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Guideline on clinical investigation of medicinal products in the treatment of schizophrenia

Draft

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Comments should be provided using this template. The completed comments form should be sent to cnswpsecretariat@ema.europa.eu

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Guideline on clinical investigation of medicinal products in the treatment of schizophrenia

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Executive summary

This document is intended to provide general guidance for the development of medicinal products for the treatment of schizophrenia. The guideline has been developed during a transitional period in which the DSM IV classification and diagnostic criteria for schizophrenia (and other psychotic conditions) are being revised in the preparation for the DSM 5.

This guideline will not address development of medicinal products for the treatment of psychotic conditions other than schizophrenia.

The main requirements for medicinal products developed for the treatment of schizophrenia, with regard to study design, patient population and outcome measures are described. Specific issues, including treatment resistant patient population and other specific patient groups (children and adolescents) are addressed. Attention is focused on alternative treatment options such as add-on and augmentation therapy. The importance of specific domains in schizophrenia including cognition and negative symptoms are discussed as well.

The change in outcomes of clinical studies performed in patients with schizophrenia in the last decades (e.g. higher placebo response, stability of clinical response) has triggered a broad discussion. Possible study design in terms of use of placebo, study duration, and patient population have been reviewed and have been redefined. The main scope is to provide guidance on the choice of clinical studies which are feasible and likely to produce interpretable results, without exposing unnecessarily patients to substances with unknown effect.

This document should be read in conjunction with other relevant EMA and ICH guidelines (see section 3).

1. Introduction (background)

1.1. Schizophrenia

Schizophrenia is a severe psychiatric disease with a heterogeneous course and symptom profile. The personal tragedy associated with schizophrenia is extreme, since it attacks the human properties considered most precious and distinguishing. The worldwide lifetime morbidity risk of the disorder is about 1 percent across diverse geographic, cultural, and socio-economic regions. The age of onset of the first psychotic episode is typically in the late teens, but can be as late as into the mid thirties. Onset prior to adolescence is rare. Age of onset is earlier in men than in women. In most patients the disease follows a chronic course with long lasting impairment.

Schizophrenia presents clinically with so-called positive and negative symptoms. The positive symptoms include delusions, hallucinations, disorganised speech, and disorganised or catatonic behaviours. Negative symptoms include affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal- directed behaviour. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas negative symptoms appear to reflect a diminution or loss of normal function.

In addition, cognitive deficits (defects of working memory, information processing, attention/vigilance, learning, reasoning and social cognition) are common. Whether these should be considered to belong to the core symptoms is currently under discussion. Cognitive deficits generally show poor improvement with current antipsychotic treatments.

Besides these predominant symptoms, schizophrenia is associated with an increased incidence of other psychiatric symptoms such as manic and depressive symptoms, anxiety or obsessive-compulsive

symptoms, substance abuse and dependence, and personality disorder. Schizophrenia with co-morbid symptoms should be distinguished from other psychotic disorders (see also section 1.3).

The current diagnostic criteria are made explicit in the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM IV) and in the International Classification of Diseases, (ICD 10). These criteria are valid for the purpose of case identification. According to DSM IV (1994) the essential features of schizophrenia are a mixture of characteristic signs and symptoms (both positive and negative) that have been present for a significant proportion of time during a 1 month period, with some signs of the disorder persisting for at least 6 months.

1.2. Schizophrenia in the paediatric population

Schizophrenia is very rare in pre-pubertal children and is more likely to be associated with chromosomal/cytogenetic variations. However, if recognized the disease is comparable at the symptom level to that in adults.

Fleeting hallucinations and delusions are common in paediatric subjects and therefore a high rate of misdiagnoses is reported. The differential diagnosis includes affective disorders (major depressive episodes and bipolar disorder), psychosis due to medical conditions, side effects of medication and/or substance abuse, pervasive developmental disorders, conduct disorders, post-traumatic disorders and personality disorders under development.

It may, therefore, often be more realistic to diagnose only the first episode of psychosis in children which, in a small proportion of cases, might finally develop into early onset schizophrenia.

Schizophrenia in adolescents may be preceded by prodromal cognitive impairment at young age but these abnormalities have neither diagnostic specificity nor predictive value. With increasing age, symptoms increasingly resemble those of adults. However, negative and cognitive symptoms (such as flat or inappropriate affect) are more prominent from the beginning. In addition the disease follows a more severe course, has lower response to treatment and a worse long-term prognosis.

Because of these characteristics in children and adolescents, for registration purposes, only patients with a definitive diagnosis of schizophrenia would be eligible for inclusion in clinical studies.

1.3. Other psychotic disorders

Several other psychotic conditions are recognised. However, their classification and diagnostic criteria are being thoroughly revised within the preparation of DSM 5. The diagnosis and treatment of psychotic conditions other than schizophrenia will not be discussed in the current guideline (see also section 2).

