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Guideline on the clinical development of medicinal products for the treatment of Autism Spectrum Disorder

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Executive summary

Autism Spectrum Disorder (ASD) is among the most common and varied disorders in paediatric psychiatry. It impacts significantly on social, occupational, or other important areas of functioning, and is a lifelong condition. Although various therapies and interventions are available, few are supported by scientific studies. Pharmacotherapies approved to date for the management of autism have been non-specific for the condition (e.g. atypical antipsychotics for the control of behavioural disturbance) and do not target the core symptoms. This guideline is intended to provide guidance on the evaluation of new products in ASD; it should be read in conjunction with other EMA and ICH guidelines, which may apply to similar conditions and patient populations.

1. Introduction (background)

Autism is a set of heterogeneous neurodevelopmental conditions, characterised by early-onset difficulties in social interaction, communication and unusually restricted, repetitive behaviour and interests. Symptoms can be recognised from a very early age but ASD is often diagnosed in more able children starting mainstream education. Management of ASD relies heavily on behavioural therapies and social and educational programmes.

1.1. Epidemiology

In recent years, reported prevalence rates for all ASDs combined, have approached 1% across U.S. and non-US countries, with similar prevalence estimates in child and adult samples (Idring 2012, Baird 2006, Wingate 2012). It remains unclear to what extent higher rates reflect an expansion of the diagnostic criteria of DSM-IV to include sub-threshold cases, increased awareness, differences in study methodology, or a true increase in the frequency of ASD. Prevalence rates in adolescents separately have been less investigated (Brugha 2009).

At least in children, ASD is more frequent in males, with ratios of 4:1 (male: female) for classic autism and as high as 11:1 for Asperger syndrome (Baron Cohen 2011). ASD may be under-recognised in high-functioning individuals, especially in females (Lai 2013). Genetic abnormalities that may have an impact on e.g. synaptic transmission and environmental factors seem to contribute to autism (Fombonne 2011, Yates 2012).

1.2. Diagnosis

Historically autism has been diagnosed on the basis of three core domains: impaired social interaction, abnormal communication, and restricted and repetitive behaviours and interests. Co-morbid symptoms are frequent, such as anxiety and depression, seizures, attention deficits, aggressive behaviours and sleep disorders.

In the International Classification of Diseases (ICD-10R, World Health Organization 1993) and the Diagnostic and Statistical manual (DSM-IV-TR, American Psychiatric Association 2000) autism comes under the umbrella term of Pervasive Developmental Disorder (PDD), with four possible diagnostic subtypes, i.e. Asperger Syndrome, Childhood Autism/Autistic Disorder, Atypical Autism and PDD-not otherwise specified.

In DSM-5 (2013) these diagnostic subtypes are combined into a single category of Autism Spectrum Disorder (ASD) and the previous use of three areas of impairment has been reduced to two main areas, namely social communication and interaction, and repetitive behaviour which include sensory integration dysfunctions.

ASD is a "spectrum disorder" as it affects each person in a variety of different ways and can range from very mild to severe. The functioning of the affected individual varies substantially depending on language abilities, level of intelligence, co-morbidity, composition of symptoms and access to services. Cognitive functioning, learning, attention, and sensory processing are usually impaired (Baird 2003).

Diagnosis may be challenging, particularly in children younger than 24 months, children or young people with a developmental age of less than 18 months, children or young people for whom there is a lack of available information about their early life, older teenagers and in children or young people with complex coexisting mental health disorders (e.g. ADHD, conduct disorder, a possible attachment disorder), sensory impairment (such as severe hearing or visual impairment), or motor disorders such as cerebral palsy (NICE clinical guideline 128).

Autism Spectrum Disorder is a persistent condition and most people with ASD are adults. The number of individuals presenting with a first diagnosis in adulthood is increasing (Wilson 2013). Social interaction/communication problems are still present in the vast majority of adults with ASD, but behavioural impairments may be more variable in adulthood (NICE clinical guideline 142).

The diagnosis of ASD is essentially clinical. Research efforts are on-going to identify potential diagnostic markers and clinical measures that may correlate with ASD symptomology. Further exploration of the possible diagnostic utility of investigations and surrogate measures is encouraged.

1.3. Differential diagnosis and comorbidities

Differential diagnosis

Most individuals with ASD do not have an identified underlying cause. However a number of clinical conditions, including primary genetic or chromosomal disorders, may be associated with autistic features and it is important to identify these.

