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Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis

Draft

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The proposed guideline will replace the guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (CPMP/EWP/422/04)

Comments should be provided using this template. The completed comments form should be sent to RIWPsecretariat@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

Executive summary

Juvenile idiopathic arthritis consists of multiple subtypes some of which have counterparts in the more frequent adult diseases of rheumatoid arthritis (RA), axial spondyloarthritis and psoriatic arthritis (PsA) although with considerable differences in phenotype at different ages. Since the Paediatric Regulation came into force, several paediatric investigation plans for new and authorised treatments in adults have been evaluated by the Paediatric Committee (PDCO). This document is based on the changes in clinical practice in JIA which have followed on from advances in diagnosis and treatment, the accumulated experience with JIA Paediatric Investigation Plans (PIPs) and on the conclusions of the EMA paediatric rheumatology expert meeting in 2010. This document is a revision of the Guideline adopted in October 2006. It takes into account recent developments relating to study design and also validated disease activity evaluation tools to assess important clinical and structural outcomes.

This guideline aims to facilitate the preparation of future MAA applications and is intended to provide guidance on the clinical development of medicinal products for the treatment of juvenile idiopathic arthritis.

A multidisciplinary approach is advocated for optimal care of JIA including patient engagement and with focus on functional and psychosocial outcomes.

In contrast to adults, NSAIDs are considered a first–line treatment option in newly diagnosed JIA, followed by glucocorticosteroids (intra-articular or systemic) and DMARDs (disease modifying anti rheumatic drugs). The latter include both synthetic (methotrexate (MTX), sulfasalazine) and biological DMARDs. For systemic JIA, high doses of systemic steroids are often indicated, in contrast to non-systemic JIA.

The most common synthetic DMARD used in JIA is methotrexate. The introduction of biological therapies has resulted in a significant advance in therapy for JIA. However there remains still a clinical need for new therapies. There is also a need for data on established therapies and for paediatric formulations.

As a result of the advances in therapies available for JIA and also in the adult RA field, therapeutic strategies are now employing more aggressive intervention in early disease, often using combinations of synthetic DMARDs with targeted biologics and these approaches have resulted in faster onset of action and more profound clinical responses than traditional approaches. Goal-directed treat-to-target strategies are now employed. This makes a modified recommendation for the assessment of these therapies necessary. A further area of clinical relevance is when to stop treatment in responders and this needs to be addressed in on going registries following authorisation.

In addition, the elements for the assessment of safety issues which should be considered when developing new pharmacological treatments have to be updated. The demonstrated safety profile will be essential for the benefit-risk balance in a defined patient population. Long-term safety of disease modifying agents requires careful attention in view of potential serious adverse events caused by immunomodulation in children.

1. Introduction (Background)

Chronic arthritis in childhood is a heterogeneous group of diseases for which various classification systems have been developed, including the American College of Rheumatology (ACR) criteria for the classification of juvenile rheumatoid arthritis (JRA), the European League Against Rheumatism (EULAR) criteria for juvenile chronic arthritis (JCA), the European Spondylarthropathy Study Group (ESSG)

criteria for spondylarthropathy, and the Vancouver Criteria for juvenile psoriatic arthritis (JpsA). Among these classification systems there are gaps and overlaps and no one system is universally accepted.

JIA refers to arthritis of at least 6 weeks duration of unknown aetiology that begins in children less than 16 years old. JIA has an annual incidence of 0.008-0.226 per 1000 children and a prevalence of 0.07-4.01/1000 children. JIA is less common than RA in adults but it is one of the most common systemic autoimmune diseases in children and adolescents. Children of all age groups may be affected although onset during the first year of life is rare and restricted predominantly to systemic JIA. In some of the categories girls predominate and there are racial differences in incidence and relative frequency of JIA subtypes.

The International League of Associations for Rheumatology (ILAR) introduced a nomenclature and classification for juvenile idiopathic arthritis (JIA). The aim of this system was to replace the combination of pre-existing systems with one classification that identifies more homogeneous populations that can be used internationally to facilitate communication and research. Although the ILAR classification may be reviewed in the future, at present this is the system which is recommended for use.