1.4. Treatment

1.4.1. Medicinal treatment

The aim of antipsychotic treatment can be categorised into: 1) acute treatment to predominantly reduce positive symptoms, and 2) maintenance of effect to consolidate control of symptoms and to prevent exacerbations. In addition to the traditional emphasis on positive symptoms, a number of clinical trial programmes have investigated products specifically for their possible effects on negative symptoms, cognitive function, and on depressive symptoms seen in schizophrenia.

The effectiveness of the first generation, so-called typical antipsychotic agents, on symptoms in schizophrenia is mostly attributed to their anti-dopaminergic effect, particularly at the D2 receptors.

The second generation or so-called atypical antipsychotic agents show in addition a varying degree of affinity for serotoninergic (notably 5-HT 2A), dopaminergic, muscarinic, cholinergic, α1 adrenergic and histamine H1 receptors, which are thought to be involved largely in the negative symptom presentation.

Recently compounds that reduce glutamate receptor activity are being studied in line with theories that dysregulation of the glutamatergic system might contribute to the pathophysiology of schizophrenia. Also drugs acting on the GABA (γ-Aminobutyric acid) system, on alpha-2 adrenergic receptors and on various serotoninergic and dopaminergic receptors including D1 receptor agonists as well as acetylcholinesterase inhibitors and muscarinic acetylcholine receptor agonists are being studied for their impact on either cognition or other symptoms not directly linked to the positive symptoms.

For patients whose psychotic symptoms are not sufficiently controlled with one medicinal product there are a number of possible augmentation strategies with various treatment objectives. Although such strategies are quite widely used in clinical practice there are no products currently approved in the EU (European Union) for use in this way at the time of writing of this document, and there is a general lack of supporting evidence.

1.4.2. Supportive treatment

In most EU countries, patients with schizophrenia are offered supportive treatment, such as standardised psychotherapy, psycho-education, social support, and counselling. These supportive treatment practices vary considerably among EU member states but have their value for sustainability of drug effects.

2. Scope

This guideline focuses primarily on antipsychotic products developed specifically for schizophrenia. Some comments are also made about treatment of psychosis as a part of other disorders. However, data requirements to support an indication for other disorders are out of the scope of this guideline.

During the development of this guideline DSM IV is under revision, and it is expected that it will be replaced by DSM 5. This might have consequences for the definitions of the disorders as given in this guideline, and these may need amending likewise.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part of the Annex I to Directive 2001/83 (as amended) and relevant CHMP and ICH guidelines, among them:

- Dose-Response Information to Support Drug Registration (CPMP/ICH/378/95 , ICH E4)
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A).
- Note for guidance on clinical investigation of drug interactions (EMEA/CPMP/EWP/560/95)
- The Clinical Evaluation of QT/QTs Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic drugs (CHMP/ICH/2/04, ICHE14)
- Guideline On The Non-Clinical Investigation Of The Dependence Potential Of Medicinal Products (EMEA/CHMP/SWP/94227/2004)
- 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 (CPMP/EWP/2863/99)

- Missing data (CPMP/EWP/177/99 Rev 1)
- Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95, ICH E1)
- Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU population (EMEA/CHMP/EWP/692702/2008)
- Note For Guidance On Clinical Investigation Of Medicinal Products In The Paediatric Population (CPMP/ICH/2711/99, ICH E11)
- Studies in support of special populations: geriatrics (CPMP/ICH/379/99, ICH E7)
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data (EMEA/CHMP/313666/2005)

4. Specific considerations when developing products for the treatment of schizophrenia

In developing medicinal products for the treatment of schizophrenia, specific issues should be considered. These include:

4.1. General strategy

4.1.1. Use of placebo

There is a debate about the use of placebo in clinical trials in the treatment of schizophrenia. Concerns about ethical issues and feasibility have been raised. However, assay sensitivity cannot be guaranteed even in well designed and conducted trials if a placebo arm is not included. Historical controls (efficacy of the older antipsychotics) are not useful for current clinical trials, since the concept of the disorder, the diagnostic criteria and the efficacy criteria have changed. In recent trials in schizophrenia, the difference in efficacy between active treatments and placebo has tended to be smaller than the difference seen in the past. Therefore, a placebo control has been considered necessary for internal validation of non-inferiority trials comparing new drugs to an active control and is highly desirable so that the 'absolute' effects (both therapeutic and adverse) of a product can be ascertained.

To avoid unnecessary risks for patients and others, placebo controlled studies should be performed in a highly controlled setting, with stringent follow-up to apply the predefined escape criteria, rescue medication and stopping rules. Provided these safeguards are in place, both short term and long term placebo controlled trials are not considered unethical, as long as patients in the placebo group receive the entire standard care except the antipsychotic medication.

