Submission of comments on draft "Guideline on clinical development of medicinal products for the treatment and prevention of bipolar disorder"

Fields marked with * are mandatory.

Introduction to the survey on draft "Guideline on clinical development of medicinal products for the treatment and prevention of bipolar disorder"

Please click here to be redirected to the guideline text. The public consultation is launched on 9 September 2024 until 31 March 2025

Those participating in the public consultation are asked to please submit comments via the EU Survey tool, by using the specific table for each section.
If you need more rows to be added to the table, please contact dora.duarte@ema.europa.eu
Please note that login is not required to fill in the survey.

Before submission, a draft of the comments can be saved in the EU Survey tool. Once submitted, comments can be edited (by 31 March 2025) by clicking on "Edit contribution" in the link https://ec.europa.eu/eusurvey/ and entering your ID contribution that can be found on the pdf copy of your submission sent via email.

Data Protection Statement

You are invited to provide your organisation or name, country and email address below for the purpose of this public consultation (for further information, please see EMA's Data Protection Statement below).

EMA Privacy Statement
All personal data provided within this survey questionnaire will be processed in accordance with Regulation (EU) 2018/1725 on the protection of individuals regarding the processing of personal data by the Union institutions and bodies on the free movement of such data.
This data protection statement provides details on how the Agency, in its capacity as data controller, will process the information that you have given in your questionnaire.
Internally, an 'Internal Controller' has been appointed to ensure the lawful conduct of this processing

operation. The contact details of the Internal Controller are the following: Datacontroller. HumanMedicines@ema.europa.eu

Collection of data

EMA will collect all the personal data in this questionnaire, such as your name, organisation, your view on the topics subject to the survey, country of residence and your contact details. Please do not reveal any other personal data in the free text fields. EMA does not directly intend to collect personal data but to use the aggregated data for the purpose of this survey.
For the collection of data in this survey, EMA relies on the EU Survey external system. For more information on how EU Survey processes personal data, please see: https://ec.europa.eu/eusurvey/home/privacystatement

The EU Survey external system uses:

- Session "cookies" to ensure communication between the client and the server. Therefore, user's browser must be configured to accept "cookies". The cookies disappear once the session has been terminated.
- Local storage to save copies of the inputs of a participant to a survey to have a backup if the server is not available during submission or the user's computer is switched off accidentally or any other cause.
- The local storage contains the IDs of the questions and the draft answers.
- IP of every connection is saved for security reasons for every server request.
- Once a participant has submitted one's answers successfully to the server or has successfully saved a draft on the server, the data is removed from the local storage.

Your consent to the processing of your data

When you submit this questionnaire, you consent that EMA will process your personal data provided in the questionnaire as explained in this data protection statement. You may also withdraw your consent later at any time. However, this will not affect the lawfulness of any data processing carried out before your consent is withdrawn.

Start of data processing

EMA will start processing your personal data as soon as the questionnaire response is received.

Purpose of data processing

The purpose of the present data processing activity is to collect the views of stakeholders and/or concerned individuals in relation to the subject-matter of the survey. Your personal data may be used to contact you in relation to the feedback you have provided in response to the survey. No further processing of your personal data for any other purposes outside the scope of this specific context is envisaged.

Location of data storage

All data is stored within a secure data centre at the EMA premises which is password protected and only available to EMA staff members.

Publication of data

The following data collected in this questionnaire will be published on the EMA website at the time of issuing the final guideline subject to this survey:

- organisation name (the entity on behalf you respond to this survey)
- or your name (only if you do not respond to the survey on behalf of an organisation)
- your view/comments on the topics concerned

Country information and your email address will not be published.

Retention period

If you complete and submit this survey, your personal data will be kept until the results have been completely analysed and utilised. Your personal data will be deleted by EMA at the latest 5 years after the questionnaire response was submitted. The file of the data as published will remain stored for archiving purposes beyond the maximum 5 years-retention time of the submitted questionnaire responses.