The currently used ILAR classification distinguishes the following JIA categories:

- Systemic JIA (sJIA)
- Polyarthritis rheumatoid factor negative
- Polyarthritis rheumatoid factor positive
- Oligoarticular arthritis (2 subcategories based on joint count after 6 months)
    - Persistent (not more than 4 joints)
    - Extended (more than 4 joints)
- Psoriatic arthritis (JIA-PsA)
- Enthesitis related arthritis (ERA)
- Undifferentiated arthritis

Rheumatoid arthritis (RA), axial spondyloarthritis, and psoriatic arthritis (PsA) are diseases in adults that correspond most closely to individual categories of JIA with similar clinical manifestations and underlying immunologic mechanisms (i.e. polyarticular JIA, ERA and JIA-PsA respectively). They are all covered by the overarching condition: chronic idiopathic arthritis (including RA, axial spondyloarthritis, PsA and JIA). In view of this any medicinal product being developed for adults should also be investigated in the paediatric population. Whenever the development of a new medicinal product is considered in any of the (above mentioned) adult diseases, the inclusion of JIA in the development is required.

Although the aetiology and pathogenesis of JIA are not fully understood, it is however known that JIA shares many of the pathological abnormalities that have been identified in RA. Increased production of cytokines (e.g.interleukin-1ß interleukin-6, TNF-α) in conjunction with osteoclastic cell activation leads to degradation of adjacent cartilage and bone. Increased knowledge of these factors may help to redefine the classification of JIA in terms of aetiology, response to treatment, risk of relapse or prognosis.

JIA is a major cause of disability in children. In addition JIA may be accompanied by chronic anterior iridocyclitis/uveitis particularly in anti-nuclear antibody (ANA) positive females. Early ophthalmology

referral, early diagnosis and treatment are the major determinants of prognosis in uveitis associated with JIA.

Additional non-articular complications may include rash, fever, serositis and macrophage activation syndrome.

Long-term complications resulting from longstanding inflammation and steroid therapy can include growth retardation with reduced final adult height, body composition changes with reduced bone and muscle mass, metabolic complications and osteoporosis. These physical complications as well as the ongoing disease itself can impair educational, social and emotional development, thereby highlighting the need for early effective treatment.

The prognosis in general depends on the clinical category of JIA, the severity, the rapidity of diagnosis, appropriate referral, initiation of optimal therapy and response to treatment.

In addition to suppressing signs and symptoms of arthritis, the ultimate goal of treatment of JIA in all categories should be the induction of remission for which, validated criteria have been described, or the attainment of minimal disease activity or inactive disease. The aim of modern treatment of JIA is rapid suppression of inflammation in order to prevent joint damage, maximise physical function and promote normal growth and development. In addition, in some categories, additional goals are relevant such as control of systemic signs and symptoms including fever, treatment of uveitis, treatment of macrophage activation syndrome and reduction of corticosteroid dose.

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, remission off treatment. Unanswered questions remain relating to how long to continue therapy once a clinical remission is achieved.

2. Scope

The scope of this guideline is to provide a European common position on pertinent issues relating to the clinical evaluation of medicinal products for the treatment of JIA.

It intends to facilitate the preparation of future MAA applications for new products being developed for the treatment of JIA.

The guideline addresses specific issues related to the extrapolation of efficacy from other age groups and corresponding arthritis diagnoses, and assessment of disease activity.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles and Part I and II of the Annex I to Directive 2001/83/EC as amended. Applicants should also refer to other relevant European and ICH guidelines (in their current version), especially those on:

- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population (CPMP/ICH/2711/99; ICH E11)
- Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)
- Reflection Paper on Methodological Issues in Confirmatory Clinical Trials with Flexible Design and Analysis plan (CHMP/EWP/2459/02.

- The Extent of Population Exposure to Assess Clinical Safety for Drugs (CPMP/ICH/375/95; ICH E1A)
- Concept paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012)
- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (EMEA/CHMP/EWP/147013/2004)
- Note for Guidance on Choice of Control Group in Clinical Trials (CPMP/ICH/364/96; ICH E10)
- Guideline on Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1).