4.1.2. Specific claims

For classical antipsychotics an effect on schizophrenia should be demonstrated before efficacy on specific domains (such as cognition or negative symptoms) can be claimed. This is to avoid unnecessary polytherapy. For other compounds with another mechanism of action that target a specific domain, specific claims could be made. Each of these claims should be supported by robust evidence and this will normally require trials specifically designed to test the specific aspect of efficacy for which a claim is to be made. The patient population studied, the comparator that is chosen, and the usefulness (validity, relevance) of the rating scales used to measure efficacy for that situation should all be justified (see section 4.5).

4.1.3. Extrapolation to other psychoses

As stated in sections 1.3. and 2, psychotic symptoms may occur in other disorders which may either be syndromes distinct from schizophrenia or prodromal to the development of full schizophrenia. Diagnostic criteria can be found in DSM IV and ICD 10. As such disorders may differ substantially in terms of patient characteristics and their natural course, it is not possible to extrapolate data from a specific psychotic disorder (e.g. schizophrenia) to another (e.g. delusional disorder). Therefore, it is not acceptable to perform studies in order to support a broad indication for treatment of psychosis.

4.2. Assessment of therapeutic efficacy

To support an indication for the treatment of schizophrenia, efficacy on main symptoms has to be demonstrated in short-term studies and maintenance of effect has to be shown in at least one long term study. Both types of data should be part of the package submitted for marketing authorisation.

It should then be acknowledged that symptoms, e.g. depressive symptoms, maybe partly or entirely secondary to schizophrenia, may represent pre-existing signs and symptoms, or be the result of treatment. When trying to determine whether a product affects these symptoms in a positive or negative way, efforts should be made to distinguish between a genuine specific effect and a 'secondary' effect.

Likewise, cognitive deficits may be at least in part secondary to causes such as psychotic symptoms, be side effects of medicinal products (especially anti-cholinergic agents), depression or under-stimulation of the patient (as a result of hospitalisation). The effect of treatment on cognitive function should be documented even if no specific indication is claimed, for purposes of safety data collection.

4.2.1. Choice of efficacy outcomes and assessment tools

Efficacy has to be measured with the use of widely accepted, reliable and validated measurement scales. In some cases alternative assessment tools may be appropriate, but the choice of other tools should be fully justified based on standard test quality criteria.

The primary efficacy measure should be a composite measure of the symptoms of schizophrenia. For this, the widely accepted tools to measure are the PANSS (Positive and Negative Symptom Scale) and BPRS (Brief Psychiatric Rating Scale), which are still considered as reliable and validated.

In addition secondary efficacy measures should be presented to assess the effect of the test product on further aspects of the disease. Clinical global impression (CGI) data should also be presented.

For assessment of negative symptoms in particular, the use of specially designed rating scales is necessary. Older assessment scales such as the BPRS give little emphasis on negative symptoms and are not suitable for this purpose. Satisfactory reliability and validity has been demonstrated for the negative symptoms subscale of the PANSS and for SANS (Scale for the Assessment of Negative Symptoms). Global assessment of negative symptoms (CGI) should be added. Due to the limitations of all available scales, the development of new scales is encouraged. Validated instruments should also be used to assess treatment effects on cognition and depression.

4.3. Clinical Pharmacology studies

4.3.1. Pharmacodynamics

The use of potential biomarkers such as receptor occupancy PET studies (e.g. D2 and 5HT 2A) and imaging techniques to detect structural changes in the brain may be useful in dose finding and proof of

concept studies in early drug development. However, specific claims will be obtained based on results from clinical outcomes and not on biomarkers, so the latter could provide only supportive evidence.

4.3.2. Pharmacokinetics

No specific requirements for medicinal products in schizophrenia are necessary (see Guideline on Pharmacokinetic studies in man). The extent to which the drug crosses the blood-brain barrier should be established.

4.3.3. Interactions

All pharmacodynamic interactions between the test drug and any other drug that may be prescribed simultaneously in clinical practice should be studied, as well as potential pharmacodynamic interactions with alcohol and CNS (Central Nervous System) active illicit substances. If relevant, pharmacokinetic studies in patients with hepatic and /or renal impairment should be performed. Reference is made to the drug interaction guideline.

4.4. Clinical efficacy trials

4.4.1. Exploratory trials

For exploratory or proof of concept studies a wide range of designs are acceptable. In these studies the emphasis tends to be maximization of the power of the study to detect a treatment effect. Methods of achieving this include using narrow inclusion criteria or other selection of patients considered most likely to respond, and excluding placebo responders (enrichment design). These design aspects are only acceptable for exploratory trials, and should not be applied to provide confirmatory pivotal evidence of efficacy.

