London, 16 April 2010
Doc. Ref. EMA/626274/2009

Overview of comments received on the draft guideline on the development of medicinal products for the treatment of alcohol dependence (CHMP/EWP/20097/08)

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

Stakeholder no.	Name of organisation or individual
1	**EFPIA**
2	**ACTIVE Group of the American College of Neuropsychopharmacology**
3	**IFAPP = International Federation of Associations of Pharmaceutical Physicians**
4	**Dr Jonathan Chick, University of Edinburgh UK**
5	**Lundbeck A/S**
6	**MSD**

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1. GENERAL COMMENTS – OVERVIEW:

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
1	Efpia believe this guidance document is very well written and provides a major step forward in representing the current thinking when developing products for the treatment of alcohol dependence. **We wish to raise the following key comments, regarding some of the concepts presented in the draft guidance document. These key points are followed by other important comments presented by section in the draft guidance. In order to streamline the document, no editorial or typographical comments are provided.** **1. Reduction of alcohol consumption as a stand-alone indication:** One interpretation of this draft guidance is that all products must be developed with an end treatment goal of achieving and maintaining abstinence. Since it is recognised that there is a clear medical need for patients unable or unwilling to pursue abstinence, we request that the guidance be clear and unambiguous that a reduction of alcohol consumption goal could be considered as a treatment indication in its own right. Requiring maintenance of abstinence as the main treatment goal is a significant challenge and, in some cases, may be unfeasible, thus resulting in fewer treatment options for patients. We believe it is now accepted that patients who reduce their alcohol consumption gain an important clinical outcome and the guidance should not diminish this treatment goal. Therefore, given the clear medical need in these patients we believe that striving for this, as a stand-alone indication should be acceptable. **2. Subject Selection Characteristics** **We agree that the inclusion of patients into the main studies should be as broad as possible, and we believe this should include patients with medium to very high risk consumption for acute problems, in order to capture the population that will use these drugs in clinical practice. Patients with medium risk consumption for acute problems have a markedly increased risk of cirrhosis of the liver and malignant neoplasms, and patients with binge drinking behaviour may not fall**	**Ref.1. Not accepted.** Justification: Clinically significant reduction of alcohol consumption and subsequent harm reduction is undoubtedly an important goal. However, the scope of the GL is solely treatment of alcohol dependence and not alcohol abuse/harmful use. The final goal in patients with alcohol dependence remains still full sustained abstinence due to neuroadaptive changes and the subsequent high risk of reinstatement. Thus, reduction of alcohol consumption can only be considered as an intermediate treatment goal in patients with alcohol dependence. The guideline offers advice how to develop products for this intermediate treatment goal in alcohol dependent patients. **Ref.2: Not accepted** Justification: The reason to recommend inclusion of only alcohol dependent patients with high or very high risk levels of alcohol consumption in the main trials is to demonstrate efficacy in patients who are clearly representing the majority of this patient population. Of note, the average daily consumption of alcohol of a typical

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	into the high or very high risk consumption categories defined by the WHO, but are still at significant risk of accidents and cardiovascular events. As depression, anxiety and other substance abuse problems are common co-morbidities in alcoholism, excluding patients with such co-morbidities from the main studies may restrict significantly the target population that would benefit from therapies approved in this indication. Inclusion of a broader population in the main studies will ensure that safety data are generated in a population more representative of the general population of alcoholics. **3. Duration of Confirmatory Trials** **It is stated in the draft guidance that the majority of relapses occur 6-12 months after the initiation of abstinence and that short-term efficacy trials should be of 3-6 months duration. However, it goes on to state that responses do not stabilise before 15 months, and therefore the overall outcome measurements should cover this period of time. We are not aware of data that support the need for a 15-month continuation phase, and we are concerned that such a long continuation phase will result in an increased number of patients lost to follow-up over time. Therefore, in order to demonstrate long-term maintenance of abstinence for a new compound intended to promote continued abstinence, we endorse an active treatment phase of at least 3 months followed by a period of 9 months after discontinuation of active treatment. For new compounds intended to promote a clinically significant reduction of alcohol consumption, we support study durations of 6-12 months where continued treatment is indicated.**	Austrian male alcohol dependent patient is 226 gram pure alcohol. Thus, alcohol dependent patients with medium risk level would be supposedly patients with only rather mild alcohol dependence with no sharp boarder to patients with alcohol abuse/ harmful use of alcohol. Nevertheless, if efficacy is established in alcohol dependent patients with high or very high consumption level, the results might then be extrapolated to alcohol dependent patients with medium level. **Ref.3 Partly accepted** Justification: Published literature demonstrates that stable results are reached not before around 15 months of abstinence. However, it is acknowledged that trials of this duration may be difficult to conduct. Thus, the recommendation is now trials with 12 to 15 month duration. Justification: There are published data from epidemiological investigations in alcohol dependent patients which demonstrate that truly stable results are not reached before 15 months of abstinence. Furthermore, there is currently a lack of data concerning trial duration of a harm reduction approach by clinically significant reduction of alcohol consumption promoted by specific medication. However, at a meeting with several European alcohol experts the consensus was to recommend a 15 month overall duration in both types of trials (relapse prevention and harm reduction trials). Nevertheless, the issues with trials of such duration are acknowledged. The recommendation in the GL is now overall duration of the confirmatory trials of at least 12, but preferably 15 months. That means 3 to 6 months active treatment in relapse prevention trials followed by a double-blind continuation phase in responders without treatment, at least until 12, but preferably until 15 months after randomization. In harm reduction trials a subsequent double-blind placebo-controlled active treatment phase in initial responders at 3 to 6 months, until 12 to 15 months after randomization is recommended.

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	4. Stratification of Patients **While it is acknowledged that it is of interest to investigate the effects of baselines characteristics and other covariates upon treatment response, it is usually recommended that the number of stratification variables be kept low in clinical trials. Therefore, we would recommend a more flexible approach for the analysis of sub-populations.**	**Ref.4: Partly accepted** Nevertheless, severity of dependence should be a stratification variable.

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2	The ACTIVE Group, comprised of representatives of academic research centres and industry in the United States and Europe and of US governmental representatives, has come together in an effort to use data sets from completed alcoholism pharmacotherapy trials as the empirical basis to resolve some of these issues. In the meantime, the ACTIVE group recommends the following modifications be considered by EMEA, which are presented in additional detail below according to their appearance in the draft guidelines: 1. A need exists to include harm reduction as a goal of its own, rather than as an intermediate step in the effort to establish abstinence. Because many heavy drinkers seek to reduce their drinking, medications that enhance that effort can provide a useful adjunct to psychosocial treatments aimed at harm reduction. Such an approach has the potential to help a large proportion of the population that drinks more than is good for them. This is not limited to "high" or "very high" risk levels of alcohol consumption. 2. A 15-month duration for treatment trials is longer than is warranted for registration trials. A mandatory one-year follow-up period is not feasible under most circumstances, due to attrition and loss of statistical power, creating a substantial obstacle to medications development. An alternative is to have studies of the duration of	**Ref.1: Not accepted.** Justification: The scope of the GL is solely treatment of alcohol dependence and not alcohol abuse/harmful use. For these alcohol dependent patients the final goal remains still full sustained abstinence due to neuroadaptive changes. The reason to recommend inclusion of only alcohol dependent patients with high or very high risk levels of alcohol consumption in the main trials is to demonstrate efficacy in patients who are clearly representing the majority of this patient population. **Ref.2: Partly accepted** Justification: Published literature demonstrates that stable results are not reached before 15 months of abstinence. However, it is acknowledged that trials of this duration may be difficult to conduct. Thus, the recommendation is now

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	effectiveness as phase IV requirements. 3. The choice of secondary outcome measures should be left to the discretion of the sponsor, with the guidelines considering the pros and cons of specific measures without specifying a single approach. Although progress has been made to develop an agreed-upon set of primary outcome measures, more work needs to be done empirically to accomplish this. In contrast, considerably more work needs to be accomplished to define secondary outcome measures and defining them at this point may be premature.	trials with 12 to 15 month duration. **Ref.3: Partly agreed** (see specific comments). Justification: Recommending several specific secondary endpoints is useful in order to allow also indirect comparisons, since an immense amount of measures currently exists. However, another choice is possible if justified accordingly.