4. Patients characteristics and selection of patients

In general patients with moderate to severe disease activity should be included to enable demonstration of a sufficient treatment response.

4.1. Patient populations to be studied

JIA is rare in children below 1 year of age. The clinical development programme should include children as young as 1 year and older unless there are significant safety concerns or signals (occurrence of significant adverse events in animals or adults) that preclude the inclusion of certain age groups.

The ILAR category of each patient enrolled into trials needs to be defined as this is important for cross-trial comparisons. However in order to facilitate translation of clinical trial results into routine clinical care The American College of Rheumatology has identified five target JIA treatment groups with distinctive clinical courses and therapeutic approaches, and use of grouping patients into these treatment groups is encouraged:

- History of arthritis of 4 or fewer joints (this will include those with 4 of fewer joints in the ILAR categories of persistent oligoarthritis, psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis)
- History of arthritis of 5 or more joints (this will include those with 5 or more joints in total throughout their disease in the ILAR categories of extended oligoarthritis, polyarthritis both RF-positive and RF-negative, psoriatic arthritis, enthesitis related arthritis, and undifferentiated arthritis).
- Active sacroiliac arthritis. (ILAR ERA category mainly)
- Systemic arthritis with active systemic features (and without active arthritis)
- Systemic arthritis with active arthritis (and without active systemic features).

The expert paediatric meeting at the EMA in 2010 (EMA/836276/2010) concluded that systemic arthritis with and without active systemic features can be considered one group and studied together.

Each of the 4 target patient population groups have to be addressed with regards to the potential benefits and risks of the proposed treatment. The development programme (clinical trial or extrapolation of efficacy analysis) should be proposed where the need exists and a therapeutic benefit is expected. If appropriate, patients from different treatment groups may be merged into one clinical trial with subgroup analysis performed. In most cases patients with ERA can be studied together with patients with polyarthritis and extrapolation of efficacy is acceptable for persistent oligoarthritis.

Systemic JIA should be studied separately, as background therapy and response to established DMARDs is different between systemic and non-systemic JIA.

Age of the patients to be studied

Clinical trials or extrapolation analysis should cover the following age groups:

- Systemic JIA : from 1 to less than 18 years
- Polyarthritis (RF pos and RF neg and extended oligoarthritis): from 2 to less than 18 years
- Oligoarticular arthritis (persistent and extended): from 2 to less than 18 years
- Enthesitis related arthritis and psoriatic arthritis: from 12 to less than 18 years

Long-term follow-up e.g. in registry type studies should include young adults as well.

For clinical programmes that include undifferentiated arthritis, seeking CHMP scientific advice is recommended.

Due to the rarity of JIA particularly in certain age groups it cannot be expected that the efficacy is fully demonstrated in all age groups. The development should consist of a mix of trial data, extrapolation data from other age-groups or other corresponding conditions and commitment to post-authorisation studies and/or registries.

4.2. Potential confounding factors

The selection of patients will require that disease related factors are documented appropriately according to the ILAR criteria. Age of onset, duration of the disease, presence/absence of ANA, extra-articular features such as uveitis, macrophage activation syndrome, disease activity and the presence of joint damage should all be fully documented at baseline.

In addition pain scores, concomitant diseases as well as the occurrence of antibodies to the drug have to be carefully documented.

The previous exposure of the trial population to anti-rheumatic therapies should be recorded, as this information may be relevant to the interpretation of study results and to the proposed indicated population. Sufficient washout of prior therapies has to be justified and be in accordance with ethical considerations.

The target population should match the proposed therapeutic indication. Relevant subgroup analyses should be prospectively planned (e.g. age group, ILAR classification).

Other treatment modalities interfering with study treatment are of particular importance. Concomitant non-pharmacological treatment (e.g. physical therapy) and medication for diseases other than rheumatic disease must be completely documented and where possible it is recommended that these treatments are standardised and predefined.