Certain psychiatric and behavioural disorders may have features that could be confused with autism. These may include attention deficit hyperactivity disorder (ADHD), affective / anxiety disorders, attachment disorders, oppositional defiant disorder (ODD), obsessive compulsive disorder (OCD) and psychoses including schizophrenia (cognitive impairment). Age of onset of symptoms is a key factor in distinguishing these conditions from ASD.

Comorbidities

Comorbid medical conditions are highly prevalent in ASD. Sleep problems are thought to affect 40–80% of children on the spectrum, estimates of gastrointestinal disorders in ASD range from 9 to 70% and epilepsy is found in 8 to 30% of cases. Over 50% of people with autism have a learning disability, although this finding is variable depending on diagnostic criteria (Lai 2013).

1.4. Treatment

Non-pharmacological interventions are the cornerstone of the management of behavioural difficulties associated with ASD. Although non-specific treatments can be used to manage problematic behaviour no specific drug therapy is currently licensed for the treatment of the core symptoms of ASD. Potential new treatments currently being studied include compounds that modulate glutamate, GABA or serotoninergic systems.

2. Scope

The scope of the present document is to provide guidance on diagnostic criteria, definition of target treatment populations, efficacy and safety criteria for clinical trials intended to establish the efficacy and safety of treatments for ASD. Specific age-category problems (childhood versus adulthood), and the need for comparative studies are also considered in this document.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction, general principles (4) and the Annex I to Directive 2001/83, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 (ICH E11)
- Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population - EMEA/CHMP/EWP/147013/2004 corr.
- Reflection paper: formulations of choice for the paediatric population. EMEA/CHMP/PEG/194810/2005
- Ethical considerations for clinical trials on medicinal products conducted with the paediatric population - Directive 2001/20/EC
- Concept paper on extrapolation of efficacy and safety in medicine development – EMA/129698/2012
- Dose-response information to support drug registration – CPMP/ICH/378/95 (ICH E4)
- Reflection paper on the extrapolation of results from clinical studies conducted outside Europe to the EU-population – EMEA/CHMP/EWP/692702/2008
- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1)

4. General considerations for clinical development

To support an indication for the treatment of autism it is necessary to demonstrate a treatment effect that is of clear clinical relevance to the patient. Due to the heterogeneity of the disease it may not be possible to achieve a significant effect on all core symptoms with a single compound. Therefore short term efficacy has to be demonstrated on at least one core symptom, supported by a positive effect on global function. Since this is a lifelong lasting disease, long term efficacy should be demonstrated as well. Maintenance of effect on both core symptoms and global function needs to be shown in longer term studies.

A clinical effect on core symptoms of ASD should be demonstrated before efficacy on other associated symptoms can be claimed. Generally the development of treatments targeting single symptoms in autism is not encouraged. Indications of this nature might be considered “pseudo-specific” and would not be approvable unless, exceptionally, it could be shown that the treatment effect on that symptom was specific to autism and would not be applicable in more general populations.

It is important to demonstrate that the effect of the medicinal product is specific for ASD and is not due to secondary therapeutic effects on psychiatric co-morbid conditions (see section 1.3). This may be especially important for existing products currently approved for other indications.

Psychological, educational and social care support are current standard of care, and pharmacological therapies and these should always be incorporated in a modular therapeutic regimen.

A clinical development programme should include sufficient numbers of patients to cover the full range of severity of ASD unless the treatment is expected to be suitable only for one section of the severity spectrum. Co-morbid conditions should be fully described and extrapolation to the overall population with ASD should be discussed.

It is strongly recommended that a sufficient number of patients from the EU should be included in the clinical development programme. Where there is reliance on non-EU data, potential differences in e.g. clinical diagnosis, clinical practice, and study population should be discussed.

Extrapolation between age groups

It is expected that the clinical development package will include sufficient numbers of patients of all ages for whom the product will be intended.

Extrapolation between paediatric age groups is of limited validity as there are differences in terms of neurodevelopment stages, including growth, sexual and cognitive development that will impact on both efficacy and safety endpoints. Also compensation strategies and management of the condition will vary between age groups. There is a need to establish the age from which treatment is beneficial. Separate studies are needed in adolescents and younger children, or if one single study is performed sufficient data should be collected to allow for assessment of consistency and interpretation in all age groups. Diagnostic instruments should be adjusted accordingly and validated for the corresponding age groups.

For adults, efficacy trials should be performed separately from the trials in paediatric patients as data from children and adolescents cannot readily be extrapolated to the adult population. A separate claim in adults may be obtained separately from a claim in children.

5. Patients characteristics and selection of patients

5.1. Diagnosis and inclusion criteria

ASD should be diagnosed and classified according to standard criteria published in an internationally acknowledged classification system. The DSM 5 or the latest version of the ICD are preferred.

