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DRAFT

**GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL
PRODUCTS FOR THE TREATMENT OF JUVENILE IDIOPATHIC
ARTHRITIS**

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Any comments to this Guideline should be sent to the EMEA EWP Secretariat by e-mail: line.jensen@emea.eu.int or by fax: +44 20 74 18 86 13 by the end of December 2005.

GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS

This Guideline is intended to provide guidance for the evaluation of medicinal products in juvenile idiopathic arthritis. This Guideline should be read in conjunction with Directive 75/318, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- Dose-Response Information to Support Drug Registration (ICH E4),
- Statistical Principles for Clinical Trials (ICH E9),
- Choice of Control Group in Clinical Trials (ICH E10),
- The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),
- Clinical Investigation of medicinal Products in the Paediatric Population (ICH E11)
- Note for Guidance on Clinical Investigation of medicinal Products in children (CPMP/EWP/462/95)
- Points to consider on the evaluation of the pharmacokinetics of medicinal products in the paediatric population (Draft 4)
- Points to consider on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis (Draft Revision 1)
- Note for Guidance on clinical investigation of medicinal products for treatment of nociceptive pain (CPMP/EWP/612/00)
- Note for Guidance on Investigation of Drug Interactions (CPMP/EWP/560/95)
- Points to consider on the choice of the non-inferiority margin (CPMP/EWP/2158/99 Draft 6)
- Note for Guidance on Fixed Combination Medicinal Products (CPMP/EWP/240/95).
- Regulation of the Council and European Parliament on medicinal products for paediatric use

This Guideline is intended to assist applicants during the development of medicinal products. It is only guidance; any deviation from guidelines should be explained and discussed in the Expert reports/Clinical Overview.

INTRODUCTION

General Information

Chronic arthritis in childhood is a heterogeneous group of diseases for which various schemes of clinical characteristics for classification have been developed. A number of classification systems currently exist, including the American College of Rheumatology (ACR) criteria for the classification of juvenile rheumatoid arthritis (JRA)^{1,2}, the European League Against Rheumatism (EULAR) criteria for juvenile chronic arthritis (JCA)³, the European Spondylarthropathy Study Group (ESSG) criteria for spondylarthropathy⁴, and the Vancouver Criteria for juvenile psoriatic Arthritis (JpsA)⁵. Among these classification systems there are gaps and overlaps.

The International League Against Rheumatism (ILAR) has introduced a new nomenclature and classification for Juvenile Idiopathic Arthritides (JIA)^{6,7}. The aim of this system was to replace the combination of pre-existing systems with one classification that identifies more homogeneous

populations according to their clinical and biological features within each diagnostic category, and that can be used internationally to facilitate communication and research⁸.

JIA refers to arthritis of at least 6 weeks duration of unknown aetiology that begins in children less than 16 years old. Estimates for prevalence and incidence cover a wide range. With an annual incidence of 0.008 - 0.226 and a prevalence of 0.07 - 4.01/1000 children JIA is less common than rheumatoid arthritis (RA) in adults but it is the most common systemic autoimmune disease in children and adolescents.⁹ Children of all age groups may be affected whereby onset of disease during the first year of life is rare and is mostly seen in the "systemic" subtype. In some of the subgroups girls predominate.¹⁰

The ILAR scheme distinguishes 7 subtypes, further on referred to as categories (Durban or ILAR criteria).^{6,7}

1. Systemic arthritis
2. Polyarthritis, RF-negative
3. Polyarthritis, RF-positive
4. Oligoarthritis (persistent, extended)
5. Psoriatic arthritis
6. Enthesitis-related arthritis
7. Other Arthritis

Meanwhile the second revision (Edmonton) has been published with clarification of the definitions of each category and precision of exclusion criteria.⁷ Sub-classification may not be performed before the first 6 months of disease according to the number of affected joints and the occurrence of extra-articular manifestations.