5. Methods to assess efficacy

5.1. Extrapolation of efficacy

An analysis of extrapolation opportunities has to be performed to spare children from unnecessary trials where reasonably accurate information may be obtained by other means. This can be the case for example in well-studied pharmacological classes or when a considerable amount of data has been collected in adults (e.g. licensed indication in one or more of the corresponding adult arthritis

categories), or in other diseases in children with the medicinal product (see Concept paper on extrapolation of efficacy and safety in medicine development, EMA/129698/2012).

Extrapolation may result in a reduction in the amount of data required (size of trial, focus on subpopulations or certain ages only, exploratory/confirmatory design of the study). In some instances it is even possible that the evidence from extrapolation may obviate the need for an efficacy trial, and the need for clinical trials might be limited to PK and dose finding studies. The results of the extrapolation analysis, if agreed and used for marketing authorisation, would have to be supported by post-marketing data.

5.2. Assessment of symptoms and disease activity

Primary endpoints

The primary endpoint chosen depends on the category of JIA being studied and the design of the trial. For parallel randomised trials in all JIA categories other than sJIA, the recommended primary endpoint is the change in ACR paediatric core set criteria.

Paediatric JIA core set:

- number of active joints,
- number of joints with limited range of motion,
- physician's global assessment,
- patient/parent's global assessment,
- functional ability
- laboratory marker of inflammation

For sJIA fever should be added to the core set parameters.

Definition of improvement: The ACR paediatric improvement criteria (Pedi 20, Pedi 30, Pedi 50, Pedi 70, Pedi 90 and Pedi 100) are measures that describe a change in disease activity relative to baseline and therefore are a tool for assessment of clinically relevant improvement in disease activity. The ACRPedi 30 requires a minimum of 30% improvement from baseline in a minimum of 3 out of 6 components, with no more than one component worsening by >30%.

The level of improvement to be met should be pre-defined, be clinically meaningful and the results should be statistically significant. The proportion of patients with at least 30% improvement at a time point no later than 12 weeks would be an acceptable primary endpoint (ACRPedi 30). This level of improvement would also be expected as minimum for the lead-in phase for a randomised withdrawal trial design. Demonstration of clinically highly relevant decrease in disease activity, such as ACRPedi 50-70 responses should be pursued.

Low disease activity, inactive disease or remission (on and/or off treatment) are alternative suitable primary endpoints.

For a randomised withdrawal design study the percentage of patients with occurrence of disease flare or the time to flare should be the primary end-point. Preliminary definitions of flare in JIA have been described, namely a ≥30 % worsening in at least three of the six JIA core set variables with a ≥ 30% improvement in not more than one of the six JIA core set variables, and justification for the definition of flare utilised will be required.

Secondary and supportive endpoints

Suitable secondary endpoints include:

- ACR Pedi 50, 70, 90, and 100
- Remission
- Individual components of the ACRPedi score
- Pain assessment using age-appropriate assessments
- Percentage of patients with flare/time to flare,
- Time course of response - additional efficacy assessments at earlier time points should be performed as secondary endpoints in order to provide information on the speed of onset of effect.
- Absolute disease activity. The limitation of a dichotomous readout (ACR Pedi percentage improvement) is that it does not provide information on the absolute disease activity. For this a validated composite disease activity score for JIA has been developed; the juvenile arthritis disease activity score (JADAS). Measurement of JADAS score should be performed as a secondary endpoint. Additional disease activity assessment tools can be considered if sufficiently validated.
- Evidence of slowing/prevention of joint structural damage (see section 5.3)
- Quality of life (e.g. CHQ), school attendance
- Juvenile Arthritis Multidimensional Assessment Report (JAMAR)
- Reduction in glucocorticoid use (particularly in sJIA)
- For specific subsets additional endpoints such as incidence/severity of uveitis or systemic inflammation could also be chosen. Tender entheseal score and modified Schober's test could be used in ERA and PASI responses for subjects with PsA.

5.3. Assessment of structural damage

Although the van der Heijde score is validated and can be used, the use of alternative methods which minimise exposure to radiation are encouraged for assessment of structural damage.

Preliminary validation of MRI techniques in JIA has been conducted and the use of MRI for older children where this can be performed without sedation and with further in-study validation would be welcomed. The use of MRI may enable detection of active synovitis in the absence of clinical signs and symptoms and may aid in a further refinement of a definition of remission in JIA. The ability of ultrasound to distinguish tendonitis from synovial inflammation could also be considered if patients with ERA are included in the trial.

