in clinical trials has been well tolerated, so not sure I agree with this statement. As with all new potential treatments data driven risk and benefit assessments should define what patient population is targeted.	"Depending on the risk/benefit profile of the psychedelic under investigation, it may be recommended to start development in a more severely affected population."	Partly accepted. Proposed wording: Due to ~~the safety profile and challenging study setup and execution~~**potential significant alterations of perception and behaviour** , it is recommended to start development in a more severely affected population, such as patients with treatment resistant depression (section 4.4.1.). See also ISCTM comment.
Certara	Specific comment	521	521	Extended or long-term trials are needed to determine the maintenance of effect for psychedelics, it is suggested that this is emphasised in the guidance.	…as well as extended or long-term trials…	Accepted.
Certara	Specific comment	525	525	More precise language is proposed.	...and interpretation of clinical trial data...	Accepted.
Psychedelic Access and Research European Alliance	Specific comment	527	529	Acknowledging the unique challenges in controlling for effects with psychedelics is important for regulatory bodies. This complexity is inherent not only to psychedelics but also to numerous other therapeutic interventions, such as psychotherapy, surgery, and chemotherapy. It arises from the current approach of considering psychedelics strictly as pharmacological interventions. Therefore, it would be helpful for regulators to either accommodate these challenges as an inherent aspect of psychedelic therapy or propose viable alternatives to address them.	Due to the obvious and easily detectable subjective effects induced by an active dose of a psychedelic 528 substance, the choice of appropriate comparator while maintaining the blinding can be 529 challenging. An effective strategy might involve systematically assessing participants' awareness of their treatment condition to ensure the reliability of blinding.	Accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	527	527	Wording is not concise. "totally different function of the brain…" is very strong language and brain function on psychedelics is dependent on multiple factors including dose and concomitant medication.	Due to potentially significant alterations in behaviour and perception of individuals under the influence of psychedelic substances…	Accepted. The sentence reads now: Due to the ~~totally different function of the brain~~ **obvious and easily detectable subjective effects induced by an active dose of a** ~~under~~ psychedelic substances the choice of appropriate comparator while maintaining the blinding can be challenging. See also similar comment by Psychedelic Access and research Alliance.
Certara	Specific comment	527	527	More precise language is proposed. Replace 'function' with 'effect'.	Due to the totally different effect of the brain under psychedelic	Not accepted. See alternative wording based on similar comments above.
Psychedelic Access and Research European Alliance	Specific comment	529	529	While this is true, experience tells us that most trials of all medicines do not monitor blinding. Moreover, many psychedelic trials use low [ineffective] doses as placebo so ensure that the patient information can truthfully specify that everyone will get at least on dose of psychedelic		Statements on the assessment of functional unblinding are included. See also section 4.3.2. and SG comments **An effective strategy might involve systematically assessing participants' awareness of their treatment condition to ensure the reliability of blinding.**
SG	Specific comment	530	536	As unblinding is of particular concern in psychhedelics trials, the importance to assess and report blinding success should be reiterated in this section	Add the following text to line 536: “Here, it is particularly important to assess and report success of blinding with appropriate methods, predefined in the trial protocol (see section 4.3.2. above).”	Accepted.

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Psychedelic Access and Research European Alliance	Specific comment	530	530	Please also note new data from the Imperial College group revealing that expectation did not affect response to psilocybin in depression but did correlate with effect in escitalopram arm https://pubmed.ncbi.nlm.nih.gov/38247730/		No change required. **Here, it is particularly important to assess and report success of blinding with appropriate methods, predefined in the trial protocol (section 4.3.2.) and to take measures of expectancy.** See comment below.
Psychedelic Access and Research European Alliance	Specific comment	531	535		531 disappointment with treatment might lead to symptom worsening or 532 safety issues (nocebo effect). Different strategies such as low dose or active placebo, i.e. 533 alternative substances with a distinct mechanism of action but with a similar psychoactive 534 effect have been used to make it more difficult to guess the treatment arm. It is recommended to assess and report on blinding efficacy, and to take measures of expectancy. The use of 535 independent and blinded external raters also could help to mitigate the effects of unblinding and expectancy, whereas including the possibility of an open-label extension for those in the control condition could mitigate disappointment and	Partly accepted. See proposal below: "**Conducting trials with different designs, e.g. offering open label treatment after the double-blind placebo controlled phase for those in the control group or including different doses (low, middle and high) without placebo could help addressing these challenges and provide complemenary information to estimate the nocebo effect**." was included
Psychedelic Access and Research European Alliance	Specific comment	536	536	And other designs work – e.g. informing people who believe correctly that they are in placebo group that at the end of the trial they will be given a full active dose – eg https://pubmed.ncbi.nlm.nih.gov/36001306/ JAMA Psychiatry alcoholism trial. It's been also used in small pharma DMT trial https://www.europeanpharmaceuticalreview.com/news/178880/major-study-on-dmt-shows-promise-for-depression/		Accepted. The following wording is introduced: **Conducting complementary trials with different designs, e.g. offering open label treatment after the double-blind phase for those in the control group or including different doses (low, middle and high) without placebo could help addressing these challenges.**
Psychedelic Access and Research European Alliance	Specific comment	536	536	Including an open-label extension possibility without jeopardizing primary outcome data or long-term maintenance of effects is one thing that a regulator could provide.		Partly accepted. See comment above.
Psychedelic Access and Research European Alliance	Specific comment	536	536	This is true but is best handled by designs that include different doses, an approach that has also been adapted to address the unblinding issue above. Presence of long-lasting therapeutic effects which are dose-dependent validates the approach.		Comments are acknowledged. "**Conducting complementary trials with different designs, e.g. offering open label treatment after the double-blind phase for those in the control group or including different doses (low, middle and high) without placebo could help addressing these challenges.**" is added.
EFPIA	Specific comment	539	540	Proposed text is considered potentially limiting and could exclude the need for individualised dosing for reasons other than those listed.	In particular, the relationship between characteristics of the acute psychedelic experience and clinical improvement, as well as the need for dose adjustment should be investigated	Partly accepted. A separate sentence is kept in line with comment of Psychedelic Access and Research European Allicance on same issue.
Psychedelic Access and Research European Alliance	Specific comment	540	540		540 experience and clinical improvement, as well as the need for individualised dosing due to inter-individual variability in drug metabolism, age, sex, personality, as well as extrapharmacological factors (so called 'set and setting') should be investigated.	Partly accepted. The following has been inlcuded: In particular, the relationship between characteristics of the acute psychedelic experience and clinical improvement, as well as the need **for dose adjustments should be investigated. This includes** individualised dosing due to inter-individual variability in drug metabolism, age, sex, ~~or~~ personality a**s well as extrapharmacological factors (so called "set and setting")**.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	542	544	In section 4.3.2 a randomized withdrawal trial is mentioned as the preferred design. Psychedelics are mainly administered as single intermittent modalities and a randomized withdrawal design is not appropriate for compounds that are not given on a chronic basis.	Removing reference to section 4.3 and replace with the following "as appropriate for the compound studies"	Partly accepted. Reference to section 4.3. deleted.
Certara	Specific comment	542	544	Can the agency suggest a time course for the evaluation of endurance of effect?		No general recommendation can be given since this depends also on the compound studied.
Psychedelic Access and Research European Alliance	Specific comment	544	544		sustainability of the action and the long-term effects, both positive and negative, of psychedelics are very limited.	Accepted with slight rewording. The experience and the available information on the sustainability of the action and the long-term effects, **both desirable and undesirable** of psychedelics **and the efficacy of re-treatment** are very limited.
Certara	Specific comment	545	546	With regards to safety, can the agency comment on how events should be handled during analysis i.e. difficult emotions, bad trips, etc brought up during the psychedelic experience could be misinterpreted as adverse events, though they can be part of the therapeutic process.		Comment is acknowledged. However, even if difficult emotions might be part of the psychedelic experience they need monitoring similarly as adverse events and reported as such. See Psychedelic Access and Research European Alliance comment.
Psychedelic Access and Research European Alliance	Specific comment	546	546		depressed patients (anxiety, derealisation, difficult experiences). Although classical serotonergic	Not accepted. Brackets are deleted. The following is included: The ability to change the perception of reality can have unknown implications for depressed patients. Therefore psychedelics need to be administered in a controlled environment. See also ISCTM comment.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	546	546	"Trips" is colloquial and thus should be put in quotation marks or use alternative suggestion.	Negative "trips" or "negative psychological experiences"	Not accepted. Brackets are deleted. The following is included: The ability to change the perception of reality can have unknown implications for depressed patients. Therefore psychedelics need to be administered in a controlled environment. See also comment above.
Psychedelic Access and Research European Alliance	Specific comment	548	548		products, depending on the mechanism of action. Headaches, mildly elevated blood pressure,	Not accepted. No need for this specific change since adverse events are mentioned in the introductory part of this section.
