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GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF ALCOHOL DEPENDENCE

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EXECUTIVE SUMMARY

Alcohol dependence is in general accepted as a psychiatric disorder with harmful physical, mental and social consequences and a high probability of a chronic relapsing course. It is considered a major public health problem in most Western societies. The aim of this guideline is to provide guidance on clinical studies for drugs developed for the treatment of alcohol dependence.

The present document should be conceived as general guidance, and should be read in conjunction with other applicable EU and ICH guidelines (see Section 3).

1. INTRODUCTION

1.1 Epidemiology and classification of alcohol dependence

Alcohol use disorders develop against a genetic, psychosocial and environmental background. Life-time prevalence estimates for all alcohol use disorders in the general population in Europe range from 12 to 24%.Alcohol related health disabilities include liver diseases, cardiovascular diseases such as alcoholic cardiomyopathy, various forms of cancer, gastrointestinal haemorrhage, pancreatitis, as well as severe neurological, cognitive and psychiatric complications. Some complications such as Korsakow syndrome are rather related to malnutrition and deprived vitamin B uptake secondary to alcohol use.

Alcohol use disorders can be categorized like other substance use disorders according to WHO/ICD-10 (among others) into harmful use and dependence or according to DSM IV-TR into abuse and dependence. Whereas there is good diagnostic concordance for dependence in both classification systems, there is markedly less agreement for harmful use and abuse respectively. Regarding dependence, both classification systems additionally assess present state, course of disease and association with physical symptoms.

The prevalence of alcohol dependence was estimated at 5-6% in men and 1-2% in women in Europe; however, the number of alcohol dependent women has been increasing recently. The average time of progression from initial problem drinking to alcohol dependence has been reported to be in the 6 to 8 year range.

In general, alcohol dependent patients are a very heterogeneous population with respect to genetic factors, personality disorders, co-morbidities, severity, cognitive impairment, age of onset, gender, motivation concerning readiness to change, social support for drinking or abstinence, craving and others. Especially psychiatric co-morbidity like depression is common in people with alcohol problems and is an essential factor influencing the course of disease and treatment. Furthermore alcohol dependence is more common in elderly males than in women and young adult males.

It is estimated that 10% of people with alcohol problems have a severe mental illness, 50 % have a personality disorder and up to 80% have a milder mood disorder. On the other hand, there is good evidence that those milder forms of anxiety and depression often resolve with abstinence in patients with alcohol dependence.

In order to address all these differences, several subtype classifications of alcohol-dependent patients were developed, but none of them is currently in widespread use or generally accepted. Rather, a paradigm shift happened in the last years from a categorical towards a multidimensional diagnostic approach regarding alcohol use disorders, which will be very probably implemented in the forthcoming DSM V and ICD 11.

The risk for relapse after initiated abstinence also may depend on multiple variables, such as general personal characteristics (like demographic background, personality factors, degree of dependence, family history), degree of stress and perceived self-efficacy and level of confidence respectively with regard to cue-situations.

1.2 Definition of dependence and (re-)lapse

According to the definitions of the World Health Organisation ICD-10, and DSM-IV-TR, alcohol dependence is characterised by a cluster of physiological, behavioural and cognitive phenomena, in which the use of this substance takes on a much higher priority for an individual than other behaviours

that once had greater value, and a return to drinking after a period of abstinence is often associated with a reappearance of the features of the syndrome (priming). Criteria for diagnosis of alcohol dependence include a strong desire or compulsion to drink alcohol despite knowledge or evidence of its harmful consequences, difficulty in controlling drinking in terms of onset, termination or level of its use, physiological withdrawal symptoms and development of tolerance.

Moderate dependence is characterized by raised level of tolerance (needing to drink more to reach the same level of intoxication), some symptoms of withdrawal and impaired control over drinking. Severely dependent patients additionally show relief drinking, morning drinking, stereotypical drinking, as well as blackouts.

According to the WHO Lexicon of Alcohol and Drug Terms relapse is defined as a return to drinking after a period of abstinence, usually accompanied by reinstatement of dependence symptoms. Some experts in the field additionally distinguish between relapse and lapse (or slip), with the latter describing an isolated occasion of alcohol use.