Diagnosis should be made by a (child and adolescent) psychiatrist or by a non–psychiatrist physician experienced in ASD and co-morbid diagnoses, and who is trained in the use of (semi-) structured interviews to confirm the diagnosis. Diagnostic scales include the Autism Diagnostic Observation Schedule-Generic (ADOS-G, Lord 2000) now ADOS-2, the Autism Diagnostic Interview Revised (ADI-R, Lord 1994) or the Diagnostic Interview for Social and Communication Disorders (DISCO, Leekam 2002). Additional scales can be used if justified.

The diagnosis of ASD requires the condition to have been present since early childhood (even if unrecognised at the time). In older patients in the milder end of the spectrum this may require verification, e.g. by medical records and school reporting. It is generally accepted that ASD can be reliably diagnosed in children from at least the age of 24 months (Bolte 2013). Assessment tools should be adjusted to each age group included.

Depending on the exact objective of the study a specific threshold on the primary outcome measure may be set as inclusion criteria for entry into the study. This cannot however be used to confirm a clinical diagnosis. The effect of such inclusion criteria on the applicability of the trial results (external validity) will need to be fully justified.

Further descriptive parameters that should be recorded, including:

- Demographic data (e.g., race, living situation such as institutionalisation)
- Detailed disease history (e.g., time of onset and duration of ASD, previous treatment outcome)
- Development pattern (e.g., cognitive profile, language development, history of regression)
- Comorbid conditions (e.g. ADHD, anxiety, genetic conditions)

Efforts should be made to stratify randomisation for variables such as age, gender, severity of symptoms and functional impairment using appropriate scales. Adjustment for these stratification variables should be made in the statistical analysis of the efficacy outcomes.

In addition a number of biomarkers are being investigated to aid clinical categorisation; these may be used if fully justified.

5.2. Exclusion criteria

Exclusion criteria for ASD trial may include:

- Severe co-morbid conditions that may interact with study procedures
- Newly initiated or recently changed pharmacotherapy
- Newly initiated or recently changed formal behavioural, cognitive or cognitive-behavioural therapy

6. Methods to assess efficacy

6.1. Main efficacy measures

Information should be obtained from at least one reliable informant and also from the subject (self-reported 'subject' rating scales) where this is possible. For children both the parent/carer and teacher should provide data where possible. In adolescents and adults the specified reliable informant will depend on the symptom and functional severity of the individuals being studied

Symptomatic scales

Symptoms should be assessed with scales validated for the full age range of patients to be studied. The use of the same rating scale for inclusion, efficacy and responder definition is recommended wherever possible.

Scales based on clinician ratings using information obtained from reliable informants are most appropriate as primary efficacy measures. Both raters (clinicians) and observers (parents, caretakers, teachers etc.) should be adequately trained, including recording of data in observer diaries or into a database. Industry standard methods should be implemented to assess inter-rater reliability.

The ADOS and the Childhood Autism Rating Scale (CARS, Schopfler 1980) are validated for the assessment of core symptoms in ASD. These scales and others are in principle satisfactory if validated on test quality criteria (reliability, validity) and sensitivity to change is demonstrated.

Functional scales

No validated scale of functioning has yet been clearly identified that would be specific to ASD. Functional scales developed for other conditions (e.g. ADHD) might have questionable applicability to ASD and might lack sensitivity for detecting a treatment effect in ASD patients. The development of a functional scale validated for autism is therefore encouraged. Adaption of an existing functional scale,

developed for another condition but adapted as appropriate for the specific requirements of a clinical trial in ASD, is a possible approach.

Global scales

The CGI-I scale is a well-established research rating tool applicable to psychiatric and neurological disorders that can easily be used by the practicing clinician (Guy 1976; Busner 2007). However it cannot be considered as a measure of function but as a global measure that reflects both core symptoms and functioning.

6.2. Other efficacy endpoints

Secondary outcome measures may also include additional symptom and/or functional rating scales, behavioural scales and miscellaneous measures of interest such as sleep disturbance.

As there are potentially a large number of secondary efficacy measures it is recommended to pre-specify a small number of the most important as key secondary endpoints in order to address potential concerns relating to multiplicity.

7. Design of clinical trials

7.1. Clinical pharmacology studies

7.1.1. Pharmacodynamics

There is currently a lack of reliable surrogate markers that might be of use as an indicator of effective therapeutic intervention in ASD. Research efforts are on-going to identify potential diagnostic markers and measures that may correlate with ASD symptomology, including eye-tracking, functional MRI, Magnetic Resonance Spectroscopy (MRS), EEG/ERP (Event Related Potential) and PET-scan. Sponsors are encouraged to engage in the development and validation of biomarkers as part of their development strategy and to use them as exploratory efficacy measures in clinical trials as appropriate. Biomarkers may have a potentially valuable role in exploring the mechanisms by which an investigational drug exerts a therapeutic effect in ASD (e.g. sensory processing).

