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

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30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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

Table of contents

Executive summary

Autism Spectrum Disorder (ASD) is amongst the most common and varied disorders in paediatric psychiatry. It impacts significantly on social, occupational and other important areas of functioning. It is a lifelong condition and although various therapies and interventions are available few are supported by scientific studies. Pharmacotherapies approved to date for the management of ASD have been non-specific for the condition (e.g. atypical antipsychotics for the control of behavioural disturbances) and do not target the core symptoms. This document 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)

ASD is a set of heterogeneous neurodevelopmental conditions, characterised by early-onset difficulties in social interaction, communication and restricted, repetitive behaviour, interests or activities. Symptoms can be recognised from a very early age, however ASD is often diagnosed in more able children with an IQ within the typical range 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 ASD are approaching 1% across in European countries with similar prevalence estimates in child and adult samples[1,2]. 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 have been studied less[3].

ASD is more frequent in males, with ratios of 4:1 (male: female)[4]. ASD may be under-diagnosed in high-functioning individuals, especially in females[5]. Genetic abnormalities that may have an impact on e.g. synaptic transmission seem to contribute to autism [6,7].

1.2. Definition of the condition

Historically ASD 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[8]) and the Diagnostic and Statistical manual (DSM-IV-TR[9]) 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[10] (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 persistent deficits in social communication and interaction, and restrictive, repetitive behaviour, interests and activities which include sensory integration dysfunctions. These symptoms are present from early childhood and limit or impair everyday functioning.

ASD is a spectrum disorder encompassing conditions that partly overlap in their external characteristics, affecting each person in a variety of different ways and ranging from very mild to severe. The functioning of affected individuals 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[11].

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[12].

ASD is a persistent condition although the number of individuals presenting with a first diagnosis in adulthood is increasing[13]. Social interaction/communication problems are still present in the vast majority of adults with ASD, but behavioural impairments may be more variable in adulthood[14].

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 symptomatology. 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, ASD tends to occur more often in people who have certain genetic or chromosomal conditions, such as fragile X syndrome, Rett syndrome or tuberous sclerosis which may be associated with autistic features, and it is important to identify these.

ASD may present associated symptoms consistent with certain psychiatric and behavioural disorders alongside core symptoms, which may confound a diagnosis. 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[5].

1.4. Treatment

Non-pharmacological interventions are the cornerstone of the management of behavioural difficulties associated with ASD. Although pharmacological treatments can be used to manage associated symptoms and 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 the design of clinical trials intended to establish the efficacy and safety of treatments for the core symptoms of ASD. Specific age-category issues (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
- 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)
- Investigation of subgroups in confirmatory clinical trials – EMA/CHMP/539146/2013
- Points to consider on multiplicity issues in clinical trials - CPMP/EWP/908/99

4. General considerations for clinical development

To support an indication for the treatment of ASD it is necessary to demonstrate a treatment effect that is of clear clinical relevance to the subjects with ASD. Due to the biological variability within the autism spectrum, it may not be possible to achieve significant effects on all commonly observed characteristics of ASD with a single compound. Short term efficacy has to be demonstrated on at least one core symptom, with demonstration of a positive effect on functioning whether from a communication or behavioural point of view. Since this is a life-long condition, long term efficacy and safety should be demonstrated as well. Maintenance of effect on both at least one core symptom and 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 should always be incorporated in a modular therapeutic regimen in all clinical trials.

A clinical development programme should include sufficient numbers of patients to inform on 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 potential extrapolation to the overall population with ASD should be discussed.

It is strongly recommended to include a sufficient number of patients from the EU in the clinical development programme that would cover all age sub-groups studied.

Extrapolation between age groups

There is a need to establish the age from which treatment is beneficial. 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 groupsis of limited validity as there are differences in terms of neurodevelopment stages, sexual and cognitive development that will impact on both efficacy and safety endpoints. Also, compensatory strategies and management of the condition will vary between age groups. For these reasons, separate studies may be needed in adolescents and younger children. Sufficient data should be collected to allow for assessment of consistency and interpretation in all age groups for which the treatment is intended. 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 and vice versa.

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 latest version of the DSM (currently DSM-5) or ICD should be used.

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 (ADOS-G[15], now ADOS-2), the Autism Diagnostic Interview Revised (ADI-R[16]) or the Diagnostic Interview for Social and Communication Disorders (DISCO[17]). 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), which will be documented. It is generally accepted that ASD can be diagnosed in children from at least the age of 24 months[18]; however, the certainty of the diagnosis may be reduced compared to that of older children, i.e. of pre-school age and older. Assessment tools should be adjusted to each age group included. The effect of novel therapies in ASD should be investigated in children as early as possible and, depending on the mode of action and properties of the product, should include children as young as possible if it is likely that they will benefit from early treatment.

Depending on the 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 include:

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

Currently a number of biomarkers that stratify patient populations according to distinct biological subtypes are being investigated to aid clinical categorisation. Stratification may also be considered according to e.g., diagnostic biomarkers if these are fully validated[19].