1.3 Risk levels of drinking

The relationship between extent of drinking and the risk for the development of alcohol dependence is consistently strong (although not simple), i.e. the main risk factor for alcohol dependence is chronic excessive drinking. If alcohol dependence is once established it influences itself pattern and extent of consumption. Furthermore there is a strong correlation between extent of alcohol consumption and subsequent harm.

According to the WHO "International guide for monitoring alcohol consumption and related harm", alcohol consumption is categorized in different health risk levels.

WHO-Criteria for risk of consumption on a single drinking day

	Males	Females
Low Risk	1 to 40g,	1 to 20g
Medium Risk	41 to 60g,	21 to 40g
High Risk	61 to 100g	41 to 60g
Very High Risk	101+g	61+g

The most desirable 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 recommends currently a limit of 7g pure alcohol and even this is considered too much for some special groups, e.g. pregnant women or patients with liver cirrhosis.

1.4 Development and maintenance of dependence

Chronic drinking leads to durable neuroadaptive changes in the brain, which are believed to form the core of alcohol dependence. It is assumed that in alcohol dependent individuals the discomfort and distress that result from these persistent changes in brain reward and stress circuits underlie the compelling motivation to drink.

Current research suggests several pathways which are involved in the development and the maintenance of alcohol dependence. One pathway involves the opioidergic and the mesolimbic dopaminergic system, which seems to cause alcohol craving and relapse due to positive reinforcing effects of alcohol consumption, especially in earlier stages of the disease. A second pathway involves several components of the glutamatergic and the GABAergic system, which seems to induce alcohol craving and relapse due to a hyperglutamatergic state. A further pathway seems to be a hypodopaminergic state, especially during alcohol withdrawal after chronic alcohol intake, which is associated with a state of dysphoria that promotes resumption of alcohol intake. However, since it is recognized now that alcohol affects more or less all major neurotransmitters or neuromodulator

systems, directly or indirectly, future research will probably indicate further pathways or combinations of pathways concerning the development and maintenance of dependence.

Most patients with (former) alcohol dependence are thought to retain a continuing vulnerability to relapse for years or even lifetime due to the neuroadaptive changes. The majority of relapses after initiated abstinence occur within a period of one year, especially within the first 6 months.

1.5 Treatment of alcohol dependence

The goals of alcohol dependence treatment include the achievement of abstinence, reduction in frequency and severity of relapse, and improvement in health and psychosocial functioning.

Qualified treatment for alcohol dependence is delivered under a continuing care model that is appropriate for a chronic illness, and usually includes a detoxification phase followed by a relapse prevention phase. Currently, some treatment programs aim at controlled alcohol consumption as a first step in the healing process. However, due to the developed addiction memory and impaired control of drinking, clinically significant reduction of consumption may be difficult to be achieved in alcohol dependent patients, at least for severely dependent ones.

Withdrawal symptoms in the detoxification phase are very individually pronounced. Symptoms of alcohol withdrawal typically begin within 4-12 hours after cessation or reduction of alcohol use, peak in intensity during the second day of abstinence, and generally resolve within several days. Serious complications include seizures, hallucinations, and delirium. Patients with severe withdrawal symptoms are usually treated for 5 to 7 days in an in-patient setting with benzodiazepines to reduce central nervous system irritability, fluids and thiamine and if necessary further medications such as anticonvulsants and antipsychotic agents.

In the subsequent relapse prevention phase different psychosocial treatment modalities are the essential components of a comprehensive treatment program, which addresses also co-occurring psychiatric and general medical conditions. Currently only relatively few alcohol dependent patients receive an adjunctive pharmacologic relapse prevention therapy.

Usually alcohol dependent patients require long-term care, although the intensity and specific components of treatment may vary over time, e.g. intensified monitoring is necessary during the early stages of treatment, times of transition to less intensive levels of care, and the first year after active treatment has ceased. The course of alcohol dependence is often characterized by periods of abstinence with recurring periods of relapses. Therefore a relapse after a longer period of abstinence should not be perceived as complete failure of therapy, but should give rise to an intensified level of treatment. In general treatment compliance is a significant determinant of treatment outcome and is known to be poorest among those patients with co-morbid medical, psychiatric, family and social problems.