Changes on appropriate rating scales can be used to study pharmacodynamic changes with a new treatment. Relationship between pharmacodynamics and pharmacokinetics may be explored. Potential differences in pharmacodynamics depending on the stage of development (including brain and pubertal development), and therefore on the age of the population being studied, should be explored.

7.1.2. Pharmacokinetics

The usual pharmacokinetic studies should be performed (see note for guidance on pharmacokinetic studies in man). Pharmacokinetic studies should start with adults for safety reasons. However, definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the medicinal product is likely to be used should be conducted in the paediatric population. The principle of sparse sampling and modelling techniques should be applied where possible.

7.1.3. Drug interactions

The note for guidance on drug interactions should be followed. Studies on potential pharmacodynamic interactions with other CNS active products may be required. Special interest should be taken in

interactions with stimulant medication, as well as with alcohol and other CNS active products that are relevant from a safety (and efficacy) perspective.

7.2. Dose response and exploratory efficacy studies

It is strongly recommended to obtain clinical data on dose-response prior to conducting confirmatory clinical trials. For these studies it is acceptable to study a narrower range of patients than would be expected in the pivotal efficacy trials, and to exclude patients with significant co-morbidities or concomitant medications, in order to maximise the ability of the trial to detect differences between treatment groups.

It is to be expected that dose requirements might differ considerably across the wide range of severity covered by the condition defined as ASD. The patient population studied should therefore be sufficient to allow an adequate assessment of dose-response, and hence inform dose recommendations, in patients in the mild, moderate and severe parts of the autism spectrum.

As far as possible the dose response relationship and the clinically effective dose range should be determined in one or more dose-finding studies. The preferred approach is a randomised, controlled, parallel-group, fixed-dose design, evaluating at least 3 separate dose levels. It is generally recommended to include placebo. The use of an additional active comparator arm may be useful if an appropriate comparator is available.

The treatment duration in dose-finding studies will depend on the pharmacodynamic properties and expected onset of action of the trial medication and should be justified.

In cases where dose-response differs significantly between adults and children (possibly related to brain development) separate dose finding studies may be required for dose justification in these populations unless otherwise justified. Where the PK characteristics are similar across all age cohorts, dose response studies may be performed in a combined paediatric population. Whether PK/PD is similar in the different age cohorts should be explored. Alternative strategies for dose finding may be necessary in the youngest age group. Mere extrapolation of pharmacokinetic data from older children may not be sufficient, and may depend on the nature of the product.

7.3. Short term confirmatory efficacy trials

The preferred design for demonstrating short-term efficacy is a randomised, double-blind, parallel group trial. The duration of these trials should be justified according to the mechanism of action of the new product and hence the expected time necessary to show a clear and stable treatment effect. Trial designs will be broadly similar in children, adolescents and adults.

Primary and secondary endpoints

The key efficacy objective is to show statistically robust and clinically relevant improvement on at least one core symptom, supported by a positive effect on global function.

An efficacy measure for one or both of the core symptoms should be specified as (co-)primary. Regardless of the primary trial objective, all aspects of the core symptoms should be evaluated using validated instruments, to ensure that improvement in one core symptom (e.g., repetitive of aggressive behaviour) is not offset by worsening in other domains (e.g., social interaction). If not defined as co-primary, the other core symptom should therefore be specified as a secondary endpoint.

Functioning must also be evaluated, although it is recognised that a significant effect on function might only be shown in long-term studies. Measures of functioning may therefore be evaluated as important secondary variable.

Active comparator control groups

Three-arm trials including placebo and active comparator are ideal. However at the time of writing there are no approved treatments for the core symptoms of ASD and placebo controlled studies without an active comparator are therefore appropriate until an approved comparator is available.

Methodological considerations

A wash-out period for prior medication may be necessary depending on the mode of action of the new compound. A placebo run-in period to exclude placebo responders is generally not acceptable as it results in overestimation of treatment effect and may impair generalisation of the results.

Confirmatory efficacy trials should be designed and powered to demonstrate a treatment effect that is clinically relevant. Primary analyses of change from baseline to endpoint on key efficacy measures should be supported by responder analyses using pre-specified criteria for response.