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3	The guideline is well written and updated to most recent scientific evidence. We have no comments or suggestions to the guideline text and contents.	-
4	A very useful document.	-

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
5	We welcome the opportunity to review this draft guideline. In general, we find it a relevant and well-written document. However, we would like to emphasise some major points of concern for consideration during finalisation of the guidance: • *(1) Reduction of alcohol consumption as a stand-alone indication* We believe that the overall purpose for any treatment of alcohol dependence must be to reduce of the alcohol related health problems. This could be achieved by alcohol abstinence, reduced total consumption and/or fewer high consumption occasions. All three options have been associated with documented health benefits. **Therefore, the reduction of alcohol consumption should be considered as an ultimate treatment goal** for people who are not able to reach abstinence, or for those who desire reducing their alcohol consumption, thereby reducing harm and resulting in improved health outcomes.	**Ref. to point 1: Not accepted.** Justification: Clinically significant reduction of alcohol consumption and subsequent harm reduction is undoubtedly an important goal. However, the final goal in patients with alcohol dependence remains still full sustained abstinence due to neuroadaptive changes and the subsequent high risk of reinstatement. Thus, reduction of alcohol consumption can only be considered as an intermediate treatment goal in patients with alcohol dependence.

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	• *(2) Definition of risk level of drinking* Only allowing patients with high risk and very high risk level for 'acute problems' (per WHO criteria) to participate in the main trials will exclude many alcohol dependent patients with a documented increased risk of ill health. In addition to the inclusion in the main trials of high or very high level of total alcohol consumption at baseline, **the inclusion of a broader range of alcohol dependent patients would better reflect actual consumption and risk patterns.**	**Ref. to point 2: Not accepted.** Justification: The reason to recommend inclusion of only alcohol dependent patients with high or very high risk levels of alcohol consumption in the main trials is to demonstrate efficacy in patients who are clearly representing the majority of this patient population. Of note, the average daily consumption of alcohol of a typical Austrian male alcohol dependent patient is 226 gram pure alcohol. Thus, alcohol dependent patients with medium risk level would be supposedly patients with only rather mild alcohol dependence with no sharp boarder to patients with alcohol abuse/ harmful use of alcohol. Nevertheless, if efficacy is established in alcohol dependent patients with high or very high consumption level, the results might then be extrapolated to alcohol dependent patients with medium level.
	• *(3) Duration of Confirmatory Trials* There seem to be no published data that support the need for a 15-month continuation phase as recommended in the guideline, and such a long continuation phase could result in an increased number of patients lost to follow-up over time. Therefore, please consider **study durations of 6-12 months for new compounds intended to promote a clinically significant reduction of alcohol consumption** where continued treatment is indicated.	**Ref. to point 3: Partly accepted** Justification: There are several published data from epidemiological investigations in alcohol dependent patients which demonstrate that stable results are not reached before around 15 months of abstinence. It is true that there is currently a lack of data concerning a harm reduction approach by clinically significant reduction of alcohol consumption promoted by specific medication. However, at a meeting with several European alcohol experts the consensus was to recommend a 15 month overall duration in both types of trials (relapse prevention and harm reduction trials). The recommendation in the GL is now overall duration of the confirmatory trials of at least 12, but preferably 15 months. **Ref. to point 4: Partly accepted**

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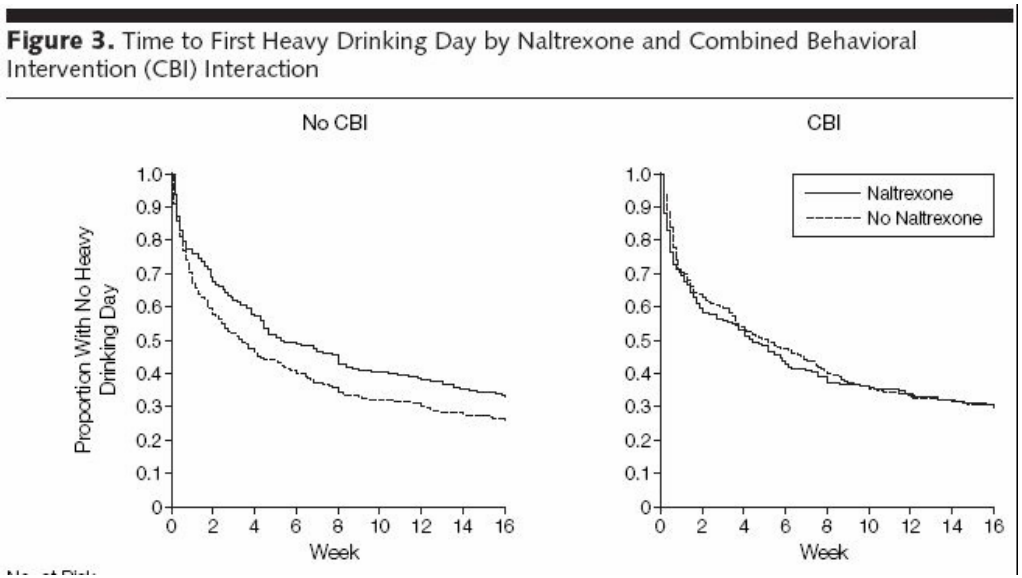
	• *(4) Methodological recommendations concerning the adolescent population* The draft guideline recommends including **alcohol dependent adolescents** in the development program. It would therefore be useful if the guideline could **clarify the main methodological considerations to make**, e.g. expected timeline for demonstration of efficacy/safety in adolescents (potential for deferral of studies in PIP), potential inclusion of adolescents in adult studies and possibilities for extrapolation. In addition, as the true alcohol dependent adolescent population corresponds to a minority of adolescents who misuse alcohol, please consider if it would it be possible to discuss a more holistic approach to the paediatric population with regards to for instance abusers or binge drinkers.	This guideline focuses on alcohol dependent persons only. Since alcohol dependence develops over years of chronic heavy drinking most of alcohol dependent adolescents will be beyond 16 years of age. Thus, an inclusion in adult trials might be possible.

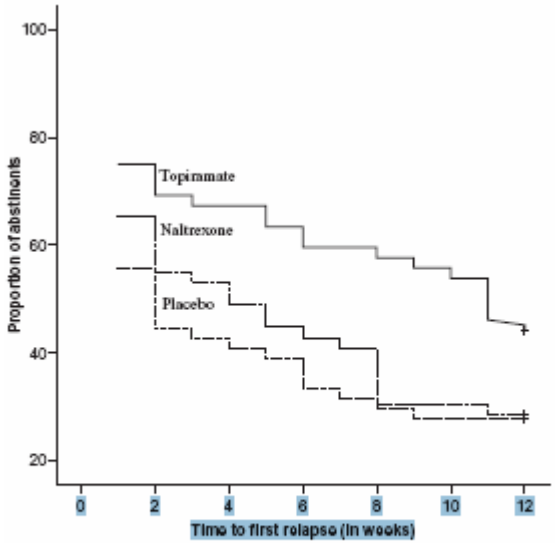
Stakeholder No.	General Comment	Outcome (if applicable)
6	None	