Your rights

You have the right to access and receive a copy of your personal data processed, as well as to request rectification or completion of these data. You may also request erasure of the data or restriction of the processing in accordance with the provisions of Regulation (EU) 2018/1725. You can exercise your rights by sending an e-mail to Datacontroller.HumanMedicines@ema.europa.eu.

Complaints

If you have any complaints or concerns about the processing of your personal data, you can contact EMA's Data Protection Officer at dataprotection@ema.europa.eu.

You may also lodge a complaint with the European Data Protection Supervisor: edps@edps.europa.eu.

* Please confirm that you have read and understood the Data Protection Statement above and that you consent to the processing of your personal data.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to possibly be contacted by EMA in relation to your survey responses to support the finalisation of the document subject this EU Survey.
  - (●) Yes
  - ( ) No

* Please confirm that you consent to the publication of your organisation name, your name (only if you do not respond to the EU Survey on behalf of an organisation) and your survey responses on the EMA website at the time of issuing the final guideline subject to this survey.
  - (●) Yes
  - ( ) No

Should you not want to give consent to publish, please send your objections to Datacontroller.HumanMedicines@ema.europa.eu.

Please be aware that the sender of the comments is responsible to not disclose any personal data of third parties in the comments.

When you have filled in the EU Survey, please use the submission button at the end of the form to submit

the comments to the European Medicines Agency.

For additional information, please consult EMA's privacy statement.

Your details

* Name of organisation or individual

EFPIA

* Country of organisation or individual

Belgium

* Email

katarina.nedog@efpia.eu

If you respond on behalf of an organization, please allocate yourself a name abbreviation to be used as "Stakeholder name" in the comment tables below. If you comment as an individual, please ignore this field and use your full name as your "Stakeholder name".

EFPIA

1. General comments

1. General comments

	General comment
1	The guideline does not mention how many trials are needed for an indication in BD, but the topics that need to be evaluated suggest that these cannot be achieved in one trial. Would CHMP accept a clinical trial design where acute treatment effect is investigated against placebo first and patients then be treated for longer follow-up and re-randomized to evaluate the maintenance of efficacy? Could this be clarified in the text on maintenance of efficacy?
2	Caregivers are not mentioned throughout the guideline. As caregivers can experience significant burden and poorer mental health outcomes (e.g. Karambelas et al, 2022), it would be useful to highlight consideration of this group in evidencing treatment benefit. Reference: Karambelas, G.J., Filia, K., Byrne, L.K. et al. A systematic review comparing caregiver burden and psychological functioning in caregivers of individuals with schizophrenia spectrum disorders and bipolar disorders. BMC Psychiatry 22, 422 (2022). https://doi.org/10.1186/s12888-022-04069-w
3	Given the substantial heterogeneity in disease course, as well as treatment history and comorbidities, it would be valuable to clarify the EMA position on use of real-world evidence in providing supporting evidence to close knowledge gaps in bipolar disorder.
4	Definition of recurrence notes the re-emergence of symptoms after a time “without medications.” As many patients are on maintenance treatment for many months or longer after recovery from an index episode, consider whether “without medication” is appropriate to include in the recurrence definition.
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2. Specific comments

Executive summary

2. Specific comments on text

Executive summary

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
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2.1. Introduction (background)

2.1. Introduction

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
1	89-90	The chronic nature of bipolar disorder is emphasised. This could be strengthened with reference to the literature on recurrence. This further emphasises the need for new medicines in this area.	Please add: Only 28% of people living with bipolar disorder stay in remission for 4 years and about 10% for 5 years (Tohen et al 1990, Miura et al 2014, Keller et al 1993). References: Keller, M. B.; Lavori, P. W.; Coryell, W.; Endicott, J.; Mueller, T. I. (1993): Bipolar I: a five-year prospective follow-up. The Journal of nervous and mental disease 181 (4), S. 238–245. DOI: 10.1097/00005053-199304000-00005. Miura, T.; Noma, H.; Furukawa, T. A.; Mitsuyasu, H.; Tanaka, S.; Stockton, S. et al. (2014): Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a systematic review and network meta-analysis. Lancet Psychiatry 1 (5), S. 351–359. DOI: 10.1016/s2215-0366(14)70314-1.