It may be valuable to present subgroup analyses for key baseline co-variates to explore which patients might benefit most from treatment. IQ >70 and some communicative speech at early school age have been identified as predictors of a relatively better outcome in treatment for autism. Consideration should be given to subgroup analyses bases on these predictors. Presence or absence of epilepsy should also be subject to subgroup analyses. The key co-variates of interest and the planned subgroup analyses should be pre-specified in the study protocol; please refer to the Guideline on Investigation of subgroups in confirmatory clinical trials.

7.4. Long-term efficacy trials

Because of the lifelong nature of ASD long-term efficacy must be demonstrated in at least one well-designed and adequately powered long-term trial to demonstrate that patients will benefit from long-term treatment.

A randomised withdrawal trial is the preferred design to show an effect on maintenance of response. Other designs that would also take into account the mode of action of the medicinal product being evaluated could be accepted if fully justified.

7.5. Studies in special populations

7.5.1. Elderly

There is no requirement to demonstrate efficacy independently in elderly populations. However the benefit/risk of psychoactive drugs may be different in the elderly compared with younger adults and dose requirements may be different in this population. Therefore data are required in a sufficient number of elderly patients to support conclusions on these aspects.

Since ASD is a lifelong condition the age range of patients included in adult clinical trials in principle has no upper limit. The diagnostic criteria are the same as in younger adults although the presence of co-morbid conditions may be different in the elderly. The data in elderly patients can be obtained from the subgroups of elderly patients included in the main adult trials.

8. Clinical safety evaluation

8.1. General recommendations

Identified adverse events (AE) should be carefully monitored and should be characterised in relation to the duration of treatment, dose and/or plasma levels, recovery time, age and other relevant variables.

Special efforts should be made to assess potential AE reactions that are characteristics of the class of drugs being investigated in view of actions on specific receptor sites.

Standardised adverse event scales should be used to capture adverse events. Clinical observations should be supplemented by appropriate laboratory tests and cardiac recordings (e.g., ECG). Beyond the regular assessment of adverse events special attention should be paid towards effects, short- and long-term, on the developing brain (see section 8.2).

Children and adolescents

Validated tests should be used for the assessment of adverse events. Long-term effects on learning, development, growth and sexual function may be studied post-marketing, but appropriate protocols should be available.

8.2. Adverse events of interest

8.2.1. Central Nervous System (CNS) Adverse reactions

Depending on the class of the investigated medicinal product and the possible interactions with various receptors, effects on cognition, reaction time and/or driving, and the extent of sedation should be studied. Likewise possible sleep disturbances, extrapyramidal effects and seizures should be assessed using appropriate tools.

Neurocognitive measures in the different age cohorts (children/adolescents/adults) should be reported. Potential adverse effects on memory, learning, school performance, etc. should be specifically studied.

Psychiatric side effects (e.g. depression, mania, self-injury, psychotic symptoms, excitability, agitation, and mood changes) should be monitored for.

Special attention should be paid to attempted and completed suicides by using a suitable suicide rating scale or review of relevant AE data. Suicidality should be prospectively assessed by using proper instruments, such as the Columbia Classification Algorithm of Suicide Assessment (C-CASA), or the Columbia Suicide Severity Rating Scale (C-SSRS) that allows documenting according to the C-CASA categories.

8.2.2. Endocrinological adverse reactions

Special attention should be paid to growth, alterations in weight, and sexual maturation. In adolescents and adults, disturbance in libido should be assessed where feasible and appropriate.

Depending on the pharmacological properties of the new therapeutic agent, the investigation of endocrinological parameters may be necessary (prolactin secretion, hypothalamic-pituitary-adrenal hormones (HPA) etc.).

8.2.3. Rebound / withdrawal / dependence

When pharmacological treatment is stopped, rebound and/or withdrawal phenomena may occur. Therefore, rebound and/or withdrawal phenomena should be systematically investigated. Unless otherwise justified, patients should be followed for a suitable time to detect possible rebound and withdrawal symptoms and differentiate them from recurrence of symptoms. This should be performed both after short- and long-term exposure to the compound.

Animal studies will be needed to investigate the possibility of dependence in new classes of compounds or when there is an indication that dependence may occur (CHMP/SWP/94227/2004).

8.3. Extent of population exposure to assess clinical safety (including long-term safety)

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

Long-term safety data are required in ASD; special attention should be given to the effects on the developing brain (e.g. adverse cognitive effects) and body, and the susceptibility to the 'known' side effects of psychotropic drugs in children, which may be altered or enhanced as compared to adults.

Long-term safety can be generated in open extension studies of short-term studies and/or by specific long-term trials. A prospective cohort design is recommended.

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