Although the aim of the ILAR criteria is to delineate for research purposes relatively homogeneous, mutually exclusive categories of idiopathic childhood arthritis, they are in a state of flux. Other classification systems may be used if adequately justified, though the ILAR classification should be preferred.

The aetiology and pathogenesis of JIA remains unclear. Abnormal immunoregulation and cytokine production, genetic disposition of immune response and latent viral infection may play a role. JIA is characterized by many of the same histologic abnormalities that have been identified in rheumatoid arthritis (RA). The production of large amounts of cytokines (interleukin-1 β and -6, TNF- α etc.) which in some subtypes of JIA even exceeds cytokine excess in RA, results in hyperplastic synovial membrane and in conjunction with osteoclastic cell activation leads to degradation of adjacent cartilage and bone. Disturbance and retardation of growth in various aspects are characteristic features of JIA.

JIA is a major cause of disability in children. The ultimate goal of treatment of JIA in all categories should be the induction of remission. However, until now no uniform, validated criteria for defining quiescent disease are in widespread use.¹¹ The aim of modern treatment of JIA is rapid suppression of inflammation in order to prevent organ damage, maximise physical function and promote normal growth and development. In addition, some categories, such as the systemic arthritis may have additional goals such as control of systemic signs and symptoms including fever and prevention of macrophage activation syndrome.

Overall, 5-10 % of patients - especially those with the systemic and polyarticular onset forms - are refractory to conventional therapies with medicines. With the development of new therapeutic agents and combination treatment strategies, more children with arthritis can experience protracted periods of low levels of disease activity and, in a limited number of cases, complete disease quiescence.

First-line therapy includes symptom-modifying (or symptom-relieving) antirheumatic drugs (SMARDs), which are mainly nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are used at the beginning of

treatment, in addition to disease-modifying antirheumatic drugs (DMARDs), or alone when disease flares are intermittent and only mild to moderate. Systemic glucocorticoids (prednisone, methylprednisolone) are used to control systemic inflammation (e.g. uncontrollable fever and systemic “toxicity”, severe anaemia, myocarditis) in systemic-onset JIA, or in severe polyarticular JIA as an adjunct at the start of treatment with DMARDs. Intra-articular injection of long-acting glucocorticoids such as triamcinolone hexacetonide directly into inflamed joints has emerged as a major advance in the treatment of children with various types of arthritis.

An increasing numbers of DMARDs are being used in JIA¹². The most common DMARD used is methotrexate which has been shown in large clinical studies to be effective^{13,14,15}. The introduction of anti-Tumour-Necrosis-Factor- α (TNF- α) therapy, appeared to have a clinically relevant impact on the outcome of patients with polyarticular JIA who were unresponsive to methotrexate.^{16,17,18} Treatment with other medicinal products such as infliximab, adalimumab, IL-1 ra, anti-IL-6 receptor and CTLA4ig are currently under clinical investigation in trials suitable to fulfil regulatory requirements.

However, because the aim of this document is to provide guidance with respect to the design of clinical studies related to therapeutic efficacy and clinical safety of antirheumatic therapy in JIA, therapeutic classification concepts do not seem appropriate in this context.

Scope

This document intends to give guidance on the investigation of medicinal products to be used in JIA.

Due to the small numbers of formal studies performed so far, medical treatment of JIA is mostly empirical thus often resulting in off-label use. The definition of improvement was internationally agreed only in 1997 by consensus.^{19,20}

There are few clinical trials assessing the therapeutic values of medicinal products in childhood chronic arthritis and most of them have been introduced in the treatment based on their efficacy in the treatment of rheumatoid arthritis in the adult population. Extrapolation from efficacy results in adult RA is inappropriate since JIA represents a complex group of diseases divided into several categories with different prognoses and variable clinical presentations within the paediatric population. In comparison to adults there are as well pharmacokinetic and pharmacodynamic differences, impacts on growth and development and differences in perception of disease depending on cognitive levels in different age groups.

I. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

A paediatric investigation plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy in all of the paediatric population that may be concerned by the medicinal product.