5.2. Exclusion criteria

Exclusion criteria for ASD trial may include:

- Severe co-morbid conditions (e.g. psychosis, epilepsy uncontrolled by medication, presence of severe visual or hearing impairment) 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

The objective is to demonstrate a treatment effect on at least one core symptom which should be supported by a positive effect on functioning. This requirement can be met using measurement tools looking specifically at core symptoms or at functioning, or scales incorporating elements of both, or a combination of all of these.

Core symptoms should be assessed with appropriate scales validated for the age range of the subjects to be studied.

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

Information should be obtained from at least one reliable informant and also from the subject (self-reported 'subject' rating scales). 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, but self-reported scales should be provided whenever possible.

To date, no outcome measure has been shown to reliably detect treatment related changes in the core symptoms of ASD. The Childhood Autism Rating Scale (CARS) and the SRS-2 are examples of scales used in ASD, although they do not capture all core symptoms of ASD and sensitivity to change may be an issue. In addition, the Vineland Adaptive Behaviour Scale-II (VABS-II) has also been used to further evaluate adaptive functioning and the Children's Yale-Brown Obsessive Compulsive Scale in ASD (CYBOSC-ASD[20]) has been used for the evaluation of repetitive behaviour. These and other potential scales are in principle satisfactory if clearly validated on test quality criteria (reliability, validity) and sensitivity to change is demonstrated.

Tools for the evaluation of functioning, such as activity of daily living, may be pre-specified (see also section 7.3). The CGI-I scale is a well-established research rating tool applicable to psychiatric and neurological disorders that can easily be used by the practising clinician[21, 22]). It reflects whether changes seen are perceived as relevant but it cannot be considered solely as a measure of function.

Additional outcome measures may include other measures of interest such as sleep disturbance. Quality of life may be measured to provide additional information using e.g. SF36.

As there are potentially a large number of secondary efficacy measures it is recommended to pre-specify a small number of the most important ones as key secondary endpoints in order to potentially address the multiplicity issue or reduce multiplicity with respect to important secondary endpoints.

7. Study Design

7.1. Clinical pharmacology studies

7.1.1. Pharmacodynamics

There is currently a lack of reliable surrogate markers that might be used either as diagnostic and prognostic tool or as indicators of effective therapeutic intervention in ASD. Research efforts are on-going to identify potential diagnostic and prognostic markers and measures that may correlate with ASD symptomatology, including eye-tracking, functional MRI, Magnetic Resonance Spectroscopy (MRS), EEG/ERP (Event Related Potential) and PET-scan[23-27]. 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).

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 exploratory studies it is acceptable to study a more homogeneous group 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.

The population studied should be sufficient to allow an adequate assessment of dose-response, and hence inform dosing recommendations. As far as possible the dose-response relationship and the clinically effective dose range should be determined in one or more dose-finding studies. A widely-used study design is the parallel, randomised dose-response study; it is recommended to use at least three active dose groups and placebo. 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.

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. Extrapolation of pharmacokinetic data from older children to younger ones may not be sufficient and will depend on the nature of the product. However, where the PK characteristics are similar across all age cohorts, dose response studies may be performed in a combined paediatric population, with exploration of variations in different age cohorts.

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 the intended therapeutic effect hence the expected time necessary to show a clear and stable treatment effect. Although a duration of 12 weeks has been used in some clinical studies, a longer duration might be required if the treatment effect is thought to be time-dependent or if tolerance could be an issue with reduced effect over time. Trial designs will be broadly similar in children, adolescents and adults and the drug should be tested on top of standard of care

Primary and secondary endpoints

It should be pre-specified if the efficacy measure for one or both of the core symptoms is considered primary. If not defined as co-primary endpoint, the other core symptom should be specified as a key secondary endpoint. Regardless of the primary trial objective, all aspects of the core symptoms should be measured 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).

Improvement in functioning must be demonstrated, either from functional components of composite measures or from specific functional measures as available.

Active comparator control groups

Trials including placebo and active comparator are the ideal, however, at the time of writing there are no approved treatments for the core symptoms of ASD. Placebo controlled studies without an active comparator are acceptable 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 planned subgroup analyses according to relevant co-variates (e.g. epilepsy) should be pre-specified in the study protocol; please refer to the Guideline on Investigation of subgroups in confirmatory clinical trials.

7.4. Maintenance of effect

As ASD is a life-long condition demonstration of continued benefit must be demonstrated in at least one well designed and adequately powered long-term trial. A randomised withdrawal trial is the preferred design to show an effect on maintenance of response on the core symptom(s) and on function. Other designs that would also take into account the mode of action of the medicinal product being evaluated could be accepted if fully justified.

In addition, long-term follow up is expected to provide sufficient safety information (please also refer to section 8 below).

7.5. Studies in special populations

7.5.1. Elderly

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.

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.

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.

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

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.

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 per the C-CASA categories.

8.2.2. Endocrinological adverse reactions

Special attention should be paid to growth, alterations in weight, metabolic disturbances 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 stoppedrebound and/or withdrawal effects should be systematically investigated. Patients should be followed for a suitable time to detect possible rebound and withdrawal symptoms and differentiate them from recurrence of symptoms both after short- and long-term exposure to the compound.

Animal studies will be needed to investigate the possibility of dependence to new classes of compounds or when there is a risk 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 longitudinal cohort design is recommended.

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