2. SPECIFIC COMMENTS ON TEXT

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
Lines 33-36	**1**	**Comments:** **The proposed addition is intended to highlight the relevance of psychiatric co-morbidities to the level of disability of alcohol-dependent patients.** **Proposed change (if any):** We propose the addition of the following text *before* the original sentence beginning on line 33 (additions in bold): "**Among those with an alcohol disorder, approximately 30-40% had a co-morbid mental disorder. People with an alcohol use disorder and a co-morbid mental disorder are significantly more disabled and have higher usage rates of health services than people with an alcohol use disorder and no co-morbid mental disorders."**	**Not accepted** Justification: Line 30 and 31 reflect this sufficiently already.
Lines 34-36	**1**	**Comments:** Please clarify what is meant by "milder mood disorder". Does this refer to disease severity? **Proposed change (if any):** Clarification of terminology is requested.	**Partly accepted** The term milder was changed to mild.
Line 51	**1**	**Comments:** "*Priming*" refers to the re-exposure to alcohol and/or the conditions associated with drinking (*i.e.,* smell, bottles, alcohol priming, or being given a priming dose of alcohol), while "*reinstatement*" (or relapse) is defined as to a return to the act of drinking after a period of abstinence, as described in the text. Therefore, reinstatement (or relapse) most accurately reflects the stated definition. **Proposed change (if any):** Please consider the following revision to Line 51: "…with a reappearance of the features of the syndrome (~~priming~~ reinstatement)."	**Accepted**
Lines 69-70	**1**	**Comments:** The cited WHO 2000 "International Guide for Monitoring Alcohol Consumption and Harm' (http://whqlibdoc.who.int/hq/2000/WHO_MSD_MSB_00.4.pdf) defines risk levels for "acute problems" based on alcohol consumption on a single drinking day. These risk levels do not refer to risk of developing alcohol dependence.	**Accepted** Additionally, this part was enlarged regarding risk of chronic harm.

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change (if any): **Please clarify that the risk referred to is the risk of acute problems, as opposed to the risk of developing alcohol dependence.** Proposed revision to Line 70: "…alcohol consumption ~~is~~ can be categorized ~~in different health risk levels~~ according to the risk of acute problems." Proposed revision to Line 71 (addition in bold): "WHO-Criteria for risk of consumption on a single drinking day **for acute problems**"	
Lines 80-81	**1**	**Comments:** **Patients with family history of alcoholism are known for their increased vulnerability, and reduced sensitivity, to alcohol. Since it is widely accepted that even low levels of alcohol consumption may trigger relapse in these patients, it is appropriate to include patients with family history of alcoholism among those for whom a daily limit of 7g pure alcohol may be too much.** **Proposed change (if any):** Please consider the following addition (in bold) to Line 81: "…is considered too much for some special groups, e.g., pregnant women **or patients with family history of alcoholism** and/or liver cirrhosis."	**Not accepted** Justification: Here only two examples are listed (it is not possible to list every single special group).
Lines 98-100	**1**	**Comments:** **Epidemiology research indicates that median time to relapse after initial abstinence is 15-30 days, which is significantly less than 6 months. Please see supportive data provided below.** **Proposed change (if any):** Please consider the following addition (in bold) to Line 100: "The majority of relapses after initiated abstinence occur within a period of one year, especially within the first 6 months, **but median time to relapse after initial abstinence is 15-30 days.**"	**Not accepted** Justification: Published data show that around 50% of patients have a relapse after initiated abstinence within 3 months, around 65% within 6 months and around 80% within 1 year. This is the reason for demanding 3 to 6 months trials for initial efficacy and 12 to 15 months overall for demonstrating maintenance of abstinence.

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Supportive evidence: From the COMBINE study (Anton et al., 2006) it can be seen that approximately 50% of patients relapse to having heavy drinking days within 4-6 weeks after the start of treatment.  **Figure 3.** Time to First Heavy Drinking Day by Naltrexone and Combined Behavioral Intervention (CBI) Interaction Baltieri et al., 2008 demonstrated that the mean time to relapse ranged between 5 to 8 weeks depending upon the treatment received.	

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		 **Figure 2** Survival curve of time to first relapse for subjects randomized to topiramate, naltrexone or placebo <u>Additional supportive references with embedded pdf files:</u> Anton *et al.* (2006) Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. JAMA **295**(17): 2003-2017 Baltieri *et al.* (2008) Comparing tompiramate with naltrexone in the treatment of alcohol dependence. Addition **103**: 2035-2044. Morley *et al.* (2006) Naltrexone versus acamprosate in the treatment of alcohol dependence: a multi-centre, randomized, double-blind, placebo-controlled trial. Addiction **101**: 1451-1462. O'Malley *et al.* (1992) Naltrexone and coping skills therapy for alcohol dependence. Arch. Gen. Psychiatry, **49**: 881-887. "anton 2006 combine.pdf" "baltieri 2008.pdf" morley2006.pdf omalley1992.pdf	

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Lines 121-124	**1**	**Comments:** Since highly effective short-term care for alcoholism is not available and long-term care is mainly necessary, it is relevant to indicate that effectiveness of long-term care is significantly limited by dropouts. **Proposed change (if any):** Please consider the proposed revision to Lines 121-124 (addition in bold): "**In the absence of effective short term treatment**, ~~Usually~~ alcohol dependent patients require long-term care, although the intensity and availability of specific components of treatment may vary over time, e.g. intensified monitoring and supportive treatment during the early stages of treatment, times of transition to less intensive levels of care, and the first year after active treatment has ceased. **However, high rates of early dropouts limit the effectiveness of long-term care."**	**Not accepted** It is probable that even if in the future, more effective specific medication for treatment of alcohol dependence is available, some kind of long term care will still be necessary.
Line 161	**1**	**Comments:** **We believe "harmful" drinking, which is not in the scope of guideline, can potentially be confused with harm reduction, which is within scope.** **Proposed change (if any):** We suggest adding a definition of "harmful" drinking;	**Accepted** Term was changed to harmful use of alcohol. The definition can be found in section 1.1.
Line 170	**1**	**Comments:** Please consider the use of "harm reduction" terminology instead of "intermediate goal", to be consistent with the approach that it is an acceptable treatment goal in itself for many patients, rather than an intermediate step to total abstinence. **Proposed change (if any):** Please consider the proposed revision to Lines 168 to 170 (additions in bold): "This includes products to prevent relapses after initiated abstinence, as well as products leading to clinically significant reduced alcohol consumption **with subsequent harm reduction** ~~as an intermediate goal on the way to full abstinence~~."	**Partly accepted** Clinically significant reduction of alcohol consumption (harm reduction approach) remains an important, but only an intermediate goal on the way to full abstinence.
Lines 196- 203	**1**	**Comments:** The first two paragraphs describe the two types of studies: harm reduction and relapse prevention.	**Accepted**

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change (if any): We suggest that definitions of the two types of clinical trials are provided at the beginning of the section in order to add more clarity throughout.	
Lines 204-206	**1**	**Comments:** **The DSM-IV-TR and ICD-10 criteria for the alcohol dependence diagnosis are based on a number of physical, psychological (lack of control), social and occupational characteristics of drinking, but deliberately do not specify a minimum level of alcohol consumption. Only allowing patients with high risk and very high risk consumption for acute problems (per WHO criteria) to participate in the main trials will exclude many alcohol dependent patients with a documented increased risk of ill health. For example, patients with medium risk consumption have a markedly increased risk of cirrhosis of the liver and a number of malignant neoplasms. Also, alcohol dependent patients with binge drinking behaviour may not fall into the very high or high-risk categories defined by the WHO, but are still at significant risk of accidents and cardiovascular events.** **Proposed change (if any):** Please consider the inclusion of a broader range of alcohol dependent patients to better reflect actual consumption and risk patterns of the alcohol dependent population.	**Not accepted** **See Ref.2 (response to general comment 2 of EFPIA)**
Lines 204, Lines 222-226	**1**	**Comments:** We would appreciate more clarification around the phrase "*general inclusion of patients should be as broad as possible*". As depression, anxiety and other substance abuse problems are common co-morbidities in alcoholism, excluding patients with such co-morbidities from the main studies may restrict significantly the target population that would benefit from therapies approved for this indication. Inclusion of a broader population in the main studies will assure that safety data are generated in a population more representative of the general population of alcoholics. The described exclusion criteria is therefore appropriate for early clinical studies, such as Proof-of-Concept, but for the main studies the proposal is to consider broadening the inclusion criteria and exclude only patients with schizophrenia and suicidal ideations. **Proposed change (if any):** Please consider the proposed revision to Lines 222-226 (additions in bold): "Patients with significant Axis-I co-morbidity (e.g., schizophrenia, major depressive disorder or severe anxiety disorders) as well as other substance use disorders (with the exception of nicotine abuse) should be excluded in **early clinical trials. In the main studies, only patients with schizophrenia and suicidal ideations should be excluded."**	**Not accepted** In the main trials it is necessary to exclude patients with marked psychiatric co-morbidities in order to avoid attribution issues. Efficacy should be clearly demonstrated in alcohol dependence and not in significant Axis I psychiatric co-morbidities. This was also recommended at the ECNP consensus meeting in 2003. However, as was stated in the Draft GL, after an effect is clearly demonstrated in alcohol