Efficacy should be established in the targeted population and cannot be projected from adults.

The efficacy of the agents should be evaluated by subtype to reflect the potential differences in response among the categories distinguished by the ILAR criteria. Patients should be grouped appropriately based on common practice and history of responsiveness of disease to particular types of agent. However, selection of patients should not be overly restrictive either. A study combining patients from multiple categories could be appropriate for categories in which patient numbers are limited. The systemic form should always be studied separately if a claim in this category is to be made.

Because of the relative rarity of the disease and the limited number of children with any of the different categories paediatric safety should not only be studied by subgroup but also in general. The age range for which safety and tolerability have been assessed is probably more important than the specific category of JIA for a determination of safety and tolerability.

Age-related differences in drug-handling resulting from different modes of application or drug-effects and pharmacokinetics which may lead to different dose requirements to achieve efficacy or to avoid adverse reactions in paediatric populations should be evaluated. Practical problems of drug substance administration with suitable formulations have to be considered.

II. METHODS TO ASSESS EFFICACY

Juvenile idiopathic arthritis efficacy criteria

To standardise the assessment of clinical response and increase the efficiency of JIA clinical trials, a core set of outcome variables and a preliminary definition of improvement (PDI) for use in children with juvenile arthritis have been developed and adopted by the Paediatric Rheumatology International Trials Organisation group (PRINTO).^{19,20} Definition of improvement according to the PRINTO criteria specifies that, to be classified as improved, a patient must show at least 30 % improvement from baseline in any three of six variables in the core set, with no more than one of the remaining variables worsening by more than 30 % (JRA 30). The core set variables are:

1. Physician global assessment of disease activity (MD global) on a 10 cm visual analogue scale (VAS); anchoring words inactive and very severe
2. Parent or patient (if appropriate in age) global assessment of overall well-being (parent /patient global) on a 10 cm VAS; anchoring words very well, very poor
3. number of joints with active arthritis (joints with swelling not due to deformity or joints with limitation of motion with pain, tenderness or both)
4. number of joints with limitation of motion
5. functional ability (Childhood Health Assessment questionnaire = CHAQ, with different versions in different countries)^{21,22}
6. ESR

Other measures may be acceptable if validated as primary or secondary endpoints (number of tender joints, number of swollen joints, duration of morning stiffness, CRP-levels, proportion of patients discontinuing due to lack of efficacy, individual components of the JRA core set, disease flare or disease remission, systemic features of systemic arthritis if a therapeutic agent is trialled for this subtype). It is very important that response criteria are adequately justified, chosen before the study is started, and thresholds are predefined. The definition of remission should be used in addition to the JRA 30 once defined as primary endpoint. However it is still being worked out, as the last consensus conference did not reach consensus.^{11,23}

A composite score can be a better representation of overall well being than single parameters but results need to be consistent with the single efficacy endpoints described. Results should not only be statistically persuasive but also clinically relevant. The clinically relevant effect size or delta in the non-inferiority setting should be specified prior to the study. Other composite endpoints may be emerging in the future, they will be accepted after validation only.

The JRA 30 was developed to assess efficacy of agents with disease modifying claim; its suitability and sensitivity for symptom relieving antirheumatic therapies has not yet been validated. The components might be generally applicable to NSAID studies apart from ESR which is not influenced by symptomatic treatment. The proportion of patients responding (i.e. improving by 30%) to each component of the JRA 30 should therefore be presented. This should be done separately for all randomised patients, the per-protocol population and all patients defined as responders in the primary analysis, and should be repeated for the proportion of patients worsening by 30% on each component.