4.4.2. Demonstration of dose response relationship

It is essential that the proposed doses for the SmPC are robustly justified. Preliminary data on the dose range anticipated to be therapeutic can be obtained from non clinical data such as animal models and receptor occupancy studies. However dose-response relationships need to be established in clinical trials using validated efficacy endpoints. The minimum effective dose and the dose at which most efficacy is obtained should be established. Flexible dose designs are unsuitable to provide this information and therefore designs with multiple fixed doses and a placebo control are required. It is preferred to make direct dose comparisons of multiple doses in a single study. It is strongly recommended to establish the dose-response of the investigational drug prior to the start of confirmatory trials (Phase 3) as the use of inadequately justified doses may hamper interpretation of the latter trials. In addition, the study population in the dose finding studies should preferably reflect the entire targeted patient population. For general strategy and design refer also to section 4.4.3.

4.4.3. Confirmatory trials

The purpose of short term confirmatory trials is to demonstrate the efficacy of the medicinal product and obtain initial information on safety in the wide patient population.

4.4.3.1. Study design for short term trials

Crossover designs are unsuitable for trials in patients with schizophrenia. Confirmatory trials should be double-blind, randomised, parallel group trials.

The study protocol should provide a justification of the choice of the active comparator – this would normally be an active comparator with a similar clinical pharmacological profile to the test product. If the product is the first in its class an appropriate active comparator would be a product licensed in the target indication or if no product is licensed in the chosen target population, a medicinal product recognised as the "gold standard" in clinical practice should be chosen as a suitable active comparator.

If the aim of the study is to demonstrate an estimate of non-inferiority to an active comparator, then a three-arm study of placebo, test product and active comparator is recommended (see also section 4.4.3.7.). Superiority to placebo should be demonstrated in order to ensure assay sensitivity of the study.

Alternatively, a two-arm study of test and active comparator would be acceptable provided superiority of the test product over an appropriately justified active comparator was demonstrated.

4.4.3.2. Study population

Patients should be diagnosed and classified according to the criteria of DSM IV or ICD 10, and subsequently classified according to the longitudinal course of their disease (e.g. exacerbation, remission, inter-episode residual symptom, or chronically ill). The diagnosis should be made by a qualified psychiatrist and confirmed with the use of a structured assessment tool e.g. the SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders). Further descriptive parameters (co-morbidity, substance abuse), demographic characteristics and a detailed disease history (duration of disease, duration and number of exacerbations, naïve or exposed status, and previous treatment outcome) should be documented.

In contrast to proof of concept studies, for pivotal efficacy studies it is important to maximise external validity without unduly compromising internal validity. This may require exclusion of patient groups that may introduce confounding by e.g. co-morbidities or concomitant medication. Exclusion criteria should be clearly justified.

Patients in an acute phase (with florid positive symptoms) may generally show a much larger response to pharmacological treatment compared to patients in a chronic phase. Therefore, if patients in different phases of the disease are included in the same clinical study, stratified randomisation is recommended to ensure that the different types of patients are evenly represented throughout treatment arms. It is recommended to include at least 20% of patients with a disease history of less than 5 years. The inclusion criteria should define the patient population in terms of severity of symptoms. Cut-off scores can be based on efficacy measurement scales (e.g. PANSS).

4.4.3.3. Study duration

The preferred design for demonstrating short term efficacy is a 6 week clinical trial. This is because so far for classical antipsychotics, a reasonable stability of effect has been observed as well as some effect on negative symptoms, often only after 6 weeks of treatment. Shorter study duration (e.g. 4 weeks) could also be considered, especially for drugs with a similar profile to existing antipsychotic drugs, although the latter carries the risk of negative results if maximal therapeutic effect is not obtained after 4 weeks, and is disadvantageous in terms of demonstrating stability of effect. For new compounds with novel mechanism of action, (different from the currently available antipsychotics) and/or targeting other domains such as negative symptoms or cognition, the study duration might need to be adapted accordingly (see section 4.5).

4.4.3.4. Co-medication

In the interests of the external validity of the trial, most types of co-medication (e.g. benzodiazepines) should be permitted and exclusion criteria for concomitant medications should be justified. It may be appropriate to place an upper acceptable limit for benzodiazepine use and to specify that patients should be on a stable dose regimen for some time before starting the trial.

Treatments that may augment the test treatment should be excluded, despite the consequences of these exclusions for generalisability of the trial results to the full target patient population. Therefore other antipsychotic drugs should be discontinued, except in the case of augmentation studies (see also section 4.4.5.).

Standardised psychotherapy, psycho-education, support or counselling may be offered as supplementary treatment, but their use should be prospectively defined in the protocol and documented in the trial report. The effects on treatment should be discussed in the dossier.

4.4.3.5. Screening and run-in periods

Subsequent to screening, qualitative and quantitative baseline assessments should be conducted in a short run-in period. Prior antipsychotic medication should be washed out, normally tapered in a single blind placebo run-in period of sufficient duration aiming at elimination of prior treatment without substantial worsening of symptoms. Typically a few days will be appropriate for run-in. Placebo responders should not be excluded from randomisation. In some instances screening, baseline assessments, randomisation and start of study medication may be performed in a single day, especially if patients are severely ill.