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			dependence, trials in patients with psychiatric co-morbidities can be of course conducted.
Lines 208-211, Lines 269-270	**1**	**Comments:** We would like to understand in more detail the expectations around the documentation requirements for both number and duration of abstinence attempts and former pharmacotherapy for drinking cessation. In principle this is achievable, however, we would like further clarification as to how this information should be utilised. For example, would past treatment be considered a proxy for severity of dependence? Prior treatment seeking behaviour could be a covariate in the analysis but not in other stratification factors such as age and severity of dependence. While it is acknowledged that it is of interest to investigate the effects of these baseline characteristics and other covariates upon treatment response, it is usually recommended that the number of stratification variables be kept low in clinical trials. Moreover, if there is large variation within a strata (as would be expected for the severity of alcohol dependence), the treatment groups may still be unbalanced. To ensure consistency with the recommendations in Line 211 regarding stratification, we propose the following revision to offer a more flexible approach to the analysis of sub-populations. **Proposed change (if any):** Please consider the proposed revision to Lines 209-210 (additions in bold): "If in a study, a mixed population is included (i.e., patients without prior treatment and treatment resistant patients), the study ~~should~~ **may be stratified or adjusted for accordingly in the analysis**."	**Ref.4: Partly accepted** Nevertheless, severity of dependence should be a stratification variable.
Line 210	**1**	**Comments:** Please clarify how "treatment resistant patients" should be defined. **Proposed change (if any):** Please consider including a definition of treatment resistant patients.	**N/A** The term was deleted.
Lines 222-226	**1**	**Comments:** Please see the comments above for Line 204.	-
Line 227	**1**	**Comments:** **Please provide examples of the "other potentially confounding co-morbid disorders" that applicants should consider excluding in primary studies.**	**Partly accepted** This section was changed.

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		Proposed change (if any): Please provide examples of "other potentially confounding co-morbid disorders".	
Lines 251-252	**1**	**Comments:** We are unclear why the following descriptive features would be valuable: • *Motivations for change assessment such as the Stages of change questionnaire* • *Treatment goal of complete abstinence (or not) as well as Client motivation*. **Proposed change (if any):** Please clarify the use of these descriptive factors.	**Accepted** Both descriptive features were deleted.
Line 263	**1**	**Comments:** We believe that the measurement of alcohol metabolites is of academic interest, but is not sufficiently available for use in clinical practice or most clinical trials. **Proposed change (if any):** Please consider the following revision to Line 263: "screening of blood, breath or urine for alcohol ~~(and alcohol metabolites)~~;"	**Not accepted** Biomarkers can be used as soon as they are validated.
Lines 269-270	**1**	**Comments:** Please see comments for Lines 208-211and Line 210. **Proposed change (if any):** Proposed revision to Lines 269-270: "Out of the list of above mentioned descriptive features, ~~it is recommended to stratify for~~ **patients may be stratified based on** severity of alcohol dependence, as well as for lack of prior treatment and treatment resistant patients, **or the analysis of data may be adjusted accordingly**".	**Accepted**
Lines 271-313, Lines 283-288	**1**	**Comments:** **The guideline describes "full abstinence goal" studies (relapse prevention after detoxification) and "intermediate harm reduction goal" studies (without prior detoxification) and gives the impression given that these two study formats are mutually exclusive.** In the "full abstinence goal" studies, the definition of relapse following the initial 6-week	**Accepted**

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		treatment period is "any amount of drinking". This does not distinguish between patients who relapse to heavy drinking and those who lapse/slip (as described in Lines 59-62). **Proposed change (if any):** We believe that secondary endpoints describing harm reduction (*e.g.,* change to baseline alcohol consumption and number of Heavy Drinking Days) should be included in the continued abstinence component of "full abstinence goal" studies.	
Lines 278-295	**1**	**Comments:** If a goal of reduction of alcohol consumption is deemed an acceptable primary indication this implies that in some cases full abstinence may not be achieved, but that reduction in heavy drinking leading to harm reduction remains a clinical important treatment goal in itself. We propose therefore, to remove reference to full abstinence in this case. **Proposed change (if any):** '~~However, as a first step a~~ Also a clearly clinically significant reduction in alcohol consumption promoted by a specific pharmacological agent, with subsequent harm reduction ~~might~~ would be a valid ~~intermediate~~ goal ~~on the way to full abstinence.~~" Similarly, remove the wording "*although only intermediate*" in line 295.	**Not accepted** See Ref.1 (response to general comment 1 of EFPIA)
Lines 280-282	**1**	**Comments:** **For studies intended to demonstrate full abstinence recovery, please clarify if applicants have a choice in one of the two primary study endpoints or if the expectation is that both endpoints must be specified as co-primary endpoints or alternative primary endpoints? If the latter, will multiplicity adjustment expected?** **Proposed change (if any):** Please clarify and expand upon statistical requirements.	Both endpoints are necessary (co-primary): the first to establish initial efficacy and the second at 12 to 15 months in order to establish maintenance of efficacy.
Lines 283-288	**1**	**Comments:** **Since onset of action depends on the therapeutic agent's mechanism of action, the initial treatment period will be defined by the agent's mechanism of action, and may deviate from the stated 6-month period.** **In addition, because it is unlikely that all cases of patients lost to follow up can be prevented, it seems more realistic to consider an endpoint imputation approach with the goal of collecting information from all patients.** **Proposed change (if any):** Please consider adding the following statements in bold:	**N/A** Paragraph was updated.

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		After the first 6 weeks, **or after a different time period determined by the compound's mechanism of action**, relapse should be defined as any amount of drinking. **Patients who are not** lost to follow up when having a relapse (or later lapse or slip), should be further assessed with respect to significant moderation outcomes i.e. more abstinent days and less heavy drinking. **However, patients who are lost to follow up should be imputed as having a relapse.**	
Lines 283-288	**1**	**Comments:** Please see comments and proposed changes above for Lines 271-313.	-
Line 291	**1**	**Comments:** Please see comments and proposed change above for Line 263.	-
Lines 292-298	**1**	**Comments:** We propose the following revision of this section to be consistent with the concept that a harm reduction goal, achieved by a clinically significant reduction in alcohol intake, is a treatment goal in itself, for the reasons given above. **Proposed change (if any):** Please consider the following revisions (additions in bold): **"~~Intermediate h~~ Harm reduction goal** In case an alcohol dependent patient is not able or willing to ~~get~~ **become** abstinent ~~immediately~~ (or *e.g.,* waiting for admission in an abstinence-oriented rehabilitation programme), ~~also~~ a clinically significantly reduced alcohol intake with subsequent harm reduction is a valid~~, although only intermediate,~~ treatment goal, since it is recognized that there is a clear medical need ~~also~~ in these patients. However, it is desirable ~~necessary~~ to aim at maintained abstinence **if a** ~~as soon as the~~ patient ~~gets~~ is ready **to commit to this** ~~for it .~~ Therefore if the study drug is ~~only~~ addressing the ~~intermediate~~ goal of clinically significant moderation…'	**Not accepted** See Ref.1 (response to general comment 1 of EFPIA)
Lines 297-301	**1**	**Comments:** **Please clarify if co-primary endpoints are required. We believe that one primary endpoint is adequate, and that the choice of primary endpoint should be relevant to the mechanism of action of the drug being studied.** **Proposed change (if any):** Please consider the following revisions (additions in bold):	**Not accepted** Both variables, total consumption of alcohol and HDD, are necessary in order to get the full picture of consumption and to cover all patterns of alcohol dependence (episodic vs.