2	91-94	Following-on from the statement on all-cause mortality in lines 91-94, it would be helpful to emphasise that, as well as suicide and psychiatric comorbidities, BD is associated with medical comorbidities including neurological, respiratory, infectious, cardiovascular, oncological, and metabolic outcomes (Kang et al, 2024). This emphasis is particularly important in bipolar disorder where 'diagnostic overshadowing' contributes to systematic under-recognition and undertreatment of conditions such as cardiovascular disease (Smith et al, 2013). This has implications for clinical development in ensuring that supportive real-world evidence reflects that diversity of individuals who experience bipolar disorder. References: Kang, J., Lee, H., Park, J., Kim, H. J., Kwon, R., Kim, S., ... & Yon, D. K. (2024). Comorbid physical health outcomes in patients with bipolar disorder: an umbrella review of systematic reviews and meta-analyses. Asian Journal of Psychiatry, 99, 104138. Smith DJ, Martin D, McLean G, Langan J, Guthrie B, Mercer SW. Multimorbidity in bipolar disorder and undertreatment of cardiovascular disease: a cross sectional study. BMC Med. 2013;11:263. doi:10.1186/1741-7015-11-263.	Please add: Bipolar disorder is further associated with medical comorbidities including neurological, respiratory, infectious, cardiovascular, oncological, and metabolic outcomes (Kang et al, 2024).
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2.2. Scope

2.2 Scope

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
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2.3. Legal basis and relevant guidelines

2.3 Legal basis and relevant guidelines

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2.4. Specific considerations when developing products for the treatment and prevention of bipolar disorder episodes

2.4.1 Clinical Pharmacology studies

2.4.1 Clinical Pharmacology studies

	Line number(s) of the relevant text *(e.g. 20-23)*	Comment and rationale	Proposed guidance text
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2.4.2. Assessment of therapeutic efficacy

2.4.2. Assessment of therapeutic efficacy

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	187-191	Usually, a binary outcome analysis, such as responder or remitter analysis, has less statistical power than a continuous outcome of change from baseline on a rating scale. Is it expected that responder/remitter analyses provide statitically significant results in individual trials and that clinical trials are powered for these analyses? That would require larger sample sizes and would not make clinical development in BD more attractive.	Please add: A difference in response/remission rate does not neccessarilly need to be statistically significant in individual clinical trials.
2	205	Terminology preferred by patients	Replace “due to committed suicide” by “due to death by suicide”
3	241-243	Why is use of a placebo lead-in period a concern? In clinical practice one wants to maximize response to whatever aspect of treatment, while in clinical trials one wants to know what added benefit the pharmacological effect brings. Reducing placebo effects helps to better define that effect and avoid flooring effects due to exaggerated non-specific (placebo) response.	delete or rephrase to allow a double-blind placebo run-in period (see comment on Lines 246-250 as well).
4	246-250	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 and demonstrate the added pharmacological effects to the overall treatment effect. Suggest deleting Lines 246-247, and rephrasing 247-250.	In case enrichment strategies that identify and segregate placebo responders from the primary analysis are applied in Phase 2 and/or Phase 3 clinical trials additional efficacy analyses, which will include the whole population and allow comparisons between placebo responders and non-responders, should be also submitted. For such studies, further discussion on the relevant estimand may be required in particular with respect to the population attribute.

5	264-265	What are the epidemiology data for the mentioned time frames for maintenance treatment phases?	Consider adding references.
6	266-269	It is not clear what is meant by these sentences or what guidance is given here. The individual duration of any mood episode cannot be predicted as historic episode duration is not predictive for future ones, so how to take episode duration into account?	Please clarify
7	270-271	Due to the currently established framework for post-authorization efficacy studies (PAES), we would encourage the EMA to provide the possibility for maintenance of efficacy (relapse prevention) to be a post-authorisation requirement rather than part of the initial MAA. This would allow clinical development to be more streamlined globally in BPD and ensure that new treatments can be submitted in the EU based initially in short-term efficacy, which is known to drive most clinical decisions on bipolar treatment. This approach has been used by the FDA for the following products approved in BPD: Vraylar (cariprazine) and Abilify (aripiprazole).	For MAA, evidence of short-term efficacy should be provided. Evidence that the short-term effect can be maintained during the current (index) episode (relapse prevention) can be provided post-marketing.
8	275-277	. How to determine the frequency of episodes in the trial population prior to initiation of a recurrence prevention trial? Based on epidemiological data or history of enrolled patients? If the latter, it will be difficult defining trial duration up front.	Please clarify or delete.
9	276	It is not entirely clear if one should look at prevention of recurrences of the same polarity as index episode, or both and define recurrence for each polarity.	Please clarify.