Treatment settings include in principle hospitals, residential treatment facilities, partial hospitalization programs, and outpatient programs. For several years though, relapse prevention treatment is increasingly conducted in an outpatient setting, as there is good evidence that patients should be treated in the least restrictive setting that is likely to be safe and effective.

1.6 Established pharmacological treatment

Medicines that are currently approved in many countries for relapse prevention in alcohol dependence are disulfiram, acamprosate and naltrexone. All three are only recommended as adjunctive to psychosocial counselling in motivated patients.

Disulfiram is classified as an aversive treatment modality and primarily applied as a test of motivation or compliance with therapy. It interferes with alcohol metabolism, causing accumulation of toxic acetaldehyde. If alcohol is consumed simultaneously (although it is strongly recommended to avoid this), Disulfiram causes severe headache, nausea, and with higher amount of alcohol also more dangerous toxic effects.

Acamprosate, a GABA agonist and functional glutamate antagonist, is used as an anti-craving substance in several EU countries for preventing relapses in abstinent alcohol users. It has shown

higher abstinence rates and longer periods of abstinence respectively, compared to placebo in several but not all trials.

Naltrexone, a non-selective opiate antagonist, binds with receptors for endogenous opioids and appears to modify some of the reinforcing effects of alcohol and to prevent the reinstatement of extinguished alcohol-seeking behaviour induced by alcohol-associated cues. Naltrexone treated alcohol-dependent patients have been reported to drink less frequently and smaller quantities. However, no benefit in continued abstinence vs placebo has been shown.

Although superior efficacy was shown compared to placebo, especially in the acamprosate and naltrexone trials, the number of patients responding to these treatments is usually modest.

Several other drugs have been tested in recent years, e.g. dopamine antagonists and (partial) agonists, various anticonvulsants, NMDA receptor antagonists and various serotonergic agents, however evidence is either limited to date or no difference to placebo could be shown.

2. SCOPE

The scope of the present document is to provide guidance in the definition of treatment goals, study design, outcome measures, and data analysis for new products that will be developed to treat alcohol dependence.

Alcohol abuse or harmful drinking, including binge drinking and heavy social drinking, are currently no target indications. They have a rather low stability during life-time and only quite rarely develop into alcohol dependence. Furthermore they can be treated successfully with psychosocial counselling alone. Additionally it is yet unclear which heavy social drinkers and binge drinkers will ultimately develop dependency. Prevention of dependency in this group of alcohol disorders by specific compounds is therefore no treatment option at this stage.

The main focus of this guideline is on products that are developed as an aid to achieve and maintain abstinence in patients with alcohol dependence. This includes products to prevent relapses after initiated abstinence, as well as products leading to clinically significantly reduced alcohol consumption as an intermediate goal on the way to full abstinence.

Of note, this guidance document is not intended for products that are developed for treating symptoms of acute alcohol intoxication, acute withdrawal symptoms, or to treat specific diseases, which are consequences of long term alcohol abuse. However, this does not imply that the development of such treatment options is considered as irrelevant.

3. LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended) and all relevant CHMP Guidelines, among them:

- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4);
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9);
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10);
- Adjustment for Baseline covariate CHMP/EWP/2863/99;
- Missing data – CPMP/EWP/177/99;
- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1A);
- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7);
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 ICH 11);
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A);
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data EMEA/CHMP/313666/2005;

- Note for guidance on the investigation of drug interactions EMEA/CPMP/EWP/560/95;
- Guideline on the Non-Clinical Investigation of the Dependence Potential of Medicinal Products-CHMP/SWP/94227/2004.

4. PHARMACOLOGICAL TREATMENT TRIALS IN ALCOHOL DEPENDENCE

4.1 Subject characteristics and selection of subjects

4.1.1 Inclusion criteria

Subjects with the intention to stop drinking, or to reduce drinking significantly as a first step in the case of harm reduction studies, should be screened by a validated screening tool such as the AUDIT questionnaire (Alcohol Use Disorders Identification Test) to assess the level of the alcohol problem and subsequently fulfil the criteria for alcohol dependence as defined in the DSM IV (TR) or ICD-10.