6. Strategy and design of clinical trials

6.1. Early Studies in Children

Pharmacokinetic aspects in different age ranges

Usual measures to determine PK/PD properties (including immunogenicity where appropriate) have to be proposed for every new product. Age-specific changes in PK profile have to be addressed (see Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population, EMEA/CHMP/EWP/147013/2004). If a modelling and simulation approach is taken, using

data from adults and other diseases; validation of the model and analysis of its applicability to all age groups and JIA subtypes must be performed.

Where appropriate, well-planned dose ranging studies should be carried out. The target plasma level in children should be based, where possible, on appropriate pharmacokinetic parameters identified in adults e.g. most commonly AUC and C_{min} for chronic dosing. If a pharmacodynamic marker is available from adult studies then this should also be used to assist dose-finding in JIA. Inter-individual differences in PK/PD relationship need to be evaluated and where appropriate individual dosing based on therapeutic drug monitoring may be necessary.

6.2. Therapeutic confirmatory studies

6.2.1. Study design

Parallel group design

In situations where extrapolation of efficacy is not possible, the parallel group design provides the most robust evidence for efficacy and safety. Ideally, randomised placebo or active comparator controlled trials (RCT) should be conducted for efficacy evaluation and this is especially required where the drug has a novel mechanism of action and there is little data available on efficacy or safety from adult exposure. It is acknowledged that there is a limited pool of patients available for clinical trials in JIA. Calculation of the sample size and a feasibility analysis should be performed and if a RCT is not possible, alternative designs can be proposed.

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 and placebo). Trials convincingly demonstrating superiority to placebo and non-inferiority or equivalence to the active comparator are regarded as high-quality evidence. In a paediatric study there may be ethical concerns about including a placebo-arm when safe and effective alternative medication is available. These concerns have to be balanced against shortcomings due to a missing placebo control.

An alternative option is a two-arm study comparing the new agent with an established active comparator, seeking to show that the test product is superior in terms of relevant endpoints. The Note for Guidance on Choice of Control Group on Clinical Trials (CPMP/ICH/364/96) should be followed. A three-arm study design (verum, active comparator and placebo) with the placebo period being short and the test and the active control arms continuing for a longer period may be considered. Add-on placebo therapy may also be used when study design requires placebo and allows for combination with other effective treatment. This can be studied in a two-arm superiority 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.

Each of these designs allows 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 in which efficacy measures are observed after randomised and blinded withdrawal is recommended.

Randomised placebo controlled withdrawal design

For products where efficacy and safety have been established in adults, randomised placebo controlled withdrawal design trials have been accepted for many authorisation studies in JIA. An initial open-label phase with the new agent is followed by randomisation of responders to a double-blind phase in which they receive either test agent or placebo. The disadvantages of such a study design are non-conventional efficacy demonstration, bias towards responders and a small safety database. However these shortcomings are expected to be outweighed by the advantages of having a feasible size of population, short placebo exposure, and better acceptability for patients, parents and health care professionals. This design does not represent an ideal method for the confirmation of safety and efficacy, therefore there is a need for long-term post-marketing observational studies (i.e. registries) to confirm effectiveness and evaluate safety in larger populations. To minimise exposure of children to ineffective treatments the futility analysis should be performed at the end of the lead-in open label phase of the randomised withdrawal trial and if the pre-defined level of improvement is not met before randomisation the study should be discontinued.

Randomised placebo controlled withdrawal design trials could also be acceptable in patients with severe JIA for whom few treatment options are available. When used with early escape rules, such as return of symptoms (disease flare) the period of exposure with poor response that a patient would have to undergo remains short.

A randomised withdrawal design in patients in remission is considered optimal to evaluate lower maintenance doses or withdrawal.

The studies whether parallel group or randomised withdrawal design should actively analyse biological or environmental causes for treatment responsiveness or resistance in individual patients. This may include detailed individual exposure/response analysis and analysis of biological samples to identify the genetic risks for and underlying mechanisms of disease manifestation and treatment responses in individual JIA subtypes.