4.4.3.6. Efficacy parameters

Primary endpoint(s) should be change from baseline in symptoms of schizophrenia. This should be presented as the difference from baseline to end measurement on the endpoint symptom score. Obtained results should be discussed not only in terms of statistical significance but also in terms of clinical relevance. Presentation of the proportion of patients with a pre-specified degree of improvement on the symptom score is valuable. For this purpose, responder analyses should be presented. Also the proportion of patients deteriorating during treatment should be documented.

In short term trials in patients with acute/exacerbated symptoms at least 30% reduction on the total PANSS compared to baseline is generally considered to be clinically relevant and can be accepted as a definition of responder. For sensitivity analyses the presentation of additional responder analyses using alternative criteria for response rates is recommended, i.e. the proportion of patients with minimal and with substantial improvement.

4.4.3.7. Statistical considerations

Reference is made to the ICH E9 statistical principles for clinical trials.

The standard three way trial design is intended to show superiority to placebo and to quantify efficacy compared to a comparator drug. Analysis populations should include the full analysis set (FAS) and the per protocol (PP) population.

A major problem with both short and longer term trials in schizophrenia relates to patient withdrawals and consequent missing data. All reasonable steps should be taken to minimise their occurrence and to follow patients regardless of adherence to protocolled treatment. Reasons for drop outs should be documented (especially to distinguish between lack of efficacy and undesirable effects). In this respect,

special attention should be drawn to the issue of compliance, which is a problem in patients with schizophrenia. Assessment of compliance should be ensured during clinical studies by measurement of drug plasma levels, tablet counting, repeated urine screenings for additional illicit psychotropic substances.

Commonly used analysis techniques and methods for handling missing data are frequently not likely to be conservative, leading to a probable bias in the results in favour of the experimental treatment. In particular, differential dropout rates (for safety/tolerability or efficacy reasons) and variable natural course of the disorder (spontaneous remissions or exacerbations) can bias the results under this method of missing data imputation.

Reference is made to the CHMP guideline on missing data in confirmatory clinical trials and the advice therein to consider the problem of missing data in advance of the trial, and provide detailed discussion of the missing data pattern observed and potential biases introduced once the trial has been completed.

4.4.4. Study design for long term trials

Due to the chronic course of schizophrenia (with exacerbations) and the need for lifelong treatment, double-blind controlled studies are necessary in order to demonstrate that the effect found in the acute phase is maintained.

To demonstrate maintenance of effect, several study designs are possible: parallel design (with placebo and/or active comparator) or randomised withdrawal design.

Extension studies may provide evidence of maintenance of efficacy as long as they stay double blind. A parallel trial using active comparator is the first possibility. When the objective is to show non-inferiority, the active control should be a product with a well documented efficacy in the maintenance of treatment effect in schizophrenia. Due to the natural course of the disease, the duration of such a trial should be 12 months and the assay sensitivity should be fully substantiated.

Another alternative is a randomised withdrawal design study, in which responders to the short-term treatment are included and randomised either to the study medication or to placebo. When this design is applied, it may be useful to first stabilise the patients in an open label treatment period of sufficient duration. Blinding patients to the time point of onset of randomised treatment is preferred to avoid unblinding due to patient awareness of treatment allocation, as this could potentially increase bias in favour of the test product.

A third alternative is a two-arm placebo controlled trial with duration of 6 months. When designing such a trial, some possible hurdles should be considered - such as recruitment of mostly chronic patients, ethical issues, and the probability of higher drop out rates. Therefore handling of missing values should be pre- specified in the study protocol.

4.4.4.1. Efficacy parameters in long term studies

The primary efficacy variables to measure maintenance of effect would depend on the design of the clinical study.

In parallel design studies, the primary efficacy should be measured as the difference between baseline and endpoint on the symptom score, as in the short term studies. Drop out rates which indicate a treatment failure could be included as a key secondary endpoint.

In a randomised withdrawal design, the primary efficacy measure would be time to exacerbation of symptoms using pre-specified criteria. Patients with exacerbations must be clearly distinguished from

withdrawals due to other reasons. The duration of the randomised treatment period should be sufficient to ensure that the number of patients with exacerbation (event rate) is sufficient for adequate statistical power for the comparison with active comparator or placebo.

In parallel and randomised withdrawal studies, the proportion of patients with exacerbations at pre-specified time points should be analysed.

In some cases, if the dose-response data from short term trials is insufficient, dose finding for long-term treatment using multiple doses of the investigational product may be required.

4.5. Specific claims

4.5.1. Efficacy on negative symptoms

If an effect on negative symptoms is claimed, specially designed studies in patients with predominant negative symptoms should be conducted. The duration of negative symptoms and onset of the current stable episode of schizophrenia should be documented. To ensure that patients with negative symptoms, other than related to depressive symptoms or EPS, are studied, the inclusion criteria should encompass:

a) Predominant and persistent negative symptoms.

b) Flat affect and poverty of speech being present as representative of core negative symptoms

c) Stable condition of schizophrenic illness for longer than 6 months, especially of the negative symptoms.