In the case of relapse prevention trials the patients should be abstinent and fully detoxified at baseline. It should be decided a priori whether detoxification occurs before or after randomisation. Prior to the study, criteria should be defined for successful detoxification. For a harm reduction study, there is no need for detoxification at inclusion.

In general inclusion of patients should be as broad as possible. However, patients included in the main trials should have a high or very high level of total alcohol consumption at baseline (see 1.3) in order to be clearly representative for moderate to severe alcohol dependent patients in the general population.

The number and duration of previous abstinence attempts and former pharmacotherapy for drinking cessation should be documented. 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. The level of dependence can be measured by validated instruments for that purpose, such as the SDAQ (Severity of alcohol dependence questionnaire) or the Addiction Severity Index.

4.1.2 Exclusion criteria

Psychiatric co-morbidity (affective and anxiety disorders, psychotic disorders, post-traumatic disorder, personality disorders) is common in people with alcohol dependence. Therefore presence of co-existing psychiatric disorders needs to be assessed and quantified by a comprehensive psychiatric evaluation. The use of a validated, reliable (semi-)structured interview for establishing the diagnosis and to apply inclusion and exclusion criteria is necessary (e.g. the structured clinical interview for DSM-IV).

Milder forms of anxiety and depression are known to often resolve within 3 weeks after detoxification. Therefore patients with such milder symptoms may be included. However, 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 the main studies. After an effect is clearly demonstrated in the main studies, trials in patients with psychiatric co-morbidities may be conducted.

Also patients with other potentially confounding co-morbid disorders should be excluded if the test-drug is known to be effective in the co-morbid disorder in order to assign observed test-drug efficacy in the trial unequivocally to a specific effect on alcohol dependence. If certain potentially confounding co-morbid disorders cannot be excluded, these disorders should be carefully documented.

The use of other medications during the studies must be adequately documented. However, any psychotropic drugs should be excluded.

4.1.3 Baseline characteristics

Since heterogeneity is existent in many aspects of alcohol dependent patients it is necessary to thoroughly characterize included patients at baseline.

The following descriptive features should be documented:

- demographic features (age, gender, ethnicity, social-economic factors);
- age of onset of drinking (early-onset or late-onset);
- the number of heavy drinking years;
- age of onset of dependence;
- the nature of dependence, whether episodic or chronic;
- the level of alcohol dependence severity measured by a validated instrument such as the Severity of alcohol dependence questionnaire (SDAQ), the Addiction Severity Index (ASI) or the Alcohol Dependence Scale (ADS);
- the extent of alcohol cue induced and stress induced craving/urge to drink (self-reported craving rating and a validated assessment tool like the Obsessive Compulsive Drinking Scale);
- alcohol consumption assessment by instruments such as Alcohol Timeline Follow Back Calendar Method (TLFB), including grams of pure alcohol/drinking day, the number of drinking days/week or month, as well as the number of heavy drinking days/week or month (defined as more than 60 grams per day for men or more than 40 grams per day for women);
- motivation for change assessment such as the Stages of change questionnaire;
- treatment goal of complete abstinence (or not) as well as client motivation;
- history of previous abstinence attempts (including duration of previous abstinence) and their treatment;
- history regarding withdrawal syndromes;
- body weight;
- general medical, neurological and psychiatric history and examination as well as consequences of alcohol dependence on the patient's cognitive, behavioral and physiological functioning;
- general health score;
- AUDADIS (Alcohol Use Disorders and Associated Disabilities Interview Schedule);
- a family parental alcohol use disorder and social economic status;
- baseline CGI severity (Clinical Global Impression Severity Score);
- screening of blood, breath, or urine for alcohol (and alcohol metabolites);
- level of validated biochemical alcohol consumption markers (γ-GT, CDT, MCV, ASAT, ALAT) and further more accurate markers, as soon as they are validated;
- urine test for illicit drugs;
- SF-36.

Stratification variables

Out of the list of above mentioned descriptive features, it is recommended to stratify for severity of alcohol dependence as well as for patients without prior treatment and treatment resistant patients.