Psychedelic Access and Research European Alliance	Specific comment	548	548	Most psychedelics can increase heart rate/ and/or blood pressure to some extent, either directly or as a result of their psychological [anxiogenic] effects. Rarely do these get into the range of being clinically relevant, rather they are equivalent to the effect of climbing a set of stairs. In studies these can be recorded and if of a clinically-relevant magnitude be reported as adverse effects.		Comment acknowledged. No change required. See comment above.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	548	550	the rationale that is given for utilization in a controlled environment is not uncommon to other antidepressant therapies - MAOI and SNRIs. It is unclear why this is called out for psychedelics. Also, suicidality has not been conclusively demonstrated with psychedelics. In light of lack of evidence, this statement may discourage potential investigators. Additionally, these potential AEs are monitored in trials for all antidepressants regardless of Mechanism of Action so should be deleted from this section as adequately addressed in the Safety section.	Strike	Partly accepted. Redundant information has been deleted in line of what is included in the introductory part of this section.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	548	550	The safety profile and the appropriate dosing need to be determined on a case-by-case basis. The AEs quoted are not specific to psychedelics.	"The safety profile of the psychedelic should be taken into account to ensure appropriate safety mitigations are in place, which may include the dosing environment."	Partly accepted. Recommendation of controlled environment is kept. See comment above.
Certara	Specific comment	548	548	Similar to comment about suicidality previously. Suggest minor revision to text.	Headaches, elevated blood pressure, tachycardia and, in some cases, suicidality, have also been reported to be associated with the use of psychedelics.	Accepted. However, suicidality is mentioned in the itroductory part of thsi section and mentioned in section 4.6.
Psychedelic Access and Research European Alliance	Specific comment	549	549		The psychological effects are usually profound and for some people, especially those with mental illnesses, can be distressing if historic traumas or fears are uncovered. However, in the case of patients they may be of important therapeutic value in allowing access to, and recovery from, repressed memories. This means they are part of the therapeutic process in the same way as anxiety and fear are an inevitable element of exposure therapy for specific phobias or PTSD. Therefore they are not necessarily adverse effects and should not be reported as such in clinical trials. At the same time, experiencing high levels of fear and anxiety might worsen therapeutic outcomes. Anxiety might be a dose-dependent phenomenon, and a two-step approach can be applied to mitigate it: low dose and, if insufficient, followed by a higher dose. As yet unpublished research from Imperial College	Comment acknowledged but proposed change not accepted. Even if some symptoms are part of the therapeutic process they need to be monitored similarly as all adverse events and are part of the benefit risk assessment. See Certara comment.
Angelini Pharma SPA	Specific comment	549	550	Comment: "That is why psychedelics need to be administered in a controlled environment" Proposed change (if any): That is why psychedelics need to be administered in a controlled environment including home administration if properly controlled. Justification for the comment: If appropriate safety data is generated.	Proposed change (if any): That is why psychedelics need to be administered in a controlled environment including home administration if properly controlled.	Not accepted. Home environment not endorsed.
Psychedelic Access and Research European Alliance	Specific comment	550	550		Headaches occur in up to 50% of people after intake of a psychedelic dose of psilocybin. The headache is transient and responsive to regular pain killers. Elevated blood pressure and tachycardia occur but varies with type of psychedelic and in any instance, is usually mild to moderate and likely without any medical implications. Suicidal ideation and suicide attempts have been reported to occur after intake of psychedelic compounds, but given that data are from patients with a diagnosis of severe major depressive disorder, it is unclear psychedelics confer a higher risk than if patients remain insufficiently treated.	Comment acknowledged. No change required.
Certara	Specific comment	551	551	Can the agency suggest a time course for long surveillance?		The following is included: **The exact time course fo long-term surveillance depends on the MOA of a certain psychedelic and could be needed up to one year.**
Psychedelic Access and Research European Alliance	Specific comment	554	554	Terminology needs to be agreed. Several terms have been used, e.g. guides, sitters, therapists. Given these carry a significant clinical responsibility to properly prepare support and integrate the patients experience, perhaps therapist might be the best term, at least (if two people are present) for the person taking the clinical lead.		Therapist is used. No change required.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	554	562	The terminology "psychotherapy" is not clear and, at some extent, confusing. It is not obvious whether the term is referring to any form of non-directive psychological support provided by specialised mental healthcare professionals (i.e., psychiatrists, psychologists, etc.) only or also refers to a group of psychological interventions under the umbrella name of psychedelic-assisted psychotherapy. Examples include but are not limited to directive psycholytic psychodynamic-oriented therapy, which evolved in Europe from the 1950s to the 1970s; and psychedelic therapy, which developed simultaneously in the United States with the existential and humanistic orientation.	The monotherapy setting with psychedelics alone may not be applicable or feasible. The application of psychedelics is usually embedded in a non-directive psychological support. Trials need to be able to demonstrate that the effect of the psychedelic assisted therapy is not due to the non-directive psychological support alone. The framework of operation (protocol) as well as preparatory and post-dose integration sessions and whether this needs to be adapted to the type of psychedelic need to be clearly defined. Type, length and frequency of non-directive psychological support and training need to be standardised to the maximum possible effect, despite ethnic and cultural differences. Extrapolation from the trial setting to clinical practise or the plan to provide specific training to therapists needs to be addressed.	Partly accepted. There is a knowledge gap what psychedelic treatment really is: a medical treatment with psychological support? a psychotherapy assisted by psychedelic medicine? or an integrated treatment modality? Some propose non-directive psychological support, others specific psychotherapeutic interventions. Especially in the latter case a factorial design may be required. The wording is amended: Psychological support /Psychotherapy. The monotherapy setting with psychedelics alone may not be applicable or feasible. The application of psychedelics is usually embedded in a non-directive psychological support. Trials need to be able to demonstrate that the effect of the psychedelic assisted therapy is not due to the psychological intervention alone. The framework of operation (protocol) as well as preparatory and post-dose integration sessions and whether this needs to be adapted to the type of psychedelic need to be clearly defined. Type, length and frequency of the psychological intervention and training need to be standardised to the maximum possible effect, despite ethnic and cultural differences. Extrapolation from the trial setting to clinical practise or the plan to provide specific training to therapists needs to be addressed.
Certara	Specific comment	556	557	Considering that pre-counselling may influence the reporting of adverse outcomes, can the agency comment on what an acceptable preparatory session might encompass.		No change required. Regulators cannot be prescriptive here. The details of the preparatory session should be justified by the developers.
Psychedelic Access and Research European Alliance	Specific comment	557	557	Protocol/Minimum treatment set The re-emergence of psychedelic therapy over the past two decades has largely been done according to a three-phase programme: a preparation session, a treatment session and an integration session [e.g. Watts et al 2017. https://journals.sagepub.com/doi/abs/10.1177/0022167817709585] that are typically given over three consecutive days by the same people – typically psychiatrists and/or psychotherapists. The rationale here is to prepare participants [either patients or healthy volunteers] for the unique and profound psychological effects of psychedelics. This preparation is designed to minimise anxiety which we know to be a predictor of worsen clinical outcomes. It also can help participants maximise the benefits of their trip especially by encouraging them not to resist the experience which can reduce its strength and value but to go with it to explore their inner self – the catch line is "in and through". Although there is little research on alternative approaches probably because it seems unlikely that ethics committees, on safety grounds, would approve studies without these elements. Moreover, patients and healthy volunteers find them reassuring and valuable. At the same time, usually various psychotherapy approaches are not being properly evidenced and demanding these specific psychotherapy approaches can potentially mean that many patients in need of the medication might not be offered appropriate treatments because of the high demand for resources. Consequently, the area of significant contention is whether more psychotherapeutic sessions add value and if so what types of psychotherapy are best? There is little systemic research on this topic in the treatment of depression with serotonergic psychedelics. Currently there are no comparative studies of different forms of psychotherapy in combination with psychedelics. The situation with ketamine is rather different. Initially ketamine treatment – either with racemic ketamine or with esketamine – was given without therapy, a procedure colloquially called liquid ECT. However this approach might have led to ketamine not performing as well as it could: one recent RCT of ketamine in alcohol addiction that showed that ketamine + mindfulness based psychotherapy performed better than ketamine + education [Grabski et al 2022 https://pubmed.ncbi.nlm.nih.gov/35012326/] (although there exist a challenge relating to difficulties in making a distinction between placebo and psychotherapy effects due to confounding). This has been developed as a manualised treatment regime with three ketamine sessions called KARE, that is now the subject of a major NIHR trial. VIA, a private health care provider, offers KARE therapy for addictions and a modified four ketamine session version [KAP] for depression and other mental illnesses. Some clinics that previously just used ketamine for depression are now beginning to offer psychotherapy interventions during the come-down phase to explore if it adds value. The most contentious issue at present in the use of psychedelics for mental illnesses is how many (if any) psychotherapy sessions [other than the integration one] should be offered. One extreme is to provide none, simply ask the patients to return to the carer that they were under prior to the psychedelic treatment. The other extreme is to provide a full course of psychotherapy by the same therapist(s) who were present during the trip. This is of course significantly more expensive than the other approach and could make psychedelic therapy too pricey for some providers, even if it could be shown to deliver better outcomes. An interesting hybrid model that some are exploring is to allow the prior therapist to be present in the psychedelic session(s). As well as being something patients ask for as it offers continuity of care with someone they know and trust, it can provide the prior therapist with insights to work on in future sessions. In addition, it begins to increase the number of therapists who have experience of psychedelic therapy, which is likely to be a limiting issue for the expansion of the field. Guidance on the acceptability of this from the EMA would be helpful Patients' opinions are also important. We know that most patients who have had psilocybin therapy are very keen on having a number of psychotherapy follow up sessions as many have lots of questions		The area of urgent research need on the role of psychotherapeutic interventions (preparatory, accompaning treatment, integration after treatment) is acknowledged. Regulators are not prescriptive here since the data on the best approach need to come out of studies and might differ depending on the psychedelic compound (and the disease). Both approaches, psychotherapy as integral part of the psychedelic treatment or a more psychotherapy agnostic approach need justification and will have impliactions on the label. No change required unless more data emerge.