6.2.2. Choice of control

Placebo

Efficacy of agents claiming improvement in disease activity and/or function is generally established by means of placebo controlled trials. Since it would be unethical to retain a child with JIA on placebo treatment long-term, the duration of placebo control must necessarily be limited. Predefined rules for early escape should be provided and a Data Safety Monitoring Board included in the protocol.

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 should be justified, taking into account licensed indications, posology, age range, JIA category, mode of action, expected treatment effect, time to onset of efficacy, duration of action, safety etc. depending on study objectives.

6.2.3. 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 improved 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 the proposed combination. In this case the possibility of drug-drug interactions need to be investigated. For guidance on fixed drug combinations see Guideline on Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1).

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

6.2.4. Study duration

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

Anti-inflammatory effects, relief of symptoms such as pain or maintenance of symptomatic improvement should be evaluated for up to 12 weeks. The earliest time point of evaluation of efficacy will be determined by the drugs expected mechanism of action and the levels of disease activity in the trial population.

For DMARDS where efficacy in adults is established, a minimum duration of 3 months is required followed by open-label extension phases. For drugs where no adult efficacy data is available the duration of the study depends on mechanism of action, PD and needs to be decided individually. If feasible additional evidence supportive of a positive effect on joint structure of a least 6-12 months is also encouraged (see section 5.3). The long-term efficacy and safety data may be provided pre- or post licensure, as justified.

Where data in the adult population are available and are consistent with the profile observed in paediatric patients, it is unnecessary to require a large efficacy and safety database at the time of submission of the marketing authorisation.

Because the marketing authorisation would be based on limited information on short-time efficacy (and safety), it is necessary to collect further data from patients treated with the medicinal product after marketing in the observational registry-type of study.

The following minimum set of data is recommended to be collected:

- Age, sex, ethnicity, country of residence
- JIA category, duration of the disease, comorbidities
- Medication history (active and concomitant treatment, previous treatments – dosage and duration)
- Uveitis, Macrophage activation syndrome – presence, past, specific treatment
- Growth and maturation parameters (weight, height, Tanner score)
- Measures of activity and damage (number of active joints, joints with limited motion, damage index)
- Patient/parent reported outcome measures (patient's/parent's and physician's global score, quality of life score)
- Laboratory parameters (ESR, CRP, ANA)
- Adverse events (serious adverse events, adverse reactions, events of specific interest)

JIA is a fluctuating, flaring disease. Moreover, for some forms of JIA, the risk of flares decreases with aging. For the trials on new drugs, mostly paediatric patients with acute flares will be included.

However, once the patients are stabilised in remission, lower maintenance dosages and even drug withdrawal may be appropriate. It is expected that options of dose-reduction and dose-interruption and re-treatment at relapse are addressed which could be performed in a randomised withdrawal phase (see section 6.2.1.)

7. Clinical safety evaluation

7.1. Specific adverse events to be monitored

Due to the lack or low number of studies and patients involved, adverse events (AE) and their frequency are not as well documented in children as in adults.

Assessment of adverse events, especially those predicted by the pharmacodynamic properties of the investigational product (events of special interest) 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 identified with high sensitivity. 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 central nervous system adverse events). Post-study/post-authorisation long-term data, either while patients are on chronic therapy or during the post-therapy period, are necessary to determine possible effects on maturation and development.

If there are concerns on the medicine's impact on the immune system that cannot be addressed in the pre-clinical development but can be answered by clinical studies in children (development of immune system, response to vaccination, etc.), appropriate studies or sub-studies should be conducted.

The long-term evaluation of safety requires collection of data from larger number of patients for a longer period of time, potentially into adulthood. Therefore safety data should also be collected in the post-marketing observational registry-type studies (see section 6.2.4.). The protocols for such studies should define and record the identifiable or theoretical risks of the medicinal product. The registry should preferably be an established disease-based (rather than product-based) clinical registry and allow collection of long-term data from patients treated with different medicinal products. Acceptance of data from disease-specific registry for fulfilment of post-marketing obligations needs to be agreed in advance.

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