4.2 Methods to assess efficacy

4.2.1 Definition of the primary endpoints

In general, depending on the (supposed) mechanism of action of new specific compounds different approaches might be appropriate. In the light of addiction research the ultimate treatment goal in alcohol dependent patients is stable abstinence by prevention of relapse after detoxification. However, as a first step also clearly clinically significant reduction in alcohol consumption promoted by a

specific pharmacological agent, with subsequent harm reduction might be a valid intermediate goal on the way to full abstinence.

- **Full abstinence goal** (relapse prevention after detoxification)

If the study drug is addressing the ultimate goal of full recovery, the continued abstinence rate after detoxification at the end-of-active treatment period and the continued abstinence rate 12 months after end-of-active treatment should be the two primary endpoints.

In the beginning of the trial (up to 6 weeks) slips or lapses, but no relapse to heavy drinking, might be allowed. After the first 6 weeks relapse should be defined as any amount of drinking. However, patients should not be lost to follow up when having a relapse (or later lapse or slip), but should be further assessed with respect to significant moderation outcomes i.e. more abstinent days and less heavy drinking. Therefore, possible relapses should be thoroughly described regarding frequency, duration and amount of pure alcohol in grams per drinking day.

Abstinence (as well as the number and severity of possible relapses) should be confirmed by patient interviews and collateral information form, measurements of alcohol use markers (alcohol and alcohol metabolites in breath, blood and urine) and qualified validated liver biomarkers.

- **Intermediate harm reduction goal** (significant moderation without prior detoxification)

In case an alcohol dependent patient is not able or willing to get abstinent immediately (or e.g. waiting for the admission in an abstinence-orientated 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 necessary to aim at maintained abstinence as soon as the patient gets ready for it. Therefore, if the study drug is only addressing the intermediate goal of clinically significant moderation, efficacy should be expressed by change to baseline in total consumption of alcohol (presented as amount of pure alcohol in grams per day) as well as 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. A clinically relevant difference compared to placebo should be demonstrated.

Further efficacy on these two variables should be reflected in a clearly expectable improved health outcome on an individual patient level. Therefore efficacy should also be evaluated in terms of responders. This could be done by evaluating the proportion of subjects with a 50%, 70% and 90% reduction in alcohol consumption as well as the proportion of patients achieving maintained abstinence. Another option would be evaluating the proportion of subjects with a significant categorical shift in WHO risk levels of drinking (i.e. proportion of patients with change of consumption to baseline from very high risk to at least medium risk level and change from high risk to at least low risk level (see also 1.3), as well as the proportion of patients with full abstinence.

Of note, in the beginning of such trials it might be necessary to slowly reduce the alcohol consumption in order to avoid marked withdrawal symptoms.

4.2.2 Definition of secondary endpoints

Secondary endpoints in case of full abstinence goal:

Important secondary endpoints:

- Time to relapse (first drink);
- CGI Severity and CGI Improvement;
- SF 36;
- Change to baseline of validated liver biomarkers.

Further useful variables to be monitored:

Compliance to treatment:

Medication compliance (pill counts, MEMS caps (Medication Event Monitoring System) etc.).

Compliance to study:

% completers, Weeks on study, Time to withdrawal.

- Further course of drinking behaviour if relapse occurs (number of drinking days since first relapse, number of heavy drinking days since first relapse, cumulative abstinence duration).
- Change to baseline in number of abstinent days (cumulative abstinence duration).
- Change to baseline in physical, cognitive and psychic functions.
- Impact on social and family life and work.
- Change in the level of alcohol dependence severity measured by the validated instrument used at baseline, such as the SDAQ (Severity of alcohol dependence questionnaire), ASI (Addiction Severity Index) or ADS (Alcohol dependence Scale).
- Craving/urge to drink assessment by interviews/patient self-report instruments and e.g. the obsessive compulsive drinking scale.

Secondary endpoints in case of harm reduction goal

Important secondary endpoints:

- Change to baseline in validated liver biomarkers;
- CGI Severity and CGI Improvement;
- SF 36.

Further useful endpoints variables to be monitored:

Compliance to treatment:

Medication compliance (pill counts, MEMS caps (Medication Event Monitoring System) etc.).