Certara	Specific comment	561	561	Spelling, suggest using practice instead of practise.		Editorial comment ccepted.
SG	Specific comment	567	596	This section almost exclusively deals with missing data and imputations. This would benefit from more general guidance on transparency and reproducibility. This section should thus list general considerations including trial registration, verifiable time stamps on pre-specification of analyses, publication of trial protocol and etc.	Add the following text to line 567: "Clinical trials should be registered from the outset on a publicly available trials database. Making other trial information (including the trial protocol and other trial documentation) public is strongly encouraged. Once the RCT is completed, trial reports should be publicly available in a timely manner (typically within 12 months) and should describe the study design, methods, and results in a clear and transparent manner."	Not accepted. Agreement with the suggested text as such, but these are very general comments applying to any clinical trial. As this is an indication-specific guidance document, these aspects are not MDD specific.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	572	574	to provide guidance to sponsors to appropriately design studies and plan for analyses	Suggest EMA provide examples of intercurrent events where data collected post-event may need to be considered as 'missing' and not utilized	Clarification will be included that data following start of an alternative antidepressant will need to be considered as missing when targeting the effect had patients not used alternative anti-depressants (hypothetical strategy). **For example, data collected following the start of alternative anti-depressants need to be considered missing when a hypothetical strategy is targeted for this intercurrent event (section 4.2.1.).**
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment - Other comments	594	594	Two periods in this line		Editorial comment accepted.

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Boehringer Ingelheim International GmbH	Specific comment	602	604	While it is correct that a recent approval for treatment-resistant depression has been based on clinical data obtained in an add-on setting, this should not in and of itself lead to negating the possibility to demonstrate efficacy for partial responders in either monotherapy or add-on setting. As the Agency acknowledges - and is reflective by clinical treatment guidelines, depression occurs on a continuum, and some patients may respond to some treatments (monotherapy or add-on), but not to others. Based on the underlying scientific rationale, there should be room to allow testing of promising medicinal products in partial responders in either monotherapy or add-on if adequately justified.	If a claim for treatment of MDD in patients with partial response is intended, the setting, i.e., monotherapy or add-on, will need to be justified. Scientific Advice is recommended.	Accepted. However, Scientific advice recommendation is not included here but under the Section Partial response.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	602	604	While it is correct that a recent approval for treatment-resistant depression has been based on clinical data obtained in an add-on setting, this should not in and of itself lead to negating the possibility to demonstrate efficacy for partial responders in either monotherapy or add-on setting. As the Agency acknowledges - and is reflective by clinical treatment guidelines, depression occurs on a continuum, and some patients may respond to some treatments (monotherapy or add-on), but not to others. Based on the underlying scientific rationale, there should be room to allow testing of promising medicinal products in partial responders in either monotherapy or add-on if adequately justified.	If a claim for treatment of MDD in patients with partial response is intended, the setting, i.e., monotherapy or add-on, will need to be justified. Scientific Advice is recommended.	Accepted. See Boehringer Ingelheim comment and below ISCTM comment on lines 645-647.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	604	604	There is no section 1.2 in the document		Accepted. It is section 1. Reference has been corrected.
SG	Specific comment	606	612	The wording suggests that the definition of TRD with regard to this guideline is strictly limited to previous attempts with pharmacological treatments ("antidepressant agents deriving from the group(s) of commonly used as first line treatment"). There is an ongoing debate in the field regarding how previous attempts with non-pharmacological treatments should be reflected in the definition of TRD (McIntyre et al., World Psych 2023 PMID: 37713549). It would be helpful to specifically state that for the purpose of this guidance, non-pharmacological treatment attempts are not part of the TRD definition.	Add the following sentence to line 612: "For the purpose of this guidance, previous non-pharmacological treatment attempts are not part of the TRD definition."	Accepted.
H. Lundbeck A/S	Specific comment	609	609	The guidance text refers to previous guidance versions in context to defining TRD. It is suggested to not refer to previous guidance versions, but rather restate what is relevant in the current version.		Accepted. Reference to previous GL versions has been deleted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	609	612	Suggest not to refer to previous guidance versions, but to restate what is relevant in the current version. The text in the last sentence of this paragraph is somewhat unclear: Inclusion should not be excluded.	Suggest rephrasing last sentence to "Inclusion of patients with one failed ..... can also be considered."	Accepted. The phrase has been changed. See Lundbeck comment.
SG	Specific comment	610	612	Current phrasing is somewhat confusing („Although the requirement of demonstration of failure of at least two antidepressants is still used for TRD trials, the inclusion of patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded")	Rephrase this section to: "Typically, TRD trials recruit patients with demonstrated history of failure of at least two antidepressants. However, inclusion of patients with only one failed treatment at a maximum tolerated dose and adequate duration may also be considered in TRD trials."	Partly accepted. See also EFPIA, ISCTM and Lundbeck comment. The following wording is proposed: **Typically,** TRD trials **recruit patients with demonstrated history of failure of at least two antidepressants** ~~has been considered as failure of at least two different antidepressant agents~~ deriving from the group(s) of **products** commonly used as first line treatment (of the same or a different class) prescribed ~~in~~ **at an** adequate dosages for **an** adequate duration, ~~and~~ with adequate affirmation of treatment adherence ~~(see previous version of the Depression Guideline EMA/CHMP/185423/2010 Rev. 2)~~. ~~Although the requirement of demonstration of failure of at least two antidepressants is still used for TRD trials~~**However,** the inclusion of patients with one failed treatment at a maximum tolerated dose and **for an** adequate duration ~~should not be excluded~~**can also be considered.The population included in the trials should be pre-specified and justified. For the purpose of this guidance, previous non-pharmacological treatment attempts are not part of the TRD definition.**
H. Lundbeck A/S	Specific comment	610	612	The text in the last sentence of this paragraph is somewhat unclear and is proposed to be clarified	"..the inclusion of patients with one failed treatment at a maximum tolerated dose and adequate duration can also be considered"	Accepted. The sentence was reworded. See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	610	612	Suggest to further justify or explain. Basing trials for TRD on different definitions limits comparability.		Comment acknowledged. Treatment resistance develops in a continuum. Sponsors should justify the population included in their trials. A sentence was added. See also EFPIA comment.
EFPIA	Specific comment	610	612	Patients who have failed only one antidepressant treatment do not meet the regulatory definition of TRD and fall far short of what psychiatrists consider in actual clinical practice to be treatment-resistant depression. Including them in these studies would provide interesting information but may make it too easy to obtain an indication for TRD. In case their inclusion is finally accepted, it would have to be defined in what proportion they can be included vs. the total sample of patients, and this proportion should be minimal.	Delete the following text [Although the requirement of demonstration of failure of at least two antidepressants is still used for TRD trials, the inclusion of patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded.]	Not accepted. Treatment resistance develops in a continuum. Sponsors should justify the population included in their trials. A sentence was added. ~~See also ISCTM comment~~
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	611	612	As written, the sentence contradicts itself by saying the inclusion of patients should not be excluded. If the intention is to say that patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded, then it would be clearer to remove "the inclusion of" at the start of this clause.	patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded.	Partly accepted. ISCTM wording suggestion to lines 609-612 above is used. See also Lundbeck comment: **However**, the inclusion of patients with one failed treatment at a maximum tolerated dose and **for an** adequate duration ~~should not be excluded~~**can also be considered.**
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	614	616	"In global trials, the requirement, as currently written, of documentation of treatment failure based solely on medical records is not feasible in some clinical trial sites in certain countries, like the United States. Obtaining medical records has been significantly challenging and even when obtained there is often insufficient information regarding response to medications. Under such circumstances, we should allow for patient interview of past treatment experience as an option to document treatment failures. This approach has been validated with the MGH-ATRQ and been used in other MAA's Chandler, G. M., Iosifescu, D. V., Pollack, M. H., Targum, S. D. & Fava, M. RESEARCH: Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci. Ther. 16, 322–325 (2010)."	Retrospective assessment of treatment failure should be primarily based on medical records of previous treatment if such records can be obtained. Additional options could include pharmacy records, and may include the patient's recollection of symptom improvement, although it is recognized this approach which may introduce some bias.	Partly accpted. "if such records can be obtained" is included. No pharmacy records usually available in Europe.