The JRA 30 reflects those signs and symptoms accepted for the evaluation of RA, though a single component of pain is not included. Relief of pain, however is an important component of the treatment response in all categories of JIA. Depending of the pharmacological rationale of the treatment-studied relief of pain should be primary endpoint in the overall evaluation of efficacy. The CHAQ (Childhood Health Assessment Questionnaire) as one component of the JRA 30 is a disease specific instrument that measures functional ability in daily living activities in children with JIA which is validated for use in children ages 1 to 19 years. It provides a parental assessment of their child's pain using a 10 cm VAS rating scale and can be administered directly to older children (>8 years). Clinical manifestations like morning stiffness and pain are probably as often encountered in JIA as in adult disease, however children may communicate symptoms more indirectly which makes careful observation and questioning

of the parent necessary. Since the child's ability to communicate pain is dependent on the cognitive level appropriate rating scales have to be chosen according to age and justified by the applicant (*VAS for older children above 5, e.g. facial expression scale in younger children*). A moderate to severe disease activity should be preferred in order to show a sufficient treatment response. Differences in pain scores should not only be statistically significant but above all be of clinical relevance.²⁴

For agents which are claimed to prevent or slow structural joint damage there is little experience in JIA. In the long-term most patients with JIA develop joint erosions and there needs to be development of a standardised assessment method.²⁵ The traditional scoring methods used for adult rheumatoid arthritis, which are based on the assessment of erosions and joint space narrowing in radiographs, may not be suitable for the evaluation of paediatric joint disease since ossification is incomplete and the width of the joint space varies with age.^{26,27,28} The conduct of the radiological analysis should be described in detail. Deviations from published and validated methodology should be justified. X-rays should be taken on fixed and predefined time points and be assessed by assessors blinded for the treatment allocation, sequence of the x-rays and initial assessment(s) of the other assessor(s). Handling of missing information should be described and justified. The method for obtaining the final score/result should be described in detail (e.g. consensus) and be predefined. Intra- and inter-observe variation should be discussed with regard to the observed differences between treatment arms.

III. STRATEGY AND DESIGN OF CLINICAL TRIALS

1. Early Studies in Children

1.2. Pharmacokinetic aspects in different age ranges

The pharmacokinetics of medicinal products to be used in JIA should be investigated following existing guidelines. Since JIA usually persists over a prolonged period of time throughout childhood and into adulthood pharmacokinetic properties should ideally be studied in the age ranges to be treated. To be in line with ICH E 11 pharmacokinetic studies should be generally conducted in patients with the disease. Maturation of organ functions in different age ranges involved in drug absorption, distribution, and elimination should be considered when extrapolating between paediatric age groups. Paediatric patient sub-populations may require age-appropriate formulations to be developed.

1.3. Dose-Response Studies

Well-planned dose ranging studies should be carried out before the confirmatory clinical trials are undertaken following existing guidelines. The aim is to develop dosing recommendations that will ensure that the patients will obtain treatment that is effective and safe. A dose range for the assessment of dose-response in children should be based on recommended doses in adults of an appropriate pharmacokinetic parameter, most commonly AUC for chronic dosing in patients.

1.4. Interactions

Whenever patients use anti-rheumatic therapy other than the one studied interaction studies have to be performed. Selection of substances for conducting interaction studies should be based on the known pharmacokinetic and pharmacodynamic properties of the agent studied, the existing anti-rheumatic agents, and other possibly interacting medications. Recommendations from the guideline on interactions have to be taken into account.

2. Therapeutic confirmatory Studies

2.1. Study design

Like in adult RA in this disease only the parallel group design is acceptable as a means of assessing efficacy and safety.

When designing a parallel group trial, there is normally a choice between a two-arm study design (verum, active comparator or placebo) and a three-arm study design (verum, active comparator, placebo). Trials convincingly demonstrating superiority to placebo where inclusion of a placebo is practical/ethical (see III.2.3.) will be regarded as high-quality evidence. In a paediatric study there might be ethical concerns about including a placebo-arm when safe and effective analgesic, anti-inflammatory medication is readily available. They have to be balanced by the ethical concerns of accepting shortcomings due to a missing placebo control. Therefore alternatives for the design of parallel group trials should be considered.