Excluded should be:

d) Major depression; low depression scores are preferable.

e) Subjects with substantially confounding extra-pyramidal symptoms and cognitive impairment.

f) Substantial non-compliance or substance abuse.

Improvement on negative symptoms should be demonstrated through validated scales (e.g. PANSS negative subscale, SANS or other), and presented as the difference between baseline and endpoint. Responder rates should be provided as well, and functional improvement as key secondary outcome is recommended.

4.5.2. Efficacy on cognitive functioning

To support a separate claim for efficacy on cognitive aspects in patients with schizophrenia, specific studies should be performed. The patient population should be clearly defined in terms of a range of relevant measures of cognitive functioning. A relatively younger patient population might be more appropriate for testing effect on cognition in schizophrenia, since with disease progression response to treatment of cognitive impairment may decline.

Similarly, the effect of treatment on cognitive functioning should also be demonstrated as the difference between baseline and endpoint on the cognitive functioning scale. Whatever tool is used, mere reduction on specific items of a larger test battery is not acceptable. The outcome should be such that relevance to the patients functioning is clear.

4.5.3. Trials to study monotherapy in treatment resistant patients

Monotherapy in patients with treatment resistant schizophrenia could be a separate but additional claim. This could be granted to compounds with an adequately substantiated general schizophrenia indication. At least one additional trial should be performed to support extension of the indication to treatment resistant patients. Subgroup analyses among treatment resistant patients in trials conducted in a general schizophrenia population are not sufficient to obtain the extended indication although they could provide useful supporting data.

The design of studies and endpoint in therapy resistant patients are essentially the same as described for other trials (see section 4.4.3.). The key differences are the choice of control and the definition of the patient population.

Treatment resistance in schizophrenia is defined as lack of satisfactory improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration with adequate affirmation of treatment adherence and abstinence from CNS-active illicit drugs. It should be clearly demonstrated that the patients included in the trial are treatment resistant indeed and for this scope at least one treatment failure should be prospectively shown.

The choice of active comparator should be clearly justified. The primary objective of a trial of this design would be to demonstrate superiority to the active comparator (the medicinal product with which an insufficient response has been achieved during the second treatment of the patient) or non-inferiority to clozapine (which has the indication treatment resistant schizophrenia). In schizophrenia superiority trials are generally preferred to non-inferiority trials because of the difficulties in assuring assay sensitivity. A three way trial in which the primary objective is to show superiority to an atypical antipsychotic, with clozapine monotherapy as a third arm to provide a context for the magnitude of the treatment effect, might be preferable to a two way design. If short term efficacy in this TRS patient population has been demonstrated, long term studies would not be required, since maintenance of effect could be extrapolated from the studies performed for the general schizophrenia indication.

4.5.4. Trials to study augmentation/add on treatment

Currently compounds which have a different mechanism of action (different from that of typical and atypical antipsychotics) are developed for augmentation strategies. The use of such compound to augment the activity of another product (antipsychotic) is worth a specific claim leading to a separate indication statement. Augmentation may particularly be useful in case of insufficient response to monotherapy. The patient population might include insufficient response to one or more antipsychotics, and the insufficient response might refer mainly to specific symptom domains. Therefore it is recommended to define the patient population to be included in the studies in terms of number of failures and domains with insufficient effect.

Treatment refractory patients (who show no change from baseline as result of treatment) are not suitable candidates for augmentation since there is no response to augment. These patients should be switched to an alternative monotherapy instead and therefore should be excluded from augmentation trials (see section 4.5.3).

In the recommended standard short term trial with parallel design for an augmentation indication patients are randomised to receive active augmentation treatment or placebo in addition to open label standard medication (prospective design). A list of appropriate baseline standard medications should be defined in the trial protocol. Trial duration of 4-6 weeks is likely to suffice for demonstration of short term efficacy although typically substantially longer durations may be necessary according to the nature of the test treatment and patient population.

A comparison with an established treatment is generally valuable in schizophrenia trials to estimate the clinical value of the test treatment. Currently no products have been approved for an augmentation indication. Therefore a third treatment arm with an active comparator cannot be recommended at present for augmentation trials.

Maintenance of effect of long term augmentation treatment can be demonstrated in a randomised withdrawal design similar to the general schizophrenia indication. In this case responders to a combination treatment of a known antipsychotic and the new compound are randomised to one of the following three treatments: combination therapy, monotherapy antipsychotic, and monotherapy new compound (if appropriate).

An alternative is a long term trial with parallel design, in which patients are randomised either to the test product or placebo added to a well established antipsychotic to which patients have shown a partial response.

Drug interactions should be studied prior to pivotal augmentation studies.