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Boehringer Ingelheim International GmbH	Specific comment	620	621	While a lot of detail is given on the criteria acceptable for the definition of TRD, these are very much lacking for partial response. As stated previously, MDD presents as a continuum where patients who do not respond to treatment exhibit progressively less response to subsequent treatments. Given the uncertainty and lack of consensus on when patients should be considered treatment resistant versus partial responders, some flexibility with regard to the number of previously failed antidepressant treatments in the current episode should be given.	Sponsors should provide and justify clear criteria for partial response to antidepressant treatments (e.g. improvement of symptoms between ≥25% and <50%). Precedence exists for including patients with 1-3 prior antidepressant treatment failures in the current depressive episodes in such trials. Scientific Advice on the detailed criteria should be sought.	Partly acccepted. 1-3 prior treatment falures is not included since this would qualify as TRD. Recommendation for scentific advice is included.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	620	622	It would be helpful if the EMA could clarify if this definition of partial response has been accepted by the Scientific Advice Working Party for development compounds in this sub-category of MDD		Yes. It is confirmed that this definition has been used. Neverheless CHMP scientific advice is recommended. **CHMP scientific advice on detailed criteria should be sought.**
Angelini Pharma SPA	Specific comment	634	634	Comment: "Monotherapy as well as add-on trials are acceptable trial designs in TRD" Justification for the comment: this could be appropriate due to the epidemiology of TRD and standard of care.	Proposed change (if any): Monotherapy as well as add-on trials are acceptable trial designs in TRD. A combined population with monotherapy and add on treatment could be considered in the same clinical trial.	Not accepted. Feasibility issues with trial design.
SU_AP	Specific comment	636	637	The approved indication according to 4.1 of the SmPC of the drug product Jatrosom and other tranylcypromine (TCP) drug products marketed in the EC is ". . . should be applied as a reserve antidepressant drug, i.e. after failure of 2 standard antidepressants (including tricyclic antidepressants)". This clearly is a description of treatment resistant depression (TRD) as the approved clinical indication of these drug products of TCP. In contrast, the draft guideline states that "Since no medicinal product has been approved for monotherapy management of patients with TRD, . . . ". and concludes that new drug products in TRD should demonstrate superiority over placebo. It is therefore recommended that new drug products in TRD may also demonstrate non-inferiority in comparison to TCP in TRD. TCP should be applied as an active control.	Delete "Since no medicinal product has been approved for monotherapy management of patients with TRD, demonstration of efficacy should be superiority over placebo." New text: "Demonstration of efficacy should be superiority over placebo. As an alternative approach or in addition to superiority over placebo, demonstration of non-inferiority to tranylcypromine may be applied."	Partly accepted. Tranylcypromin is not centrally approved. However, wording has been adapted since active comparator trials are in principle an option: ~~Since no medicinal product has been approved for monotherapy management of patients with TRD, demonstration~~ **Demonstration** of efficacy should be superiority over placebo **or an appropriate comparator**. Non-inferiority design not accepted due to unclear definiton of non-inferiority margin. See section 4.2.
Boehringer Ingelheim International GmbH	Specific comment	645	647	Given the heterogeneity in treating MDD in clinical practice both nationally and globally, narrowing add-on trials in patients with partial response down to one failed antidepressant would result in clinical trials that are not feasible. Rather a number of antidepresssants should be specified in this setting. Also based on the different approaches to MDD treatment in clinical treatment guidelines as well as the limited options for treating patients with partial response, trials testing novel medicinal products in the monotherapy setting should be considered, if justified.	Study designs may be conducted in an add-on setting to the antidepressant(s) for which partial response is shown or in a monotherapy setting if justified. In the add-on setting, the comparator should be the antidepressant(s) to which the new product is added plus placebo in a superiority design.	Accepted. See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	645	647	"Given the heterogeneity in treating MDD in clinical practice both nationally and globally, narrowing add-on trials in patients with partial response down to one failed antidepressant would result in clinical trials that are not feasible. Rather a number of antidepressants should be specified in this setting. Also based on the different approaches to MDD treatment in clinical treatment guidelines as well as the limited options for treating patients with partial response, trials testing novel medicinal products in the monotherapy setting should be considered, if justified."	Study designs may be conducted in an add-on setting to the antidepressant(s) for which partial response is shown or in a monotherapy setting if justified. In the add-on setting, the comparator should be the antidepressant(s) to which the new product is added plus placebo in a superiority design.	Accepted. See Boehringer Ingelheim comment and ISCTM comment lines 602-604 above.
H. Lundbeck A/S	Specific comment	648	657	The relapse rate under known ADT + placebo may be lower than pure placebo despite TRD. This may have to be taken into account in establishing the duration of follow-up during the randomized period.	"….it needs justification and should be verified with scientific advice before starting it (section 4.3.2.2). As the relapse rate under the known antidepressant plus placebo may be different than under placebo alone, the duration of the randomized observation period should be considered."	Partly accepted. ..it needs justification and should be verified with **CHMP** scientific advice before starting it. As the relapse rate under the known antidepressant(s) plus placebo may be different than with placebo alone**, this has to be taken into account in the duration of the randomized observation period (section 4.3.2.2.).** See also EFPIA comment.
Boehringer Ingelheim International GmbH	Specific comment	652	655	Given the heterogeneity in treating MDD in clinical practice both nationally and globally, narrowing add-on trials in patients with partial response down to one failed antidepressant would result in clinical trials that are not feasible. Rather a number of antidepresssants should be specified in this setting.	In the latter case responders to a combination treatment of a known antidepressant(s) and the new compound should be randomized to one of the following two treatments: combination therapy of the test product and the known antidepressant(s) versus the known antidepressant(s) plus placebo.	Accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	652	655	Given the heterogeneity in treating MDD in clinical practice both nationally and globally, narrowing add-on trials in patients with partial response down to one failed antidepressant would result in clinical trials that are not feasible. Rather a number of antidepressants should be specified in this setting.	In the latter case responders to a combination treatment of a known antidepressant(s) and the new compound should be randomized to one of the following two treatments: combination therapy of the test product and the known antidepressant(s) versus the known antidepressant(s) plus placebo.	Accepted.
EFPIA	Specific comment	657	657	Regarding maintenance of effect: The relapse rate under known ADT + placebo may be lower than pure placebo despite TRD. This may have to be taken into account in establishing the duration of follow-up during the randomized period.	… scientific advice before starting it (section 4.3.2.2.). As the relapse rate under the known antidepressant plus placebo may be different than under placebo alone, the duration of the randomized observation period should be considered.	Partly accepted. See also Lundbeck comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	658	667	The relapse rate under known ADT + placebo may be lower than pure placebo despite TRD. This may have to be taken into account in establishing the duration of follow-up during the randomized period.		Comment does not refer to the lines indicated. See EFPIA and Lundbeck comment on this issue and proposed rewording: **As the relapse rate under the known antidepressant(s) plus placebo may be different than with placebo alone, this has to be taken into account in the duration of the randomized observation period (section 4.3.2.2.).**
Boehringer Ingelheim International GmbH	Specific comment	663	665	Given the evolution in neuroscience, it should not be ruled out that there may be investigational medicinal products that could address certain (clustered) symptoms across more than one DSM-5 entity. Rather than categorically ruling such a possibility out, it would be welcomed if the Agency were open to discuss such an approach in a Scientific Advice procedure.	While this guideline is specific to depression, there may be situations where the aim is to demonstrate efficacy in the targeted (cluster of) symptoms should not only in depression but also in other conditions. If this is the case, early Scientific Advice should be sought.	Not accepted. The guideline is on MDD. The diagnostic criteria in DSM5 excluded comorbidities that can form alternative explanations for mood disturbances. If a claim in depression associated with for instance Parkinson is pursued the compound should be studied in that population. However, the last part of the sentence is deleted: The efficacy in the targeted (cluster of) symptoms should be specific for depression ~~and not applicable to the same (clustered) symptoms in other conditions~~. See similar ISCTM and EFPIA comment.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	663	665	Given the evolution in neuroscience, it should not be ruled out that there may be investigational medicinal products that could address certain (clustered) symptoms across more than one DSM-5 entity. Rather than categorically ruling such a possibility out, it would be welcomed if the Agency were open to discuss such an approach in a Scientific Advice procedure.	While this guideline is specific to depression, there may be situations where the aim is to demonstrate efficacy in the targeted (cluster of) symptoms not only in depression but also in other conditions. If this is the case, early Scientific Advice should be sought.	Not accepted. See comment above. See similar EFPIA and Boehringer Ingelheim comment. The aim of the GL is about the development of medications for treatment of MDD and not for symptomatic treatment.
EFPIA	Specific comment	663	666	The current wording suggests that it is established that the pathophysiology for the claimed mechanism of action to treat a specific symptom (sleep disturbance, cognitive dysfunction, anhedonia) is specific to a condition (e.g. depression or schizophrenia). However, if a drug is effective for a symptom cluster (for example, insomnia/anhedonia/decreased concentration, anxiety) in depression, it cannot be ruled out that it may be applicable to the same symptom cluster in other neuropsychiatric conditions. Indeed, biomarkers/neural activity/genetics may be used in the future to identify common pathological mechanisms in transdiagnostic populations that share symptom clusters. A drug that targets that common pathological mechanism could be used to treat the same symptoms across diagnoses. As such it is recommended that the relevant text be deleted.	Delete the following text [The efficacy in the targeted (cluster of) symptoms should be specific for depression and not applicable to the same (clustered) symptoms in other conditions. Thus, a pathophysiological justification for the claimed mechanism of action to treat specific symptoms will be required.]	Partly accepted. See comment above. The efficacy in the targeted (cluster of) symptoms should be specific for depression ~~and not applicable to the same (clustered) symptoms in other conditions~~. See simiar Boehringer Ingelheim and ISCTM comment.