Another possibility is a two-arm study comparing the new agent with an established active comparator, seeking to show that the test product is superior or at least non-inferior to the active comparator (within the same class if possible) in terms of relevant endpoints. However, there are no generally accepted criteria for comparability of treatments in JIA.²⁹ The note for Guidance on Choice of Control Group on Clinical Trials (CPMP/ICH/364/96) should be followed.

Trials convincingly demonstrating superiority to an active with known efficacy will be regarded as high-quality evidence. Trials convincingly demonstrating non-inferiority to an active reference with known efficacy can provide good evidence if a placebo-arm is included. Trials convincingly demonstrating non-inferiority to an active reference with known efficacy but without a placebo arm are difficult to assess because of concerns over assay sensitivity. Non-inferiority margins have to be pre-specified prior to the trial. (see Points to consider on the choice of the non-inferiority margin CPMP/EWP/2158/99 Draft 6)

Add-on placebo therapy may also be used when study design requires placebo and allows for combination with other effective treatment. One option is a two-arm study in which patients in both arms receive an established active treatment but are randomised to receive in addition either the new agent or placebo. Alternatively to the latter design, a three-arm study where patients receive, additionally to established active treatment, either the new agent or another established comparator or placebo, can yield valuable data to position the efficacy of the new treatment within the available established therapeutic options for JIA. Each of these designs allow the continuation of randomised therapy for sufficient time to establish effects on chosen endpoints. In all of these designs current ideas favouring early treatment should also be taken into account.

Symptomatic treatment as rescue medication may be used, but should be documented carefully and the possible influence on the results and the way to analyse this should be indicated in the protocol.

In order to explore the degree to which treatment effects are sustained in the long-term, a study design may be employed in which efficacy measures are observed after randomised and blinded withdrawal from a long period of treatment.

To establish a long-term efficacy and at the same time maintain the period of placebo exposure as short as possible a randomised withdrawal study design can be chosen and is recommended for patients with severe JIA for whom few treatment options are available. An initial open-label phase with the new agent can be followed by randomisation of responders to a double-blind phase in which they receive either test agent or placebo. When used with an early escape endpoint, such as return of symptoms (disease flare) the period of exposure with poor response that a patient would have to undergo remains short.

2.2. Target population

The selection of patients in studies of outcome in childhood chronic arthritis markedly influences the results and disease related factors such as number of affected joints and ongoing systemic symptoms or systemic symptoms at onset have to be documented appropriately according to the ILAR criteria. Duration of the disease and disease activity should as well be documented.

The initial symptoms and signs of active disease (core set 1-6 of Point II above) have to be recorded as a minimum. In addition pain scores, radiographs, presence of non-articular symptoms and signs, concomitant diseases as well as the occurrence of autoantibodies and antibodies to the drug have to be carefully documented.

The previous exposure of the trial population to antirheumatic therapies should be discussed, as this information may be relevant to the interpretation of study results. Sufficient washout of prior therapies has to be justified in accordance with ethical considerations.

The target population should match the proposed therapeutic indication. Relevant subgroup analyses should be prospectively planned, e.g. early cases, degree of structural damage at baseline, concomitant medication, cases refractory to other treatments.

Other treatment modalities interfering with study treatment are of particular importance. Careful registration for example of concomitant non-pharmacological treatment (physical therapy of various types etc.) has to be performed and medication for diseases other than rheumatic disease must be completely documented.

Whenever possible it is recommended that these treatments be standardised and previously defined.

2.3. Choice of control

2.3.1. Placebo

Efficacy of drug substances claiming improvement in disease activity and/or function are generally established by means of placebo controlled trials. Since it would be unethical to retain a child with JIA on placebo treatment indefinitely, the duration of placebo control must necessarily be limited. Depending on the severity and the activity of the disease 4 weeks to three months is acceptable. Special study designs are recommended (see III.2.1). For ethical reasons it is recommended that predefined rules for withdrawal from placebo are provided.