10	276-277	We would propose that guidelines consider allowance for other criteria to be considered in recurrence definitions. For example, as some patients may discontinue from a study due to a worsening of their illness and may not return for further evaluation, these patients would not be considered as having a recurrence per proposed guidance, yet clearly demonstrated significant clinical worsening. Similarly, a patient who is hospitalized during a clinical trial for worsening symptoms and treated accordingly may return to the research site after hospital discharge and no longer meet symptom severity threshold criteria, yet their symptoms were severe enough to warrant hospitalization.	
11	288	SCID-5 is the updated version for DSM-5 and DSM-5 does not use the axis system	SCID-5 (Structured Clinical Interview for DSM-5 Disorders)
12	311-313	Does this mean analyses on subgroup(s) with and without additional therapies?	Please clarify.
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2.4.3. Methodological features

2.4.3. Methodological features

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	336-339	Would a superiority trial without placebo qualify as evidence for label claim (e.g. with psychedelics)? It is accepted in the recently published EMA guidance on MDD.	Please add copied text from the MDD guidance: 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.
2	342-348	It is unclear why this paragraph is added to the guideline, in particular since placebo run-in for enrichment is not advocated. Screening and washout periods are generally applied in all clinical trials, so why is treatment with placebo during this period advised here?	Consider deleting as not specific to BD.
3	372	The use of plural “studies” suggests that multiple studies are required to characterize the long-term effefcts of treatment. Could one trial evaluating recurrence of a mood episode irrespective of polarity suffice?	

4	372-383	The 3+9 weeks studies require a larger sample size to have enough power at week 12 for non-inferiority analysis in this population where the dropout rate is especially high. 3 weeks placebo-controlled study and maintenance of effect study should be considered to demonstrate efficacy in manic episodes.	4.3.1.2.1. Mania 3 weeks placebo-controlled study and maintenance of effect study should be considered to demonstrate efficacy in manic episodes.
5	372-388	Possible designs are described for maintenance of efficacy trials for mania and MDD separately. Could a separate trial showing maintenance of efficacy by relapse of any mood episode be an option to reduce the number of required trials?	Consider including trial design focussing on relapse prevention of any mood episode
6	403-405	Could results from actigraphs and electronic devices be used for claims in the SmPC? Please describe which type of information is intended, as eCRF data are also collected via electronic devices.	Please clarify which type of data could be used to substantiate a claim.
7	406	Interesting, but how to see this prospectively in the light of maintenance of efficacy and prevention of recurrence? Should life charts include rating scale results, or be purely PROs?	Please clarify further.
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2.4.4. Specific claims

2.4.4. Specific claims

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	448	The target would be recurrence of a mood episode, irrespective of its polarity.	The duration of the study should be long enough to demonstrate an effect on recurrence of any mood episode.
2	450	Generally, recurrences occur to a larger extent to the polarity of the diagnosis at trial entry (e.g. manic to manic, MDE to MDE). Powering for an effect to the opposite polarity would require a much larger trial. In addition, when recurrence to the opposite pole occurs, a treatment intervention will be needed. and the patient is lost or at least compromised for assessment for the recurrence of an episode of the initial pole. This may make the trial infeasible. Recurrence of any mood episode is the preferred endpoint.	
3	468	Should extrapolation be done in any case to get a claim on cognition or only if one wants to claim an effect on cognition in an elderly population? What is meant by and older population (age?) and how should extrapolation be done?	Please clarify the extrapolation expected to be submitted
4	469-471	Does the EMA recommend particular measures of cognitive function as specified for mania symptoms, depressive symptoms and suicide?	Clarification requested.
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2.4.5. Bipolar disorder with specifiers