Boehringer Ingelheim International GmbH	Specific comment	668	671	Depending on the mechanism of action of an investigational medicinal product situations could be perceived where this compound may be adddressing some specific symptoms considered relevant by patients with MDD without treating MDD as such. In such a scenario, openness for discussion from the side of the Agency would be welcomed.	If both a claim for treatment of depression overall and that of specific symptoms is sought, the effect of an antidepressant on the specific symptom or in a specific domain has to be demonstrated in addition to and independently from the improvement of depressive symptoms using clinically meaningful endpoints.	Accepted. See similar ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	668	671	Depending on the mechanism of action of an investigational medicinal product situations could be perceived where this compound may be addressing some specific symptoms considered relevant by patients with MDD without treating MDD as such. In such a scenario, openness for discussion from the side of the Agency would be welcomed.	If both a claim for treatment of depression overall and that of specific symptoms is sought, the effect of an antidepressant on the specific symptom or in a specific domain has to be demonstrated in addition to and independently from the improvement of depressive symptoms using clinically meaningful endpoints.	Accepted. See similar Boehringer Ingelheim comment.
EFPIA	Specific comment	668	671	Comment/rationale: Utilizing specific symptoms and domains within MDD can be used in drug development in 2 ways: 1. Measuring the improvement in the specific symptom/domain using clinically meaningful endpoints. 2. Using the specific symptom/domain to select patients who respond better to treatment (predictive enrichment). In the first scenario, measurement of the effect of an antidepressant on depressive symptoms and the specific symptom/domain would be required. However, in the second scenario, using the specific symptom/domain for predictive enrichment should not necessitate demonstration of an effect on the specific symptom/domain. This is in alignment with ICH E8 (R1) that states that a study population may be narrowly defined to reduce the risk to study participants or to maximise the sensitivity of the study for detecting a certain effect. In this case, a study population could be narrowly defined with the specific symptom/domain to maximise the sensitivity of the study for detecting improvement in depression. This patient selection/enrichment approach is accepted and utilized across a number of diseases including cardiovascular, oncology, pulmonary disorders (among others) for upfront selection of patients in confirmatory studies or as clinical trial endpoints through a strong understanding of the at-risk population, disease biology and mechanism of action of the drug. These development approaches are supported by EMA guidelines in other diseases (i.e., Clinical Evaluation of Anticancer Medicinal Products) as well as FDA guidance (i.e., Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biologic Products).	Delete the following text [The effect of an antidepressant on the specific symptom or in a specific domain has to be demonstrated in addition to and independently from the improvement of depressive symptoms using clinically meaningful endpoints.]	Not accepted. See Boehringer Ingelheim and ISCTM comment. The sentence reads: **If both a claim for treatment of depression overall and that of specific symptoms is sought,** the effect of an antidepressant on the specific symptom or in a specific domain has to be demonstrated in addition to and independently from the improvement of depressive symptoms using clinically meaningful endpoints.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	681	687	This is an opportunity to provide clarity on the patient population and expectations for cognition as a targeted symptom. If there is not an established route - this could be stated	Some guidance on trial design to disentangle these constructs would be welcomed - whether the exploration of effects of cognition could be explored within an acute MDE trial and/or as a residual symptom in partial or incomplete response	Further down a recommendation for CHMP scientific advice is given.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	688	689	"To narrow the options to clinical outcomes type with more objective capacity to measure cognitive performance. The original text, leaves it quite open. Of note that section 5.1 of the Brintellix (vortioxetine) SmPC contains section on cognitive measures indicating they are accepted by EMA: see section ""Effects of vortioxetine on the Digit Symbol Substitution Test (DSST), the University of California San Diego Performance-Based Skills Assessment (UPSA) (objective measures) and Perceived Deficits Questionnaire (PDQ) and Cognitive and Physical Functioning Questionnaire CPFQ (subjective measures) scores"	There is a lack of consensus on best tools to accurately and efficiently assess cognition in clinical settings, although performance-based outcomes (PerfO) measures provide satisfactory measurement objectivity regardless of patient awareness of the cognitive health.	Partly accepted. There is a lack of consensus on best tools to accurately and efficiently assess cognition in clinical settings**, although performance-based outcomes (PerfO) measures could provide satisfactory measurement objectivity.**
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	697	697	Consider adding additional depression specifiers including depression with mixed features and psychotic features		Not accepted. These additional specifiers have been discussed in detail prior to releasing the Draft GL for consultation. The introductory sentence should be sufficient to cover all specifiers without making more specific references to specifiers, which have not been frequently researched. The current text remains. Only those specifiers were include where Scientific advice was given.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	701	705	To define the population for this type of study - it would be helpful to specify if the diagnosis with specifier is sufficient for inclusion or if the diagnosis plus severity is recommended/acceptable for inclusion. For example - diagnosis of MDD with HAMD of X and HAM-A of Y is necessary		Partly accepted. There are several tools for measuring anxiety in depressed patients. As mentioned in the comment, the Hamilton Anxiety Scale (HAMA) is one of them. The following is proposed: **The Structured Clinical Interview for DSM Disorders (SCID) and the Mini-International Neuropsychiatric Interview (MINI) are examples of suitable diagnostic instruments for assessing co-occurrence of depressive and anxious symptoms in MDD. The severity of symptoms can be assessed with the use of more specific tools such as the Hamilton Anxiety Scale (HAMA).** see also EFPIA comment
EFPIA	Specific comment	704	705	Additional guidance is sought regarding assessing the co-occurrence of depressive and anxious symptoms in MDD beyond merely the anxious distress specifier. This should include information on diagnostic instruments that are recommended for assessing co-occurrence of depressive and anxious symptoms in MDD.	From a regulatory perspective the population in which benefit/risk is demonstrated will be described in the label. The Structured Clinical Interview for DSM Disorders (SCID) and the Mini-International Neuropsychiatric Interview (MINI) are examples of suitable diagnostic instruments for assessing co-occurrence of depressive and anxious symptoms in MDD.	Accepted. See also ISCTM comment above.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	713	and throughout the document	Preferably the word “elderly” should not be used. Also, a more concise definition of “older” should be provided earlier in this paragraph. "Older people" is the accepted EMA term - see https://www.ema.europa.eu/en/human-regulatory-overview/research-development/medicines-older-people. Previously geriatric and subsequently elderly were used. Also in ICH	Older patients	Accepted. The proposal for new text is: 4.5.1. **Older** patients 715-717: In ICH E7 it is indicated that the efficacy and safety for the older people population can be derived from the total database, provided that a sufficient number of **older** patients is included, unless there are specific reasons not to do this. .... 719-720: This suggests a different pattern of response to first line antidepressants in the **older** patients' population. 885-889: 4.6.1.13. **Older** patients Certain adverse events such as anticholinergic effects, delirium, sedative effects, cardiovascular and hypotensive effects, dizziness, falls, effect on food intake and functional decline, have been observed in **older** patients treated with certain antidepressants and these should be monitored in the trials designed for **older** patients. Changes are also required for the Table of Contents
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	716	717	For this sentence, it would be helpful to clarify the age range to which "elderly" refers, as many trials only go up to 65 years old. Again, more clarity on what a "sufficient number" is would be helpful, but adding the age range is necessary here. Note that line 739 refers to patients over 75 years of age, but this appears to be a specific subgroup within the overall elderly population.	provided that a sufficient number of elderly patients (e.g., 65 years of age or older) is included	Accepted. ...provided that a sufficient number of **older** patients **(e.g. 65 years of age or older)** is included
EFPIA	Specific comment	723	724	It would be beneficial for sponsors to have further guidance regarding extrapolation of dosing in elderly patients.	Moreover, extrapolation of the adult dose may be difficult due to pharmacokinetic properties of the product and/or to a different sensitivity in the older people for the pharmacodynamics of the product. Potential different sensitivities to pharmacological targets in the elderly, compared to adults, need to be considered to drug response as appropriate.	Accepted slighltly modified: Potential different sensitivities to pharmacological targets in **older** compared to **younger adults** need to be considered **to achieve an appropriae drug response**. Ref to ISCTM comment on the use of the term older versus elderly.
EFPIA	Specific comment	726	727	Pharmacokinetic studies may support the choice of the dose and should be conducted. The guideline should allow the possibility of the alternative approach of using population pharmacokinetics.	Pharmacokinetic studies or population pharmacokinetics may support the choice of the dose.	Accepted.