4.6. Special populations

4.6.1. Paediatric population

There are a number of significant differences in the typical clinical presentation, severity and natural course of schizophrenia in adolescents compared to adults. Extrapolation of adult data to adolescents is not considered appropriate and specific studies are necessary to provide sufficient data on efficacy and safety. Because of the difficulties in diagnosis and low prevalence in younger children, it is not considered necessary to perform clinical studies in children under the age of 13 years.

With regard to the adolescent patient population, similar diagnostic criteria (DSM IV) apply. Compared with adults there is a high degree of co-morbidity (e.g. autism) and overlap with symptoms of other psychiatric conditions. Because misdiagnosis at young age is a problem, a thorough and critical assessment including psychiatric, psychological and physical examination should be performed by clinical experts. In general the diagnosis of schizophrenia can only be established if all criteria are met and alternative psychiatric, neurological or other medical causes of symptoms have been excluded.

Studies in adolescents should include sufficient patients of each age range. The age distribution should reflect the target patient population. Stratification of patients into two groups by age, e.g. 13-15 years versus 16-18 years, or by sexual development stage is recommended since the clinical features and incidence of schizophrenia may differ between strata. Separate studies in subgroups are not required.

Early treatment of prodromal symptoms or prevention of progression to full schizophrenia is not sufficiently investigated to be applicable at this moment.

The design of the studies and measurement tools are in general similar to the adult studies. It may be preferable to amend the rating scale tailoring it to the requirements of the adolescent population, and such amendments should be well justified and discussed.

Efficacy measures should include cognitive and functional outcomes. Efficacy in acute treatment should be demonstrated in at least one short term trial of 4-6 weeks duration (or longer). Maintenance of efficacy (6-12 months) and long term safety data (2 years) should be generated as well. Special attention should be given to possible adverse effects on sexual maturation, cognition, endocrine function and other aspects of development. Undesirable effects relating to changes in prolactin levels should be actively studied (see section 4.7).

4.6.2. Elderly

For the general indication "treatment of schizophrenia" no specifically designed trials in elderly patients are necessary. However, information for this group concerning dose recommendations and safety is necessary. Therefore the number of elderly patients included in the studies should suffice to generate this data. Safety data should be analysed separately with special attention to safety concerns relevant to this age group e.g. (cardio-) vascular and stroke events, as well as diabetes and CNS effects.

4.7. Safety evaluation

In general the content of ICH E1 should be taken into consideration.

Identified adverse events (AEs), including serious AEs and AEs leading to withdrawal, should be characterised in relation to duration of treatment, dosage, recovery time, age, and other relevant variables. Adverse event scales should be standardised for use in studies with psychotropic drugs (e.g. UKU scale). Clinical observations should be supplemented by appropriate laboratory tests and other appropriate investigations (e.g. ECG). AE rates should be presented for the test treatment, placebo and active comparators.

As treatment durations including the long term open label trials will generally be longer for the test treatment as compared to other treatments (e.g. placebo), the data should be presented in a suitable way for comparisons of event rates.

Special efforts should be made to assess potential AEs that are characteristics of the class of drugs being investigated in view of actions on specific receptor sites. Particular attention should be paid to anti-dopaminergic, anti-cholinergic or cholinergic, anti-histaminergic, serotoninergic and a-adrenergic, and to glutamatergic or anti-GABAergic AEs, if relevant.

4.7.1. Specific adverse events to be monitored

Extrapyramidal symptoms (EPS)

For dopaminergic products rates of extrapyramidal symptoms should be presented. In addition the extent and severity of EPS should be actively measured using validated and specifically designed rating scales. Dose – response relationships of EPS should be explored. During the wash out phase prior to acute studies, possible tardive EPS should be measured to distinguish this from acute EPS due to the test treatment.

Any claims concerning a lower incidence of EPS as compared to alternative treatments should be substantiated by robust comparisons with at least one active control with consideration of both clinical and statistical significance.

Tardive dyskinesia occurs late in treatment and is reported for both atypical and typical antipsychotics. The possibility that a test drug might cause tardive dyskinesia cannot be excluded in the typical clinical development programme and therefore the possibility should be mentioned in the SPC even if there are no reported cases.

Specific claims regarding propensity to cause tardive dyskinesia must be substantiated using the same criteria as for other types of EPS.

Psychiatric adverse events

Psychiatric adverse events typically represent a large proportion of the AEs reported in trials in schizophrenia patients. These events may be related to the disorder itself as well as to the study medication. In order to explore the risk of an adverse effect on the severity of the disorder being treated, the proportion of patients deteriorating during treatment should be documented using the primary efficacy measure.

As part of the adverse event data, undesirable psychiatric effects including depression and anxiety should be measured using validated rating scales.

Adverse effects on cognitive functioning

A detrimental effect on cognition should be monitored using validated rating scales, which may be identical to those used to support an efficacy claim. Effects on cognition, reaction time, driving and severity of sedation should also be studied. In the adolescent population specific issues such as memory, learning, school performance, etc. should be studied in relation to both the safety and efficacy perspective.