Compliance to study:

% completers, Weeks on study, Time to withdrawal.

- Course of alcohol consumption over time.
- Change to baseline in number of abstinent days (cumulative abstinence duration).
- Change to baseline in physical, cognitive and psychic functions.
- Impact on social and family life and work.
- Change in the level of alcohol dependence severity measured by the validated instrument used at baseline, such as the SDAQ (Severity of alcohol dependence questionnaire), ASI (Addiction Severity Index) or ADS (Alcohol dependence Scale).
- Craving/urge to drink assessment by interviews/patient self-report instruments and e.g. the obsessive compulsive drinking scale.

Of note, validated biomarkers (CDT, GGT, MCV, ASAT, ALAT) should be used at baseline and followed during the course of treatment as secondary outcome variables to monitor the effect of treatment. However, currently used biomarkers reflect only damage and can be confounded by age, gender, other substances and diseases, e.g. MCV is superior in women and only a marker of second choice in men. Therefore combination of markers is necessary. In future probably new biomarkers will be validated e.g. different direct ethanol metabolites (with possible verification or exclusion of relapses or amount of alcohol intake in different periods of time). This new validated biomarkers should then be used in addition to customary biomarkers.

4.3 Strategy and design of clinical trials

4.3.1 Pharmacokinetics/Pharmacodynamics

PK studies should be performed in accordance to guidance on Pharmacokinetic Studies in Man. Furthermore trials which prove the assumed mechanism of action should be conducted.

Pharmacokinetic and pharmacodynamic interactions with, especially CNS-active, drugs expected to be frequently used in alcohol dependent patients, should be investigated, unless there is clear evidence that an interaction is unlikely to occur.

A tolerability and pharmacokinetic study should be performed in subjects with hepatic dysfunction, as this condition is very common in alcohol dependent patients, unless the product is not metabolised.

4.3.2 Dose response

Dose response studies should be performed in a placebo-controlled, parallel group, double-blind, randomised, fixed-dose design, using at least three dosages, to establish the lower end of the clinical effective dose range and the optimal dose. Investigation of drug plasma levels might be supportive for dose-selection.

4.3.3 Therapeutic confirmatory studies

Confirmatory studies should be randomised, double-blind, parallel-group and placebo controlled and designed to demonstrate superiority. In case of inclusion of an active control the choice and dose of the comparator should be justified on the basis of placebo-controlled evidence of efficacy of the comparator. Currently available treatments have shown only inconsistent, modest treatment effects. Due to this a definition of a reliable non-inferiority margin is deemed hardly possible and therefore a non-inferiority trial versus an active control is currently not considered to provide convincing evidence for efficacy of a new treatment.

a. Duration of confirmatory trials

The duration of the active treatment period of confirmatory phase 3 trials strongly depends on the time of onset of any treatment effect and the mode of action of the new compound, as demonstrated in pharmacodynamic and exploratory studies. In the past, significant reductions of dependence or alcohol use compared to placebo could be shown in alcohol dependence studies after active treatment of 3 to 6 months, using total abstinence rate or variables indicating reduction of alcohol consumption as the primary outcome criterion.

Therefore, in order to establish short-term efficacy, an active treatment period of 3 to 6 months, followed by a sufficiently long randomized withdrawal phase in order to investigate possible rebound phenomena, is necessary. Additionally preliminary information regarding maintenance of effect should be demonstrated.

However, since treatment results after the first 3 to 6 months remained very unstable in prior investigations and usually become really stable not before around 15 months, the overall outcome measurement should cover such a period of time. This is necessary in order to establish if stable treatment results have been achieved that do no longer need pharmacological support.

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 by a double-blind continuation phase without treatment until 15 months after randomization.

In principle the same applies for a new compound aiming to promote stable clinically significant moderation for the longer term. However, it is acknowledged that in these patients there might be the need of continued administration of active treatment. In this case a subsequent double-blind placebo-controlled phase in initial responders until 15 months is recommended. However, as mentioned before, it is absolutely necessary to aim at maintained abstinence as soon as the patient gets ready for it

b. Methodological considerations

Relapse prevention trials (or relapse prevention phase if detoxification is part of the trial) as well as harm reduction trials should be conducted in an outpatient setting, since this reflects the most naturalistic setting.