Certara	Specific comment	728	730	Can the agency specify if population PK modelling activities are acceptable to select dose for a dedicated study in elderly patients (using PK and/or exposure-safety relationships).		The following is considered sufficient: Pharmacokinetic studies **or population pharmacokinetics** may support the choice of the dose.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	731	731	MDD at age 65 does not necessarily have the same aetiology as in very elderly because of impact of vascular impairment and co-morbidities	Need to specify definition by age, and sub-groups e.g., very elderly	The subgroups mentioned in the Table of the ARs could be mentioned here. The following three subgroups of older patients are of interest: age 65-74, 75-84 and 85+
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	743	743	Recommend inclusion of PRO measures in this sentence and revision to reflect use to assess secondary endpoints not as secondary endpoints.	Global, functional, and patient-reported outcome measures should be included to assess secondary endpoints.	Partly accepted. Global and/or functional **and/or patient-reported outcome measures** should be included as secondary endpoints.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	743	778-779	Recommend inclusion of PRO measures in this sentence and revision to reflect use to assess secondary endpoints not as secondary endpoints. Carers (informal carers as relatives, partners, tutors, etc.) use to be the ones which can be aware of patient evolution. These are rarely included as source of information in clinical trials. It is worth suggesting methods that could impact on the actual efficacy of clinical trials.	Global, functional, and patient-reported outcome measures should be included to assess secondary endpoints. Carers' opinion on patient severity may also be considered	Accepted with slight amendments. Global and/or functional **and/or patient-reported outcom**e measures should be included as secondary endpoints. **The input of carers may help to interpret the severity of symptoms**
H. Lundbeck A/S	Specific comment	747	787	As seen in recent years the requested paediatric programmes make it very difficult to obtain informative data, proving efficacy. Hence several potential efficacious treatments are not made available to the paediatric population, where there is an unmet need. There is a need to look at the requested paediatric programme taking extrapolation into account, and to consider the optimal study design including relevant study design details. Instead of requesting ‘Efficacy in acute treatment should be demonstrated in at least one short-term placebo-controlled trial’ (line 771) a more pragmatic approach should be considered to extrapolate acute treatment effects from adults and instead utilising the more optimal design in MDD, randomised withdrawal study, in the paediatric population proving maintenance of effect. In addition, it would also generate the short- and long-term safety data in the paediatric population. Consider including extrapolation of acute treatment effects from adults and utilising an appropriate study design to demonstrate maintenance of effect in the paediatric population (and generate the short- and long-term safety data in the paediatric population)	Revised text should include considerations on extrapolation of acute treatment effects from adults and utilising an appropriate study design to demonstrate maintenance of effect in the paediatric population (and generate the short- and long-term safety data in the paediatric population).	Not accepted. Dedicated short-term trials in children are needed. See also EFPIA comment.
EFPIA	Specific comment	747	787	As seen in recent years the requested paediatric development programmes make it very difficult to obtain informative data, proving efficacy. Hence several potential efficacious treatments are not made available to the paediatric population, where there is an unmet need. Given this, it is not clear why the guidance advocates for additional studies rather than utilising other approaches, such as extrapolation. Consider including extrapolation of acute treatment effects from adults and utilising an appropriate study design to demonstrate maintenance of effect in the paediatric population (and generate the short- and long-term safety data in the paediatric population).	No specific text proposed	Not accepted. Dedicated short-term trials in children are needed See also Lundbeck comment.
EFPIA	Specific comment	748	750	ICH E11 and CHMP guidelines (EMEA/CHMP/EWP/147013/2004) give the following age ranges: - children 2-11, adolescents 12-17. Line 748 notes depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years. The age groups should be aligned to ICH guidance.	Depressive disorders conforming to adult diagnostic criteria rarely present before the age of seven years. Hence, the relevant age groups for juvenile depression are children (7-11 years of age) and adolescents (12-17 years of age).	Accepted. See also ISCTM comment.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	749	750	The definition of children and adolescents in this sentence differs from that used in lines 765-766 on the next page. Placing age 12 with the adolescents is consistent with how we divide children from adolescents, and this change should be made on lines 749-750 so that the guideline is consistent. The accepted paediatric age groups here should be 7 - 11 years of age and 12 - 17 years of age - as an example please see the approved EMA Paediatric Investigation Plan (PIP)for vortioxetine, page 8/10 Clinical studies 6 & 7: https://www.ema.europa.eu/en/documents/pip-decision/p-0337-2022-ema-decision-10-august-2022-acceptance-modification-agreed-paediatric-investigation-plan-vortioxetine-brintellix-emea-000455-pip02-10-m09_en.pdf	children (7-11 years of age) and adolescents (12-17 years of age).	Accepted. Also for lines 765-766. See also EFPIA comment.
H. Lundbeck A/S	Specific comment	755	757	The guidance text mentions that psychopharmacologic approaches should normally be integrated in a stable psychosocial treatment setting. Although the intention is understood it likely makes it even more difficult to show a placebo-drug difference (than in adult studies). Reference is also made to the general comments above on section for Children and adolescents.		Point well taken but a development guideline should be in accordance with treatment guidelines. No change required. See also ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	755	759	although the intention is understood it likely makes it even more difficult to show a placebo-drug difference (than in adult studies)		Point well taken but a development guideline should be in accordance with treatment guidelines. No change required. See also Lundbeck comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	759	800	Comment: As seen in recent years the requested paediatric programmes make it very difficult to obtain informative data, proving efficacy. Hence several potential efficacious treatments are not made available to the paediatric population, where there is an unmet need. Instead of requesting 'Efficacy in acute treatment should be demonstrated in at least one short-term placebo-controlled trial' a more pragmatic approach should be considered to extrapolate acute treatment effects from adults and instead utilising the more optimal design in MDD, randomised withdrawal study, in the paediatric population proving maintenance of effect. In addition, it would also generate the short- and long-term safety data in the paediatric population	Proposed change (if any): There is a need to look at the requested paediatric programme taking extrapolation into account per the EMA guideline on extrapolation in the paediatric population (EMA/189724/2018), and to consider the optimal study design including relevant study design details.	Not accepted. Extensive discussions on the requirements for children and adolescents have taken place There is the requirement for one short-term placebo-controlled study to be conducted in the specific paediatric population. Maintenance of effect and long term data can then be extrapolated from adults. See also Lundbeck and EFPIA comment.
Certara	Specific comment	764	764	Instead of 'full extrapolation' suggest alternative wording so this guideline is in line with wording proposed by the draft ICH E11A guideline i.e., not using discrete categories with regards to different approached to pediatric extrapolation.	Extrapolation of adult efficacy and safety data based on PK data alone is not considered appropriate.	Accepted.
Certara	Specific comment	767	767	In addition to stratification, an age-staggered approach may also be appropriate.		Accepted. The sentence was included.
EFPIA	Specific comment	770	770	Further guidance on the dose selection in adolescents is requested for inclusion.	…wherever possible. The PK in adolescents is often similar to the PK in adults, hence the doses for the adolescent population derived using adult data or population pharmacokinetics and scaling approaches with limited confirmatory PK data could be considered sufficient for the characterization in this age-group (EMA guidance EMEA/CHMP/EWP/147013/004 Guideline on the role of pharmacokinetics in the development of Medicinal products in the paediatric population). The initial dose selection to inform adolescent dosing can be based on allometric scaling without the need to conduct a dedicated Pk study and based on allometric scaling of adult PK data to match target adult exposures.	Not accepted. The follwing senctence is added: Extrapolation of adult efficacy and safety data **based on PK data alone** is not considered appropriate. **Therefore, short-term** efficacy data should be generated... Rationale: Recent examples (e.g. Valdoxan) that similar exposure might not be reflected in similar efficacy.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	773	773	It is not recommended to start a sentence with a number. In this case, proposed revision to start with the word Trials.	Trials of 4-6 weeks in duration are usually recommended	Editorial comment accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	788	788	Sex seems to be the more appropriate term - the following reference from the Council of Europe describes different definitions of sex Vs gender from WHO, etc: https://www.coe.int/en/web/gender-matters/sex-and-gender#17. The term gender should be replaced throughout the guideline with "sex" as at present the terms are used interchangeably. Finally, this bullet point should be revised as there is no section on drug metabolism differences (Section 4.5.3 discusses sex-relates to differential 5-HT-related responses in animal models, and discusses higher prevalence of MDD in women combined with sex-related differences in suicide attempts Vs completed suicide - so no recommendations regarding sex-related differences in drug metabolism. So suggest changing this bullet to match the title of 4.5.3.)	Sex-related differences and considerations	Accepted.
Certara	Specific comment	788	788	To harmonise with previous sections, it is suggested the gender is referred to as 'sex (gender)'		Accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	797	798	Sex is a more appropriate term.	Predefined analyses of sex- specific groups are welcomed.	Partly accepted. The proposal for new text is: However, at present, these differences cannot be considered sufficient for specific recommendations for trial populations, which should be an accurate reflection of the patient population in clinical practice. Predefined analyses of **sex** ~~gender~~ specific groups are welcomed. Data should be presented **specific for sex and ideally for gender, as well** , age, race etc. to allow an estimate of potential differences.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	798	799	Sex is a more appropriate term.	Data should be presented specific for sex, age, race etc. to allow an estimate of potential differences.	Partly accepted. See comment above.