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		'Therefore, if the study drug is ~~only~~ addressing the ~~intermediate~~ goal of clinically significant moderation, efficacy ~~should~~ **could** be expressed by change to baseline in total consumption of alcohol (presented as amount of pure alcohol in grams per day~~) as well as~~ or by reduction in number of Heavy Drinking Days (HDD defined as more than 60 grams of pure alcohol in men and 40 grams in women). Both are considered primary variables, since HDD are associated with specific risks such as acute cardiovascular outcomes or accidents. **The choice of primary variable should be justified on the basis of the mechanism of action of the molecule being studied.** A clinically relevant difference compared to placebo should be demonstrated.	continuous drinking) and which are associated with different risks. Thus, co-primary endpoints are required.
Lines 304 - 311	**1**	**Comments:** **For studies intended to demonstrate harm reduction, please clarify whether responder analyses are considered secondary endpoints.** **Proposed change (if any):** Please consider the following revision (additions in bold): "Therefore efficacy should also be evaluated, **as a secondary endpoint,** in terms of responders". Alternatively this section may be moved to "Important secondary endpoints" (line 316).	**Accepted**
Lines 320, Line 338	**1**	**Comments:** Given that baseline liver biomarker measures are often abnormal in the alcohol dependent population. Therefore, normalisation to of these measures should be assessed. **Proposed change (if any):** We proposed that normalisation of liver biomarkers to healthy population-based reference intervals or some similar range reflecting a healthy biological state be measured as opposed to a change to baseline.	**Partly accepted** Normalisation of liver biomarkers might be investigated additionally.
Lines 330-341	**1**	**Comments:** Please clarify that the endpoints listed under "*Further useful variables to be monitored*" are recommended, as appropriate, but not required. **Proposed change (if any):** Please consider revising the heading as follows (additions in bold): **"**Further useful variables to be monitored **as appropriate***".*	**Accepted**

Lines 355-362	**1**	**Comments:** **Based on the acknowledged confounding factors that impact interpretation of current validated biomarkers, and their limited specificity and sensitivity, their inclusion as optional exploratory endpoints seems appropriate if optional. The use of exploratory biomarkers has the potential to be more informative and will offer more flexibility for the validation of other biomarkers.** **Proposed change (if any):** Please consider the following revision to the sentence on Line 359 (additions in bold): "…choice in men. Therefore, **interpretation of findings from biomarkers should be considered exploratory** ~~combinations of markers is necessary~~**.** In future…"	**Not accepted** The limitations of current biomarkers are known and mentioned in the GL. However, they provide useful information and thus should be used as secondary outcome variables. Additionally the GL clearly endorses the use of new, if more appropriate, validated biomarkers.
Lines 385-407	**1**	**Comments:** In the section describing the study design requirements to support long-term maintenance of abstinence for a new compound intended to promote continued abstinence, we are unclear as to whether a 3 month + 12 month treatment period or a 3 month + 15 month treatment period is indicated. It is stated on Line 100 the majority of relapses occur within 6-12 months, and we are not aware of data that support the need for a 15 month continuation phase. We are concerned that such a long continuation phase increases the probability of patients being lost to follow-up over time. **Therefore, in order to demonstrate long-term maintenance of abstinence for a new compound intended to promote continued abstinence, we endorse an active treatment phase of at least 3 months followed by a period of 9 months after discontinuation of active treatment. For new compounds intended to promote a clinically significant reduction of alcohol consumption, we support study durations of 6-12 months where continued treatment is indicated.** **Proposed change (if any):** Please consider the following revision for the sentence starting on Line 400 (additions in bold): "Therefore, in order to establish long-term maintenance of abstinence in case of a new compound aiming to promote continued abstinence, the active treatment phase of at least 3 months should be followed up by a ~~double-blind continuation phase without treatment until 15 months after randomisation~~ **period of no more than 9 months after the discontinuation of active intervention period.**"	**Partly accepted** Overall duration of the trials should be 12 to 15 months. See Ref.3 for details (response to general comment 3 of EFPIA)

		Please consider the following revision to the section beginning on Line 405 (additions in bold): "In this case, a subsequent double-blind placebo-controlled phase in initial responders, **of up to 12 months duration** ~~until 15 months~~, is recommended."	
Lines 385-407	**1**	**Comments:** For new compounds intended to promote continued abstinence please clarify the following regarding the study design requirements for demonstrating long-term maintenance: • Is it expected that the follow-up phase includes psychosocial treatment or if all treatments are to be stopped (not just pharmacological treatment) at the end of the 3-6 month active treatment period? • Further detail is requested regarding what is meant by "randomised" in the "long randomised withdrawal phase". We assume that following end of the treatment phase all subjects will treated in the same way and will either be receiving placebo or not taking any study medication at all. • Would a single relapse or lapse during the withdrawal period classify a patient as a study failure, or is it anticipated that measures regarding harm reduction will provide useful information?	1. Psychosocial intervention, as already offered in the active treatment period, might be continued unchanged. 2. This section was reworded. 3. Patients with relapse should be classified as study failure with respect to sustained abstinence. However, measures regarding harm reduction (as recommended) will provide useful information.
Lines 392-395	**1**	**Comments:** **Since a rebound effect has not been demonstrated in currently approved treatment for alcohol dependence, the need to demonstrate the absence of a rebound effect should depend on the agent's mechanism of action, or may be data driven.** **Proposed change (if any):** Please consider the proposed revision to Line 393: "A sufficiently long randomized withdrawal phase to investigate possible rebound phenomena **may be** necessary **depending upon the mechanism of action of the drug or clinical data**."	**Not accepted** Possible rebound should be investigated.
406-407	**1**	**Comments:** **For the reasons discussed previously abstinence represents the ideal clinical goal but in reality many patients may never be ready to commit to abstinence. It certainly could not be considered as an absolute necessity for every patient and harm reduction in such patients is clearly a suitable endpoint.**	**Not accepted** See Ref.1 (response to general comment 1 of EFPIA)

		Proposed change (if any): Please consider the following proposed revision (additions in bold): "~~However, as mentioned before, it is absolutely necessary to~~ **Ideally, one should aim for the patient to achieve maintained abstinence as soon as they are ready for it**".	
433	**1**	**Comments:** **For discontinuing patients, please advise if applicants should also be followed up on TLFB data collaboration? If so, please clarify how the data would be incorporated into the analysis?** **Proposed change (if any):** Please provide clarification.	**Accepted** Sentence was changed to "discontinuing patients may be followed up".
447-449	**1**	**Comments:** We agree that the number of alcohol dependent adolescents is rare, therefore obtaining an efficacy profile in this population would be challenging. In addition, the inclusion of adolescents may not be appropriate depending on the efficacy profile of a new compound, observed in adults. **Proposed change (if any):** Please consider the following proposed revision (additions in bold): "~~Nevertheless, the number of adolescents with alcohol use disorders in general is increasing in Europe and also due to the new paediatric regulation (EC) No. 1901/2006 it is recommended to include alcohol dependent adolescents in the development program according to the prevalence in the general population (see Section 3 of this guidance document.~~ **Inclusion of alcohol dependent adolescents in the development program should be considered. However, due to the low prevalence of this age group in the alcohol dependent population, inclusion of adolescents in Phase III studies may not be feasible or very limited. Therefore, specific efficacy conclusions in this population would not be possible**."	**Partly accepted** **New wording:** Due to the paediatric regulation (EC) No 1901/2006 it is recommended that inclusion of alcohol dependent adolescents in the development program should be considered according to the prevalence in the general population (see Section 3 of this guidance document). However, due to the low prevalence of this age group in the alcohol dependent population, inclusion of adolescents in Phase III studies might be very limited. Therefore, specific efficacy conclusions in this population might not be possible."
481	**1**	**Comments:** Please confirm that preclinical evidence is adequate to evaluate the addiction potential of a new compound in the first instance.	**Partly accepted** Addiction potential should also be evaluated in the clinical trials.