Currently all methods to verify continued abstinence status or establish extent of alcohol consumption have their own advantages and limitations. Therefore, a combination of these methods is necessary. 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. Furthermore the TLFB results should be correlated with the results of the validated biomarkers. Companies are encouraged considering additional use of further more objective measuring methods of alcohol consumption, e.g. regular use of breathalyzers, better biomarkers or other innovative developments as soon as they are validated. Regular visits, at least every two weeks, should be scheduled throughout the active treatment period. Concerning long-term follow-up, the visits should take place at least once a month.

Psychosocial interventions are currently the backbone of treatment in alcohol use disorders (such as Brief Intervention und Motivational enhancement) and licensed pharmacological treatments for alcohol dependence are indicated only as adjunctive, therefore psychosocial interventions should be allowed in alcohol dependence trials. However, it is important that the demonstrated effects in the trials are not primarily due to these interventions. In order to assign a certain part of the effects to the specific pharmacologic treatment, the kind of psychosocial intervention should be prospectively and exactly defined in the protocol, have a known effect size, should be fully standardized as well as kept to a low and constant level during the trial for all included patients.

In order to minimize poor treatment adherence and high discontinuation rates, which frequently led to compromised validity of the results in prior alcohol dependence studies, efforts should be made in the design to enhance compliance to treatment (which should be monitored) and to reduce the number of discontinuations. Discontinuing patients should be followed up and the reasons for discontinuation should be documented. The effect of missing values will need to be taken into account in the efficacy analysis and the method to address this problem needs to be pre-specified.

For references to the methodological EMEA guidance documents, see Section 3.

4.4 Studies in special populations

Children

Studies in children are not deemed necessary, since alcohol dependence is not a problem in this age group.

Adolescents

Alcohol use in general (above all binge-drinking) is the leading risk factor for premature death in this population especially due to alcohol-related accidents, violence and suicide. However, this guideline focuses on alcohol dependent persons and since alcohol dependence develops over years of chronic heavy drinking it rather rarely is an issue in adolescents. 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).

Gender

Women appear to be more vulnerable for the toxic effects of alcohol due to less body water and lower activity of gastric alcohol-dehydrogenase. They also show a different course of disease with faster development of alcohol dependence than men, a higher risk for alcohol-related diseases and more additional substance abuse. Furthermore major depressive disorders and anxiety disorders are twice as high in female alcoholics then in men. Therefore in clinical trials stratification might be considered. In any case, the number of included women should reflect the prevalence of alcohol dependence in women in the general population. Pharmacokinetic data should be gathered in both females and males.

Elderly (aged 65 or older)

The pattern and prevalence of alcohol related disorders is still poorly documented in elderly. Risky drinking and combination of psychotropic drug(s) and alcohol have been reported in a significant percentage of elderly in both genders. Alcohol dependence (with very late onset) is often undiagnosed. The expected benefits from alcohol dependence treatment are important, particularly for the elderly patients with underlying co-morbidities which may increase organ-alcohol damages.

The main aspects to be investigated in this special population are: 1) pharmacokinetic profile, relevant as guidance for dose adjustments; 2) safety with focus on drug interactions and cardiovascular effects related to possible concomitant/underlying cardiovascular disorders. For safety assessments, a sufficient number of elderly subjects should be included in the trials (see Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7, section 4.5.1) and the Concept Paper ICH E7(R1) published in 2008 for guidance on this point).

Psychiatric co-morbidity

See Section 4.1.2

4.5 Clinical safety evaluation

4.5.1 General considerations

For references to the relevant safety guidance, see Section 3.

4.5.2 Specific adverse events

Pharmacokinetic and pharmacodynamic interaction studies with alcohol are obligatory before starting phase III, since subjects will be allowed to drink (in case of harm reduction trials) or might have relapses during active treatment.

Patients should be carefully monitored regarding possible suicidal ideation or suicide attempts.

Addiction potential

Reinforcing/addiction potential of the test drug should be assessed to rule out switch of addiction.

DEFINITIONS

The WHO glossary should be used for definitions.
http://www.who.int/substance_abuse/terminology/en/

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