H. Lundbeck A/S	Specific comment	804	804	The guideline specifies that AE's should be characterized (and take ICH E1 into consideration). Nor the guideline, nor E1 specify the duration of reporting of AE's after discontinuation of the treatment.	"… duration of treatment, dosage, recovery time, age, frailty and other relevant variables. After discontinuation of treatment, AEs should be reported for an adequate time (e.g., 5 times half-life)"	Accepted. The additional sentence was included: **After discontinuation of treatment, AEs should be reported for an adequate time (e.g., 5 half-lives).**
Boehringer Ingelheim International GmbH	Specific comment	804	805	Depending on the mechanism of acition of the investigational medicinal product, adverse event scales may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed.	Adverse event scales should be standardised for use in studies with psychotropic drugs, if considered relevant.	Accepted. See also ISCTM comment. The sentence now reads: **Adverse event scales should be standardised for use in studies with psychotropic drugs.**

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	804	805	Depending on the mechanism of action of the investigational medicinal product, adverse event scales may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed. Remove reference to UKU scale. UKU scale is not widely used in US and clinical trial data from both US and Europe are used in regulatory applications. Standardization of AE collection between US and EU is highly desirable. The UKU scale creates solicited and unsolicited AEs.	Adverse event scales should be standardised for use in studies with psychotropic drugs, if considered relevant.	Partly accepted. See also Boehringer Ingelheim comment The sentence now reads: **Adverse event scales should be standardised for use in studies with psychotropic drugs.**
Boehringer Ingelheim International GmbH	Specific comment	815		Provide an introduction after 4.6.1 mentioning that some of the adverse events are knwon for specific classes of AD or mode of action and that scientifc advice is recommended in case specific AEs are to be monitored.		Partially accepted. See also ISCTM comment. All AEs during a clinical trial should be captured and evaluated. The following is added as introductory part immediately after 4.6.1.: **Some of the below mentioned adverse events are typical for some drug classes or MOA but may not apply to all MOAs. Applicants should justify the safety monitoring during the clinical trial.**
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	819	820	The agency should provide an introduction directly after 4.6.1 , indicating that some of the mentioned adverse events are typical for some drug classes or mode of action (e.g. serotonin syndrome) and therefore more relevant to be monitored compared to other mode of actions. In case of known MOA this could be part of a scientific advice to focus on some of the below mentioned aspects.	Please add that only when these events occur during the clinical trial at a higher rate or increased severity compared to baseline will these events be captured as AEs.	Partially accepted. See also Beoheringer Ingelheim comment. All AEs during a clinical trial should be captured and evaluated. The following is added as introductory part immediately after 4.6.1.: **Some of the below mentioned adverse events are typical for some drug classes or MOA but may not apply to all MOAs. Applicants should justify the safety monitoring during the clinical trial.**
H. Lundbeck A/S	Specific comment	820	822	For the risk of an adverse effect on the severity of the disorder being treated, the proportion of patients deteriorating during treatment should be documented using the primary efficacy measure. But in order to assess the effect, a comparison is required between active medication and placebo.	In order to explore the risk of an adverse effect on the severity of the disorder being treated, the proportion of patients deteriorating during treatment should be documented using the primary efficacy measure, preferably for both the active treatment and the placebo treatment.	Accepted. It should be clear but was added for the sake of clarity. In order to explore the risk of an adverse effect on the severity of the disorder being treated, the proportion of patients deteriorating during treatment should be documented using the primary efficacy measure, **preferably for both the active treatment and placebo.**
H. Lundbeck A/S	Specific comment	823	828	The guidance text states cognitive rating scales should be used, but we would question if this should this be done for all trials/compounds? This will increase the number of scales to be applied and may increase the placebo effect (see references below). It is suggested the guidance text is revised to indicate that the use of multiple scales of this kind should be carefully considered and perhaps apply only if an effect has been identified in early trials or is clearly related to the MoA. From: Potter, W. Z., et al. (2014). "Controlling Placebo Response in Drug Development: Lessons Learned from Psychopharmacology." Pharmaceutical Medicine 28(2): 53-65: "Guico-Pabia et al. [49] in an analysis of 31 MDD studies found that placebo response tended to increase, and drug– placebo effect size tended to decrease, with more assessments per visit. However, confounding of design features limits causal interpretation as both placebo response and number of assessments pervisits has increased over time. Therefore, it is unclear whether increased assessment drives the increased placebo response or is simply an artifact of having more assessments in later trials where [58] W. Z. Potter et al. placebo response was greater. Nevertheless, this finding is consistent with the findings of Posternak and Zimmerman [48] in that more interaction with caregivers was associated with increased placebo response.	The guidance text to be revised to indicate that the use of multiple scales of this kind should be carefully considered and perhaps apply only if an effect has been identified in early trials or is clearly related to the MoA.	Accepted. The following is added: **The use of additional scales is especially required if an effect has been identified in early trials or is related to the MOA. The use of additional scales should be carefully considered since increased interactions with caregivers might increase placebo response.** Ref: Posternak MA, Zimmerman M. Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. Br J Psychiatry. 2007 Apr;190:287-92. doi: 10.1192/bjp.bp.106.028555. PMID: 17401033. See also ISCTM, SG, EFPIA comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	823	828	The text states cognitive rating scales should be used, but should this be done for all trials/compounds? This will increase the number of scales to be applied and thus increase the placebo effect. Suggest using scales only if an effect has been identified in early trials or is clearly related to the MoA		Accepted. The following is added: **The use of additional scales is especially required if an effect has been identified in early trials or is related to the MOA. The use of additional scales should be carefully considered since increased interactions with caregivers might increase placebo response.** See also EFPIA , Lundbeck and SG comment.
EFPIA	Specific comment	823	828	The text states cognitive rating scales should be used, but we would question if this should this be done for all trials/compounds? This will increase the number of scales to be applied and may increase the placebo effect (see below). Suggest using scales only if an effect has been identified in early trials or is clearly related to the MoA. "Guico-Pabia et al. [49] in an analysis of 31 MDD studies found that placebo response tended to increase, and drug– placebo effect size tended to decrease, with more assessments per visit. However, confounding of design features limits causal interpretation as both placebo response and number of assessments per visits has increased over time. Therefore, it is unclear whether increased assessment drives the increased placebo response or is simply an artifact of having more assessments in later trials where 58 W. Z. Potter et al. placebo response was greater. Nevertheless, this finding is consistent with the findings of Posternak and Zimmerman [48] in that more interaction with caregivers was associated with increased placebo response. " From Potter, W. Z., et al. (2014). "Controlling Placebo Response in Drug Development: Lessons Learned from Psychopharmacology." Pharmaceutical Medicine 28(2): 53-65.	No specific text proposed. Suggest to revise wording to indicate that the use of multiple scales of this kind should be carefully considered and perhaps apply only if an effect has been identified in early trials or is clearly related to the MoA.	Accepted. See above.

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SG	Specific comment	824	824	Text states „A detrimental effect on cognition should be monitored using validated rating scales. Effects on cognition, reaction time, driving and severity of sedation should also be studied." This is unspecific and may be interpreted as requiring full scale neuropsychological testing, thereby putting undue burden on participants and investigators.	Requirements should be specified (e.g. "cognition may be assessed using single items of validated scales such as the MADRS" or "by participant self report using open questions on cognitive difficulties, reaction time and / or relevant activities of daily living including driving").	Not accepted. See proposal above: **The use of additional scales is especially required if an effect has been identified in early trials or is related to the MOA. The use of additional scales should be carefully considered since increased interactions with caregivers might increase placebo response.**
Boehringer Ingelheim International GmbH	Specific comment	824	825	Depending on the mechanism of action of the investigational medicinal product, assessment of a detrimental effect on cogntion may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed.	If relevant, a detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim.	Accepted. See ISCTM comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	824	825	Depending on the mechanism of action of the investigational medicinal product, assessment of a detrimental effect on cognition may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed.	If relevant, a detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim. (section 4.4.2.1).	Accepted. See Boehringer Ingelheim comment
Certara	Specific comment	824	828	Can the agency suggest if there are any specific criteria for trials in elderly populations with underlying cognitive deficit? Furthermore, could the agency consider addressing the issue that comorbidities and polypharmacy could complicate treatment in this age group. Drug-drug interactions, changes in metabolism and organ age can affect treatment/PKPD.		No specific guidance is given in the context of this guideline as this would apply to all diseases.
Boehringer Ingelheim International GmbH	Specific comment	831	831	To align with other guidelines where the corrected QT intervall needs to be measured.	QTc-prolongation	Partly accepted. See ISCTM comment QT is also kept. **QT/QTc-prolongation** is used.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	831	831	To align with other specific guideline where the corrected QT interval needs to be measured.	QTc-prolongation	Accepted. But QT is also kept. **QT/QTc-prolongation** is used. See Boehringer Ingelheim comment
SG	Specific comment	836	837	Text states „narrative summaries of suicidal patient statements or behavior should be provided". This seems unrealistic and participants may not be willing or able to provide such statements	Delete this sentence.	Not accepted. The sentence was modified: ...and narrative summaries of suicidal patient statements or behaviours should be provided **if available.**
Boehringer Ingelheim International GmbH	Specific comment	843	843	Depending on the mechanism of acition of the investigational medicinal product, assessment of these haematological side effects above and beyond standard monitoring may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed.	If relevant, special attention should be paid to incidence of neutropenia, agranulocytosis and aplastic anaemia.	Not accepted. In this case it is preferred that the conduct of the trial is done with more vigilance with respect to these AEs. The current text remains. See ISCTM comment
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	843	843	Depending on the mechanism of action of the investigational medicinal product, assessment of these haematological side effects above and beyond standard monitoring may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed.	If relevant, special attention should be paid to incidence of neutropenia, agranulocytosis and aplastic anaemia.	Not accepted. In this case it is preferred that the conduct of the trial is done with more vigilance with respect to these AEs. The current text remains. See Boehringer Ingelheim comment.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	844	844	Important endocrinological effect that can affect mood	Suggest to include thyroid dysfunction in text	Accepted. **Thyroid dysfunction can affect mood and should also be monitored.**
SG	Specific comment	845	846	Text states: "The effects on sexual functioning, galactorrhoea and gynaecomastia should be evaluated. Investigation of neuro-endocrinological parameters relating to prolactin is necessary." This (apart from sexual functioning) seems to be important only when anti-dopaminergic antipsychotics are examined. Prolactin testing for each and every antidepressant seems excessive and may place undue burden on participants and investigators.	This should be clarified, e.g. "The effects on sexual functioning should be assessed. In case anti-dopaminergic substances are tested, effects on galactorrhoea and gynaecomastia should also be evaluated and the investigation of neuroendocrinological parameters relating to prolactin is necessary."	Accepted. See also ISCTM and Boehringer Ingelheim comment. **Special attention should be paid to the effect on sexual function and libido.The potential for the test product to precipitate sexual dysfunction can be actively measured using a validated rating scale. In case anti-dopaminergic substances are tested, effects on** galactorrhoea and gynaecomastia should also be evaluated **and the i**nvestigation of neuro-endocrinological parameters relating to prolactin is necessary.