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
Lines 196-197	**2**	**Comments:** Drinking reduction is a legitimate goal of treatment, rather than simply "a first step in the case of harm reduction studies." **Proposed change (if any):** Omit "as a first step"	**Not accepted** (see Ref.1/ response to general comment 1 of ACTIVE)
Lines 204-207	**2**	**Comments:** The use of guidelines for risky drinking appears to conflate average daily consumption with daily maximum drinking. There is a reference to section 1.3, which addresses the issue of total consumption on a particular day, while the text in these lines refers to total alcohol consumption as though that is a daily average. **Proposed change (if any):** Differentiate clearly between heavy drinking on a specific day and heavy daily average consumption, since although these are highly correlated, they may differentiate two populations of heavy drinkers that may benefit from a pharmacological intervention: intermittent very heavy drinkers (whose risk may stem more from accidents and social harm) and regular heavy drinkers (whose risk may stem more from medical problems).	**Partly accepted** Justification: Section 1.3 is now enlarged by WHO criteria for risk of consumption in relation to chronic harm. These numbers are now referring to average daily consumption. In the trials co-primary variables are demanded in order to get the full picture of consumption and to cover different harms (i.e. HDD and total consumption).
Lines 209-213	**2**	**Comments:** "If in the study a mixed population is included (i.e., patients without prior treatment and treatment resistant patients) the study should be stratified for these groups." "Additionally it is recommended to stratify subjects according to their level of dependence." Because stratification increases the total sample required to yield adequate statistical power, stratifying on these variables may make it very difficult to recruit an adequate study sample and costly to conduct a trial that addresses these issues adequately. Further, history of alcohol withdrawal severity is a variable that, although correlated with alcohol dependence severity, may be qualitatively different from it. Because it appears to account for additional variance in treatment response, it would profitably be added to the list of variables that should be considered as balancing variables.	**Partly accepted** Justification: To stratify for severity of dependence is necessary since scope of treatment is alcohol dependence and since severity of dependence is a major factor for outcome. Stratification for Possible differences between outcome of patients with and without prior treatment should be evaluated, but

Line No of the first lines affected.	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change (if any): The recommendation might be that prior treatment, severity of alcohol dependence, and alcohol withdrawal history be measured and considered as potential balancing variables during randomization, in which case *post hoc* analyses could be used to examine their moderating effect on treatment response. Although such analyses would be only exploratory, there would not be a negative impact on statistical power for the primary analyses. Also, please add a definition of "treatment resistant patients."	stratification is not mandatory.
Lines 231-232	**2**	**Comment:** The blanket exclusion of patients taking psychotropic drugs significantly limits the capacity to generalize the findings of a trial to the general population of alcohol-dependent patients, who have a high rate of use of such medications. **Proposed change (if any):** Patients being treated with psychotropic drugs that are likely to interfere with the mechanism of action of the medication being evaluated should be excluded.	**Not accepted.** In the main trials it is necessary to exclude intake of other psychotropic drugs in order to avoid attribution issues.
Line 251	**2**	**Comment:** It is unclear how an instrument such as the Stages of change questionnaire (which presumably refers to the SOCRATES) can be operationalized to be useful in a pharmacotherapy trial. **Proposed change (if any):** Expand on how the SOCRATES could be used in this capacity or omit this descriptive feature.	**Accepted** This instrument was deleted.
Line 260	**2**	**Comments:** Although reference is made earlier to the SCID, the AUDADIS is recommended here. Since the AUDADIS was designed for use in epidemiological studies, it may be less useful in clinical trials than the SCID or another clinical diagnostic instrument. **Proposed change (if any):** Replace this bullet with the following: • a validated structured or semi-structured psychiatric diagnostic instrument such as the Structured Diagnostic Instrument for DSM-IV (SCID)	**Accepted**

Line 264	**2**	**Comments:** The utility of the listed biochemical alcohol consumption markers for application to pharmacotherapy trials is unclear. At best, given their limited sensitivity/specificity profiles, they can be used to validate self-reported drinking. **Proposed change (if any):** Acknowledge the limitations and/or specify more clearly the utility of these measures.	**Not accepted** Already stated at end of section 4.2.2.
Line 267	**2**	**Comments:** The SF-36, although widely used to measure quality of life (QOL), should not be prescribed, but used as an example of one possible measure of QOL **Proposed change (if any):** Replace this bullet with the following: • a validated measure of quality of life, such as the SF-36	**Accepted**
Lines 269-270	**2**	**Comments:** Please see the comment re: Lines 209-213	See answer above
Lines 273-278	**2**	**Comments:** Please see the comment re: Lines 196-197. The ultimate goal of treatment in patients with mild alcohol dependence may also include reduced drinking below level considered hazardous or harmful. **Proposed change (if any):** Add “severely” to follow “…ultimate treatment goal in…” (so abstinence is the ultimate treatment goal for “severely alcohol dependent patients”) Also, in the following sentence, omit “as a first step” and change “valid intermediate goal on the way to full abstinence” to read “valid goal for individuals who may be able to sustain drinking that is below hazardous levels”	**Not accepted** (see Ref.1/ response to general comment 1 of ACTIVE)

Lines 280-282	**2**	**Comments:** A 12-month post-treatment follow-up period for abstinence will result in substantial attrition from the study, which will reduce statistical power. Further, harm reduction treatment may require continued medication administration, so that a post-treatment follow up may not be relevant to such studies. **Proposed change (if any):** A shorter post-treatment follow-up period (e.g., three months) will allow for the evaluation of enduring effects of treatment. Alternatively, Phase IV studies may best provide the opportunity to evaluate the duration of medication effects	**Partly accepted** Overall duration of trials is now 12 to 15 months (see Ref. 2 / response to general comment 2 of ACTIVE)).
Lines 283-284	**2**	**Comments:** The onset of action is unknown for most medications being developed for the treatment of alcohol dependence. **Proposed change (if any):** Except for medications that are known to exert an immediate beneficial effect on drinking behaviour, a “grace period” consisting of the first 4-6 weeks of treatment should be considered.	**Accepted**
Line 290	**2**	**Comments:** Information provided by collateral informants is often invalid due to lack of information on the part of the informant, so that the substantial effort required to obtain such information is not justified. **Proposed change (if any):** Remove “collateral information form”	**Partly accepted** Not strongly recommended any longer.
Line 292	**2**	**Comments:** Please see the comment re: Lines 196-197. **Proposed change (if any):** Remove the word “Intermediate” so that the text reads “Harm reduction goal (…)	**Not accepted** (see Ref.1/ response to general comment 1 of ACTIVE)
Lines 293-313	**2**	**Comments:** Please see the comment re: Lines 196-197.	**Not accepted** (see Ref.1/ response to general comment 1 of ACTIVE)