Suicide

The potential for the test product to precipitate suicidal thoughts and behaviour should be actively measured using validated rating scales (e.g. InterSePT Scale for Suicidal Thinking, Columbia Classification Algorithm for Suicide Assessment). Rates of suicidal events (from suicidal ideation to completed suicide) should be presented and narrative summaries of suicidal patient statements or behaviours should be provided.

Metabolic risk factors

The effects on weight, glucose metabolism and lipid metabolism should be actively measured using standard laboratory measures. The metabolic profile of the test product should be thoroughly characterised in comparison with placebo and active comparator(s).

Neuroleptic malignant syndrome (NMS)

Neuroleptic malignant syndrome (NMS) has been reported for all antipsychotics. Therefore possible cases should be thoroughly investigated and reported. The possibility that a test drug might cause NMS cannot be excluded in a typical clinical development programme. Therefore the possibility should be mentioned in the SPC for drugs of this class even if there are no reported cases.

Haematological adverse events

Special attention should be paid to incidence of neutropenia, agranulocytosis and aplastic anaemia.

Endocrinological adverse events

Special attention should be paid to effects on sexual functioning, galactorrhoea, gynaecomastia and weight gain. Investigation of neuro-endocrinological parameters relating to prolactin is necessary. In the adolescent population effects on growth and sexual maturation require specific attention and should be closely monitored.

Cardiovascular adverse events

Due to the known cardiovascular effects of this class of drugs, cardiac adverse events should be actively monitored. Reported adverse events that might represent orthostatic hypotension or arrhythmia (including syncope, loss of consciousness, etc) should be presented where relevant. The effect on QT-interval prolongation should be investigated in accordance with the ICH E14 guideline.

4.7.2. Long term safety

The total clinical experience should include data on exposure of a large and representative group of patients in line with the guideline on population exposure (ICH E1).

References

Addington AM, Rapoport JL., 'The genetics of childhood-onset schizophrenia: when madness strikes the prepubescent.' *Curr Psychiatry Rep*. 2009 Apr;11(2), pp 156-61.

American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. *J Am Acad Child Adolesc Psychiatry*. 2001 Jul;40(7 Suppl):4S-23S.

Chan WY, McKinzie DL, Bose S, Mitchell SN, Witkin JM, Thompson RC, Christopoulos A, Lazareno S, Birdsall NJ, Bymaster FP, Felder CC., 'Allosteric modulation of the muscarinic M4 receptor as an approach to treating schizophrenia.' Proc Natl Acad Sci U S A. 2008 Aug 5;105(31):10978-83. Epub 2008 Aug 4.

Chavez A, Greenstein D, Addington A, Gogtay N. 'Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited'. *J Am Acad Child Adolesc Psychiatry.* 2009 Jan; 48(1): pp 10-8.

Conley & Kelly, 'Management of Treatment Resistance in Schizophrenia'. *Biol Psychiatry*, 50, 2001, pp 898-911.

Galletly, C: Recent advances in treating cognitive impairment in schizophrenia. *Psychopharmacology 2009: 202: 259-273.*

Hambrecht & Hafner, 'Sensitivity and specificity of relatives' reports on the early course of schizophrenia'. *Psychopathology*, 30, 1997, pp 12-19.

Leach K, Loiacono RE, Felder CC, McKinzie DL, Mogg A, Shaw DB, Sexton PM, Christopoulos A., Molecular mechanisms of action and in vivo validation of an M4 muscarinic acetylcholine receptor allosteric modulator with potential antipsychotic properties.' Neuropsychopharmacology. 2010 Mar;35(4):855-69. Epub 2009 Nov 25.

Liddle, PF: Cognitive impairment in schizophrenia: its impact on social functioning. *Acta Psychiatrica Scandinavica 400 (2000): 11-16.*

McClellan J, et al., 'Early-onset psychotic disorders: Course and outcome over a 2-year period.' J *Am Acad Child Adolesc Psychiatry*, 1999, 38(11), pp 1380–1388.

McClellan J, McCurry C., 'Early onset psychotic disorders: Diagnostic stability and clinical characteristics.' *Eur Child Adolesc Psychiatry* 8 Suppl 1, 1999, pp 113–119.

Nuechterlein, KH et al. The MATRICS Consensus Cognitive Battery, Part 1: Test Selection, Reliability and Validity. *American Journal of Psychiatry Februari 2008: 165:2, 203-213.*

Ulloa RE, et al., 'Psychosis in a pediatric mood and anxiety disorders clinic: Phenomenology and correlates.' *J Am Acad Child Adolesc Psychiatry*, 2000, 39(3), pp 337–345.

Welham, J. et al.: The antecedents of non-affective psychosis in a birth cohort, with a focus on measures related to cognitive ability, attentional dysfunction and speech problems. *Acta Psychiatrica Scandinavica 2009, Aug epub ahead of print.*