Boehringer Ingelheim International GmbH	Specific comment	845	846	Depending on the mechanism of acition of the investigational medicinal product, assessment of these side effects above and beyond standard monitoring may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed. Prolactin or prolactin-associated investigations should only be required if warranted due to the mechanism of action of the investigational medicinal product.	If relevant, the effects on sexual functioning, galactorrhoea and gynaecomastia should be evaluated. Investigation of neuro-endocrinological parameters relating to prolactin may be necessary.	Partly accepted. See also ISCTM and SG comment. **Special attention should be paid to the effect on sexual function and libido.The potential for the test product to precipitate sexual dysfunction can be actively measured using a validated rating scale. In case anti-dopaminergic substances are tested, effects on** galactorrhoea and gynaecomastia should also be evaluated **and the i**nvestigation of neuro-endocrinological parameters relating to prolactin is necessary.

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International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	845	846	Depending on the mechanism of action of the investigational medicinal product, assessment of these side effects above and beyond standard monitoring may not always be necessary. Hence, more flexibility with regard to their implementation would be welcomed. Prolactin or prolactin-associated investigations should only be required if warranted due to the mechanism of action of the investigational medicinal product.	If relevant, the effects on sexual functioning, galactorrhoea and gynaecomastia should be evaluated. Investigation of neuro-endocrinological parameters relating to prolactin may be necessary.	Partly accepted. See SG and Boehringer Ingelheim comment. **Special attention should be paid to the effect on sexual fucntion and libido.The potential for the test product to precipitate sexual dysfunction can be actively measured using a validated rating scale. In case anti-dopaminergic substances are tested, effects on** galactorrhoea and gynaecomastia should **also** be evaluated **and the i**nvestigation of neuro-endocrinological parameters relating to prolactin is necessary.
Boehringer Ingelheim International GmbH	Specific comment	851	852	To align with other guidelines where the corrected QT intervall needs to be measured.	QTc-interval	Accepted. See also ISCTM comment. **QT/QTc-prolongation** is used.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	851	852	The E14 guideline speaks also about the QTc measurement	QTc-interval	Accepted. See also BI comment. **QT/QTc-prolongation** is used.
H. Lundbeck A/S	Specific comment	853	853	It is mentioned that special attention should be paid to sexual dysfunction, and that effects should be evaluated. It is proposed that the guidance text provides information on how this can be done.	The potential for the test product to precipitate sexual dysfunction can be actively measured using a validated rating scale (e.g. Arizona Sexual Experiences Scale).	Partly ccepted. The following sentence was inserted: **The potential for the test product to precipitate sexual dysfunction can be actively measured using a validated rating scale.** The ASEX is not explicitly mentioned since there are still issues on content and construct validity. Hyperfunction might not be adequately captured.Further data are needed on sensitivity to change.
Certara	Specific comment	858	858	More precise language is proposed.	Therefore, if antipsychotics with a strong dopaminergic mode of action are used…	Accepted.
SG	Specific comment	865	865	Serotonin syndrome (SS) is described but no statement on if/how to monitor or assess this Is included in the guidance. It should be specified under which circumstances this is expected and what measurement approaches may be acceptable.		Only partly accpetd with the introduction of two explanatory sentences. **Serotonin syndrome is typically caused by the use of two or more serotonergic medications or drugs**. The clinical symptoms include neuromuscular hyperactivity, autonomic hyperactivity and altered mental status. **Diagnosis is based on a patient´s symptoms and history of medication use.** Since this is no treatment guideline no further recommendations are given.
SG	Specific comment	882	884	Text states: "The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure of at least 12 months." We believe that 12 months will be very hard to accomplish and believe 6 months would be sufficient here	Consider rephrasing, e.g. "The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure of at least 6 months."	Not accepted.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment - Other comments	1216		Recommend adding two references by EM Laska on onset of antidepressant effect: Laska EM and Siegel C. Characterizing onset in psychopharmacological clinical trials (1995) and Laska et al Assessing onset of treatment benefit in depression and anxiety: conceptual considerations (2009)		Accepted. References are inlcuded in the list. Laska EM, Siegel C. Characterizing onset in psychopharmacological clinical trials. Psychopharmacol Bull. 1995;31(1):29-35. PMID: 7675985. Laska EM, Mallinckrodt CH, Mundt JC, Leber P, Vaccarino AL, Kalali AH, Greist JH. Assessing onset of treatment benefit in depression and anxiety: conceptual considerations. J Clin Psychiatry. 2009 Aug;70(8):1138-45. doi: 10.4088/JCP.09cs05129.
Certara	Specific comment - Other comments	13 (footer)		Update of EMA contact information required.		Accepted and updated.
Psychedelic Access and Research European Alliance	Specific comment	550, 556-557	550, 556-557		psychedelics need to be administered in a controlled environment and accompanied by well-trained therapists support. Trials need to be able to demonstrate that the effect of the psychedelic assisted 557 therapy is not due to the psychotherapy alone. Similarly, it is currently unknown what the optimal dosage of psychotherapy would be in combined treatment, which is something that has major implications for costs and benefits. The framework of operation (protocol) as well	Partly accepted. Some rewording also according to ISCTM comment. Costs of psychotherapy setting is more an HTA issue and not included in the regulatory guideline.
International Society for CNS Clinical Trials and Methodology (ISCTM)	Specific comment	584-587	588	lines 584-587: Suggest to add clarity or guidance on the criteria to decide whether retrieved drop out provide sufficient information to impute missing data for patients discontinuing treatment lines 587-588: Suggest to clarify what is meant by 'regardless of treatment changes'	lines 587-588: Similar considerations apply for estimation of the effect regardless of add-on and background treatment changes (treatment policy strategy for 'change in background treatment').	Not accepted lines 584-87: Clear guidance on how to decide whether retrieved data are sufficient to support a corresponding analysis is out of the scope of this guidance document. It depends on many factors including the frequency of intercurrent events and the amount that can be followed up. lines 587-88: clarification is already included in the brackets
Angelini Pharma SPA	Specific comment	610-611-612	610-611-612	Comment:" Although the requirement of demonstration of failure of at least two antidepressants is still used for TRD trials, the inclusion of patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded". Justification for the comment: In order to better clarify your broader TRD definition.	Proposed change (if any):" Although the requirement of demonstration of failure of at least two antidepressants is still used for TRD trials, the inclusion of patients with one failed treatment at a maximum tolerated dose and adequate duration should not be excluded. This could allow to achieve a label in patients who failed one treatment and TRD patients.	Not accepted. We do not comment on potential labelling claims in the Guideline since this a matter of assessment.

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Certara	Specific comment - Other comments	Throughout, 1424		Consistent use of abbreviations needed throughout is recommended. The abbreviations table requires an update.		Accepted and done. Abbrevaition table was shifted to the beginning of the document.
Psychedelic Access and Research European Alliance	Specific comment - Other comments			Also we suggest consideration is given to terms that relate to pharmacokinetics. The onset and offset time of psychedelics can vary according to the drug, the formulation, and the route of administration. A shorthand has developed that refers to some e.g. DMT and 5-MEO-DMT as short acting and others e.g. LSD and psilocybin as long acting. This is scientifically unsound and misleading and should be replaced with more accurate terminology. For example, DMT when smoked/inhaled or given i.v. has a fast onset and short duration of action but it can be infused i.v. to give a rapid onset but a long duration of action up to hours. And when DMT is taken orally in the brew ayahuasca it has a slow onset and a long duration of action of many hours. Psilocybin taken orally builds up to a maximum effect over an hour and lasts for 4-6 hours. But when given i.v. its effects are almost immediate and last less than an hour. For these reasons we suggest eliminating the use of terms such as short-acting and replacing them with specific details of route and duration of activity and type of administration [and in the case of i.v. use either bolus or infusion]. See table of suggestions: kinetics by route of administration Drug Route Time to max effect Duration of effect DMT Smoked/ i.v. bolus 2 mins 20 mins DMT Oral[ayahuasca] 1-2 hours 4-6 hrs DMT I.v. infusion 5-10 mins Up to hrs LSD oral 1-2 hours 10-14 hrs I.v. bolus 1 -2 hours 10-14 hrs Psilocybin oral 1 hour 4-6 hrs iv 5 min 1 hr 5-MEO-DMT Smoked/ intranasal 2 mins 15 mins Salvia smoked 2-5 mins 10 -15 mins Amanita Muscaris oral 30 mins 3-6 hrs Ketamine oral 1 hr 3-4 hrs I.v. bolus 5-10 mins 2-3 hrs Intranasal (esketamine) Ibogaine /nor-ibogaine oral 1-3 hrs 24_+ hours		Comment is acknowledged, however no detailed recommendations are given for the route of adminatration and formulation of psychedelics for this guidance document. No change required.

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