		Proposed change (if any): This text would benefit from re-wording to avoid the emphasis on total abstinence as the ultimate goal and harm reduction as only an intermediate goal for individuals who either do not meet criteria for alcohol dependence or whose alcohol dependence is mild in severity.	
Line 317	**2**	**Comments:** Time to relapse (first drink) is not a useful endpoint because it is subject to many influences unrelated to drug efficacy **Proposed change (if any):** Omit time to relapse (first drink) as a secondary endpoint	**Not accepted** It is often used and furthermore only recommended as a secondary endpoint.
Lines 372-376	**2**	**Comments:** In some medication studies, flexible titration may be needed**.** **Proposed change (if any):** Add the following: "Under some circumstances, flexible-dose designs may be utilized to evaluate dose-response."	**Not accepted.** See GL on dose-response information
Lines 396-407	**2**	**Comments:** Please see the comment re: Lines 280-282. **Proposed change (if any):** Replace "15 months" with "6 months" (to reflect a shorter post-treatment follow-up period) or identify Phase IV as the appropriate opportunity to evaluate durability of effects) to ensure adequate statistical power and feasibility of registration trials.	**Partly accepted** (see Ref.2/ response to general comment 2 of ACTIVE)
Lines 414-416	**2**	**Comments:** Although "it is recommended to integrate information from patient interviews, reliable informants (collateral reporting) and (electronic) patient diaries in a combined result in the Timeline-follow-back calendar method, applied by a specifically experienced investigator," there are no clear methods to perform such integration. Also, please see comment on Line 290 re: collateral information. **Proposed change (if any):** Acknowledge that this approach, although of theoretical utility, will require further methodological advances to permit its application. Also omit the following: "reliable informants (collateral reporting)"	**Not accepted** At a meeting with several European alcohol experts in 2008 this approach was considered feasible.

Line No of the first lines affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
200-203 and 279 - 317	**4**	**Comments:** Confusion of definitions of 'types of trial' e.g. 'relapse prevention trial' and 'harm reduction study' whereas in 4.2.1 the terms used are 'full abstinence goal' and 'intermediate harm reduction goal' **.** **Proposed change (if any):** in Line 200, insert after 'relapse prevention', *abstinence goal*	**Accepted**
364-371	**4**	**Comments:** **Proposed change (if any):** Consider recommending studies into psychomotor or other behavioural interactions between the study drug, and consumption of ethanol, because subjects may take alcohol having consumed study drug. E.g. potentiating sedative effect of the drug.	Already stated in section 4.5.2.
233-267	**4**	**Comments:** The list of baseline characteristics is over-inclusive. Usefulness of baseline 'motivation to change' measures is doubtful **Proposed change (if any):** Some baseline charactersitcs measures should be OPTIONAL	**Accepted**
260	**4**	What is AUDADIS . No reference given. An alternate might be TrinC	**Partly accepted** Now no specific tool is recommended, but a validated structured or semi structured psychiatric diagnostic instrument.
503	**4**	Caetano, not Caetanoe	**Accepted**
510	**4**	Dawson not Dawsons	**Accepted**
304	**4**	Expectable: the English version of the document should be read by a native English speaker to improve vocabulary	**Accepted**

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
Lines 33-36	**6**	**Comments:** The proposed addition is to highlight the relevance of psychiatric co-morbidity as defined in the first paragraph of Section 4.1.2 (Lines 215-220) without differentiation of severity, which assures consistency throughout the document. **Proposed change:** Propose to have the following text added before the original on line 33: **Among those with an alcohol disorder, approximately 30-40% had a co-morbid mental disorder. People with an alcohol use disorder and a co-morbid mental disorder are significantly more disabled and have higher usage rates of health services than people with an alcohol use disorder and no co-morbid mental disorders.**	**Not accepted** Justification: Line 30 and 31 reflect this sufficiently already.
Line 51	**6**	**Comments:** As per definition, priming refers to the re-exposure to alcohol and/or the conditions associated with drinking (i.e., smell, bottles, alcohol priming, or given a priming dose of alcohol), while reinstatement (or relapse) corresponds to a return to the act of drinking after a period of abstinence as described in the text. Therefore, reinstatement (or relapse) most accurately reflects the stated definition. **Proposed change:** Propose to use **reinstatement** (or **relapse**) instead of priming.	**Accepted**
Lines 69-70	**6**	**Comments:** The cited WHO 2000 "International Guide for Monitoring Alcohol Consumption and Harm' (http://whqlibdoc.who.int/hq/2000/WHO_MSD_MSB_00.4.pdf) defines the criteria for risk of consumption on a single drinking day as shown in the table included in lines 71-76, which is based on acute alcohol-induced problems. The goal of the proposed change is to correctly indicate that the definitions of health risk levels refer to acute problems, and to ensure that the table is interpreted within the appropriate context. Such change will	**Accepted** Additionally, this part was broadened.

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		avoid confusion that the cited different health risk levels refer to the development of alcohol dependence. **Proposed change:** Proposed a sentence to substitute for original sentence. Proposed addition in bold: 'According to the WHO "International guide for monitoring alcohol consumption and related harm" alcohol consumption**, in relation to acute problems,** is categorised in different health risk levels.' In addition suggest including in the list of references the WHO link to this report [http://whqlibdoc.who.int/hq/2000/WHO_MSD_MSB_00.4.pdf].	
Lines 77-79	**6**	**Comments:** Since products to prevent relapse after initiated abstinence, as well as products leading to clinically significant reduced alcohol consumption as an intermediate goal on the way to full abstinence are in the scope of the present guideline (as indicated in section 2), the definition of an **acceptable** rather than **desirable** level of consumption seems more appropriate. **Proposed change:** Use **acceptable** instead of desirable (line 77); use **accepts** instead of recommends (line 79). 'The most **acceptable** level of consumption (apart from abstinence) concerning health outcome both at short- and long-term use is the low risk level (1 to 40g pure alcohol on a single drinking day for men and 1 to 20g for women). Of note for really everyday consumption, WHO **accepts** currently a limit of 7g pure alcohol … '	**Partly accepted**
Lines 80-81	**6**	**Comments:** Patients with family history of alcoholism are known for their increased vulnerability and reduced sensitivity to alcohol. Since it is widely accepted that even low levels of alcohol consumption may trigger relapse in these patients, it is appropriate to include patients with family history of alcoholism among those to whom a daily limit of 7g pure alcohol may be too much. **Proposed change:** Add the following statement in bold (line 81): …is considered too much for	**Not accepted** Justification: Here only two examples are listed (it is not possible to list every single special group).

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		some special groups, e.g., pregnant women **or patients with family history of alcoholism** and/or liver cirrhosis.	
Lines 98-100	**6**	**Comments:** Epidemiology research indicates that median time to relapse after initial abstinence is 15-30 days, which is significantly less than 6 months. For clarity purposes consider the addition of the proposed statement. **Proposed change:** Add the statement in bold (line 100): The majority of relapses after initiated abstinence occur within a period of one year, especially within the first 6 months, **but median time to relapse after initial abstinence is 15-30 days.**	**Not accepted** Justification: Published data show that around 50% of patients have a relapse after initiated abstinence within 3 months, around 65% within 6 months and around 80% within 1 year. This is the reason for demanding 3 to 6 months trials for initial efficacy and 12 to 15 months overall for demonstrating maintenance of abstinence.
Lines 108-109	**6**	**Comments:** It is widely accepted that re-exposure to drinking [alcohol] and/or the conditions associated with drinking (i.e., alcohol priming, or given a priming dose of alcohol) significantly limits successful reduction of consumption. For clarity purposes, consider specifying that clinically reduction of consumption may be difficult to be achieved due to priming. **Proposed change:** Add **'mainly due to priming'** (line 108-109)**: ...**clinically significant reduction of consumption may be difficult to be achieved in alcohol dependent patients **mainly due to priming.**	**Accepted**
Lines 121-124	**6**	**Comments:** Since highly effective short-term care for alcoholism is not available and long-term care is mainly necessary, it is relevant to indicate that effectiveness of long term care is significantly limited by dropouts. **Proposed change:** Propose to use '**In the absence of effective short term treatment'** instead of '**usually**' (line 121), and add the statements/sentence on bold (line 124): **In the absence of effective short term treatment**, alcohol dependent patients require long-term care, although the intensity and availability of specific components of treatment may vary over time, e.g. intensified monitoring and supportive treatment during the early stages of treatment, times of transition to less intensive levels of care, and the first year after active treatment has ceased. **High rate of early dropout**	**Not accepted** It is probable that even if in future more effective specific medication for treatment of alcohol dependence is available some kind of long term care will still be necessary.