2.3.2 Established comparator

Comparative studies against established active treatment may be preferred from an ethical point of view. In order to demonstrate the relevance and appropriateness of the comparison, the choice of the active comparator (within the same class if possible) should be justified, taking into account licensed indications, posology, age range, JIA category, mode of action, time to onset of efficacy, duration of action, safety etc depending on study objectives. Whenever these requirements are not met the inclusion of a placebo arm might be preferred in order to control for all potential influences on the actual or apparent course of the disease (natural history of the disease, observer or patient expectations, use of other therapy and subjective elements of diagnosis or assessment).

The need for a comparator is determined by the intended therapeutic position of the product with the extremes of first line or last resort. A demonstration of the superiority of the test drug to an appropriate comparator in at least one study is more persuasive of its efficacy than a demonstration of equivalence or non-inferiority.

2.3.3 Combination therapy

Treatment with a combination of different drugs/medicines is gaining popularity at least in patients in whom monotherapy has failed. The development is guided by the therapeutic claims and the suggested expectations based on mode of interaction: increased efficacy, additive or synergistic, or safety. A pharmacological rationale should be presented and the choice of doses justified. Claims of additive or synergistic efficacy would be required to be supported by specific efficacy data using a proposed combination. In this case the possibility of drug-drug interactions need to be investigated. (see Note for Guidance on Fixed Combination Medicinal Products CPMP/EWP/240/95).

Rescue medication, if allowed for as a combination therapy should be predefined in the study plan.

2.4 Study duration

The required duration of exposure depends largely on the type of trial, the chosen endpoint, the sensitivity of applied and accepted assessment methods, and the nature and the magnitude of the effects of the agent studied.

Anti-inflammatory effects, or improvement of symptoms such as pain, may for example be evaluated between at least 4 up to 12 weeks. For disease modifying therapies study duration of not less than 6 months is necessary, alternative study designs such as randomised withdrawal study design should be considered (see 2.1).

Efficacy data from adults should be supplemental to the efficacy determination in children.

The requirement for long-term efficacy and safety data to be provided for paediatric patients should be balanced against the need to make effective treatments available to a population of patients with a clear unmet medical need. Where data in the adult population are available and are consistent with the profile observed in paediatric patients, it would appear to be unnecessary and potentially unethical, to require a large efficacy and safety database, including data from long-term exposure, to be provided for paediatric patients.

IV. CLINICAL SAFETY EVALUATION

1. Specific adverse events to be monitored

Assessment of the potential adverse events (AE) according to the mechanism of action should be performed using a systematic and planned methodology. It is important to realise that because of the chronic nature of JIA implying long-lasting medical treatment in vulnerable phases of physical and social development adverse drug reactions must be detected as early as possible and signals be identified with high sensitivity. Due to the lack or low number of studies and patients involved adverse events and their frequency are not as well documented in children as in adults. Special attention should be paid to the fact that the spectrum of adverse reactions might differ in children in comparison to adults (e.g. with NSAIDs less gastrointestinal but more centralnervous system adverse events). Long-term data, either while patients are on chronic therapy or during the post-therapy period, are necessary to determine possible effects on skeletal, behavioural, cognitive, sexual and immune maturation and development.

With drug substances severely affecting important physiologic organ functions the early detection of the comprehensive adverse reaction profile for any newly introduced drug substance and especially any newly introduced therapeutic class presents a considerable challenge.

2. Extent of population exposure to assess clinical safety

The ICH/EU E1A guideline (Note for Guidance on Population Exposure: the Extent of Population Exposure to Assess Clinical Safety) should be followed in addition to other relevant guidelines.

3. Long-term safety

To assess clinical safety and identify relevant adverse reactions an observation period of not less than twelve months is required. Taking into consideration the chronicity of the disease and the need for long-term treatment longer periods may even be more appropriate. The safety database should be supported by reference to available data on the use of the product in other indications (e.g. adult RA) and through extensive monitoring in the post-marketing setting.