2.4.5. Bipolar disorder with specifiers

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	477-478	If indication in sub-population is sought, can the program entirely consist of participants with the specifier? If so, could the size of trials in this sub-population be reduced?	Please clarify
2	496-499	The prevalence of mixed features in bipolar episodes varies depending on the criteria. For instance, DSM-5 seems to offer more sensitivity to detect features of the opposite end than DSM-4. In general, the prevalence of mixed features seems to be around 30% in maniac episodes vs 18% in depressive episodes. Even acknowledging the differences between pure and mixed features, the primary endpoint scales for both populations will be the same with the differences lying into the secondary endpoints. The reduced numbers of the mixed population may result in challenging recruitment if dedicated studies are required, not to mention the addition of complexity to the overall clinical development program preventing a streamlined global clinical development. Based on the above, our proposal is to conduct one unified study per type of episode with or without mixed features (E.g. manic episode with or without mixed features) with the mixed feature subpopulation as a distinct subgroup or through stratification within the study cohort. This methodology enhances the generalizability and applicability of research findings, ensuring that therapeutic interventions are assessed in a context that mirrors real life clinical scenarios.	4.5.2. Mixed features A separate claim specifically in patients with mixed features may be conducted as part of a unified study population (e.g. manic episode with or without mixed features). Subjects exhibiting mixed features should be included as a distinct subgroup or through stratification within the study cohort. The included patient population will need to be clearly defined in the inclusion criteria and may affect the final label recommendations. Used endpoints should cover both the mood episodes itself and the features of the opposite end.
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2.4.6. Special populations

2.4.6. Special populations

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	517-523	Patients 13-18 years of age need to be included to address the pediatric patients group in the EU while other authorities may require patients from 10 years and above. The studies will be powered to assess the population 10 or 13-17 years of age. The guidance should clarify that sub-group analyses should not be required for age-ranges below 15 vs 15 and above. Based on the epidemiology, the 10 or 13-14 years old group will be smaller and studies are not powered to demonstrate statistical and clinical significance on their own.	There is insufficient evidence for the existence of BD in childhood (<13 years of age). No studies are recommended in this age group. In regular studies for BD, adolescents can be included as of 13 years of age. Sufficient patients should be included to allow a separate analysis for this younger patient group (13-18 years of age). Full extrapolation of efficacy and safety data from adults is not considered appropriate. Short term-efficacy data need to be generated either in a subgroup analysis or a dedicated study with adolescents. MAHs should make a reasonable attempt to enroll pediatric patients across the 13-18 years old age-range to allow safety analysis of data for the 13-14 year old and 15-18 year old according to the prevalence of disease within these age groups. Efficacy analysis is intended in the entire pediatric cohort 13-18 years old.
2	534	Are 'women and girls of childbearing potential' a noted subpopulation of interest given recent restrictions on the use of valproate in this population? Inclusion of this subpopulation would help to contextualize the need for new medicines.	Clarification requested.
3	542-545	The paragraph on 'sex issues/differences' is followed by a sentence on 'predefined analysis of gender specific groups'. Please clarify whether analyses are suggested by sex and/or gender subgroups?	Clarification requested.
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2.4.7. Safety evaluation

2.4.7. Safety evaluation

	Line number(s) of the relevant text (e.g. 20-23)	Comment and rationale	Proposed guidance text
1	550-551	Are all these scales required? In general, quite a number of scales are included in clinical trials in BD, contributing to patient burden and non-specific effects. Will data from scales like UKU be included in the SmPC, additionally to the ADR table(s)? If not, can one do without and submit analyses of AEs of special interest (AESIs) based on MedDra standardized search terms?	Adverse Events of Special Interest (AESIs)for psychotropic drugs should be analysed using standardised MedDra search terms and AESIs should be reported in separate tables.
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References

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Other comments

Other comments

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Thank you

Thank you for your contribution.

Contact

Contact Form