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		limits the effectiveness of long-term care.	
Line 162	**6**	**Comments:** Editorial suggestion for an appropriate grammatical format **Proposed change:** Suggest using **not** instead of **no**. … "are currently **not** target indications."	**Accepted**
Line 166	**6**	**Comments:** Editorial suggestion for an appropriate grammatical format **Proposed change:** Suggest using **not** instead of **no**. … "is therefore **not** a treatment option..."	**Accepted**
Lines 196-203 (Section 4.1.1)	**6**	**Comments:** The two first paragraphs describe the two types of studies considered: harm reduction and relapse prevention. Suggestion to provide an upfront definition of the two types of clinical trials in order to add more clarity throughout the section. **Proposed change:** Add sentence - line 196: **Two types of clinical studies may be conducted: harm reduction studies and relapse prevention trials.**	**Accepted**
Lines 209-210	**6**	**Comments:** In order to assure consistency with the Agency's recommendation of stratification, as specified on line 211, the proposed language offers a more flexible approach on how to handle the analysis of sub-populations. **Proposed change:** Consider modifying the last part of the sentence as shown in bold (line 210): If in the study a mixed population is included (i.e., patients without prior treatment and treatment resistant patients) the study **may be stratified or adjusted for accordingly in the analysis.**	**Accepted**
Lines 222-226	**6**	**Comments:** As depression, anxiety and other substance abuse problems are common co-morbidities in alcoholism, excluding patients with such co-morbidities from the main studies may restrict significantly the target population that would benefit from therapies approved for this indication. Inclusion of a	**Not accepted** In the main trials it is necessary to exclude patients with marked psychiatric co-morbidities in order to avoid attribution issues.

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		broader population in the main studies will assure that safety data are generated in a population more representative of the general population of alcoholics. The described exclusion criteria is therefore appropriate for early clinical studies, such as Proof-of-Concept, but for the main studies the proposal is to consider broadening the inclusion criteria and exclude only patients with schizophrenia and suicidal ideations. **Proposed change:** Consider modifying the following sentences as shown in bold (lines 224 – 226) : Patients with significant Axis-I co-morbidity (e.g., schizophrenia, major depressive disorder or severe anxiety disorders) as well as other substance use disorders (with the exception of nicotine abuse) should be excluded in **early clinical trials. In the main studies, only patients with schizophrenia and suicidal ideations should be excluded.**	Efficacy should be clearly demonstrated in alcohol dependence and not in significant Axis I psychiatric co-morbidities. This was also recommended at the ECNP consensus meeting in 2003. However, as already stated in the Draft GL, after an effect is clearly demonstrated in alcohol dependence, trials in patients with psychiatric co-morbidities can be of course conducted.
Line 270	**6**	**Comments:** In order to assure consistency with the Agency's recommendation of stratification, as specified on line 211, the proposed language offers a more flexible approach on how to handle the analysis of sub-populations. **Proposed change:** Consider adding a new sentence on line 270: **These patient variables may be stratified or adjusted for accordingly in the analysis.**	**Accepted**
Lines 280-282	**6**	**Comments:** Since alcohol dependence is well known to be a chronic illness with high rates of relapse, continued abstinence rate after detoxification at the end-of-active treatment period and/or the continued abstinence 12 months after end-of-active treatment are of high clinical relevance. From a medical perspective either of these endpoints is clinically relevant and, individually or not, is an acceptable primary endpoint. **Proposed change:** Propose to use '**or'** instead of '**and'** (line 281).	**Not accepted** The goal is sustained abstinence.
Lines 283-288	**6**	**Comments:** Since onset of action depends on the therapeutic agent's mechanism of	**Accepted**

Line No of the first line(s) affected	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		action, the initial grace period will be defined by the agent's mechanism of action, and may deviate from the stated 6-month period. In addition, because it is unlikely that all cases of patients lost to follow up can be prevented, it seems more realistic to consider an endpoint imputation approach with the goal of collecting information from all patients. **Proposed change:** Consider adding the following statements in bold: After the first 6 weeks, **or after any other time period determined by the compound's mechanism of action**, relapse should be defined as any amount of drinking. **Patients who are not** lost to follow up when having a relapse (or later lapse or slip), should be further assessed with respect to significant moderation outcomes i.e. more abstinent days and less heavy drinking. **However, patients who are lost to follow up should be imputed as having a relapse.**	Paragraph was updated.
Lines 355-362	**6**	**Comments:** Based on the acknowledged confounding factors that impact interpretation of current validated biomarkers, and their limited specificity and sensitivity, their inclusion as exploratory endpoints seems to be more appropriate if optional (i.e., exploratory) rather than mandated. The use of exploratory biomarkers has the potential to be more informative and will offer more flexibility for the validation of other biomarkers. **Proposed change:** Propose to modify the sentence starting on line 359 as follow: '…choice in men. Therefore **interpretation of findings from biomarkers should be considered exploratory.** In future…'	**Not accepted** The limitations of current biomarkers are known and mentioned in the GL. However, they provide useful information and thus should be used as secondary outcome variables. Additionally the GL clearly endorses the use of new, if more appropriate, validated biomarkers.
Line 379	**6**	**Comments:** For clarification purpose. **Proposed change:** Add '**versus placebo** ' at the end of the sentence. '…designed to demonstrate superiority **versus placebo**.'	**Accepted**

Lines 392-395	**6**	**Comments:** Since rebound effect has not been demonstrated in currently approved alcohol treatments, the need to demonstrate absence of rebound effect will depend on the agent's mechanism of action or may be data driven. **Proposed change:** Propose adding the following statements in bold: A sufficiently long randomized withdrawal phase to investigate possible rebound phenomena **will be** necessary **if rebound phenomena are expected based on mechanism of action or clinical data**.	**Not accepted** Possible rebound should be investigated.
Lines 396-399	**6**	**Comments:** These statements appear to generate confusion with the previous paragraph (line 392) that indicates the duration of active treatment for a study designed to establish short-term efficacy to be of 3 to 6 months. In addition, it is unclear when it requires that outcome measures be continued after the end of the active treatment. While currently available treatment have modest efficacy in the first 3-6 months of treatment, the minimum treatment duration and efficacy should be determined by the agent's mechanism of action. The proposed differentiation of efficacy timeframes – i.e., short-, intermediate- and long-term – would offer clarity and flexibility in view of the agent's mechanism of action, and would preclude unnecessarily long studies that likely would not provide additional useful efficacy information and may expose patients to unnecessary risks. **Proposed change:** Suggest to have the following paragraph replacing the current paragraph: **Establishment of short-, intermediate- or long-term efficacy will be determined by the agent's mechanism of action, which will inform the duration of the active treatment period, respectively, to: 3-6 moths (short-term), 6-12 months (intermediate term) and 12-15 months (long-term).**	**Partly accepted** The section was updated for clarification. However, overall study duration should cover 12 to 15 months. In relapse prevention trials 3 to 6 months of active treatment should be followed by a follow-up period without treatment until 12 to 15 month after randomization. In contrast, in harm reduction trials there might be usually the need for continued administration. In this case a subsequent double-blind placebo-controlled active treatment phase in initial responders at 3 to 6 months, until 12 to 15 months after randomization is recommended.