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

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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)

Keywords	Juvenile idiopathic arthritis, Systemic JIA, Oligoarthritis, Polyarthritis, Enthesitis related arthritis, Extrapolation

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

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List of abbreviations

ACR	American College of Rheumatology
ACR Pedi	ACR paediatric improvement criteria
ANA	Anti-nuclear antibody
AUC	Area under the curve
CHMP	Committee for Human Medicinal Products
CRP	C-reactive protein
DMARD	Disease modifying antirheumatic drug
EMA	European Medicines Agency
ERA	Enthesitis related arthritis
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
ESSG	European Spondylarthropathy Study Group
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILAR	International League of Associations for Rheumatology
JADAS	Juvenile arthritis disease activity score
JIA	Juvenile idiopathic arthritis
MAS	macrophage activation syndrome
MRI	Magnetic resonance imaging
MTA	Methotrexate
C_{min}	Minimum concentration
NSAID	Nonsteroidal anti-inflammatory drug
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PD	Pharmacodynamic
PASI	Psoriasis area and severity index
PsA	Psoriatic arthritis
RCT	Randomised controlled trial
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SmPC	Summary of Medicinal Product Characteristics
sJIA	Systemic JIA
TNF-α	Tumor necrosis factor-alpha

Executive summary

Juvenile idiopathic arthritis (JIA) is currently grouped in multiple categories 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 (PIPs) 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 that have followed on from advances in diagnosis and treatment, the accumulated experience with JIA PIPs and on the conclusions of the European Medicines Agency (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 marketing authorisation applications and is intended to provide guidance on the clinical development of medicinal products for the treatment of JIA.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered a first–line treatment option in most cases of newly diagnosed JIA, followed by intra-articular glucocorticosteroids and disease modifying antirheumatic drugs (DMARDs). The latter include both synthetic (methotrexate (MTX), sulfasalazine) and biological DMARDs. For systemic JIA (sJIA), high doses of systemic steroids are often indicated, in contrast to non-systemic JIA. The introduction of biological therapies has resulted in a significant advance in therapy for JIA. However there still remains 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 and treat-to-target strategies. A modified recommendation for the assessment of these therapies is therefore necessary. A further area of clinical relevance is when to deescalate treatment in responders and when to stop after achieving remission. These points need to be addressed e.g. in extension studies and 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, the European League Against Rheumatism (EULAR) criteria for juvenile chronic arthritis, the Vancouver Criteria for juvenile psoriatic arthritis, and others not formally evaluated in children such as the European Spondylarthropathy Study Group (ESSG) criteria for spondylarthropathy. Among these classification systems there are gaps and overlaps and no one system has been universally accepted.

The International League of Associations for Rheumatology (ILAR) has introduced a nomenclature and classification for 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 recommended system for use.

The currently used ILAR classification distinguishes the following JIA categories:

- Systemic arthritis (sJIA)

- Polyarthritis rheumatoid factor (RF) negative

- Polyarthritis RF positive

- Oligoarthritis (2 subcategories based on joint count beyond 6 months)

    o Persistent (not more than 4 joints)

    o Extended (more than 4 joints)

- Psoriatic arthritis (JIA-PsA)

- Enthesitis related arthritis (ERA)

- Undifferentiated arthritis

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 2-20 cases per 100 000 population and a prevalence of 16-150 cases per 100 000 population. 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 sJIA. In some of the categories girls predominate whereas in ERA boys predominate, and there are racial differences in incidence and relative frequency of JIA categories.

RA, axial spondyloarthritis, and 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 all are 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 is required, unless there is a reason to believe that the product is likely to be ineffective or unsafe in part or all of the paediatric population, or that the product has no potential therapeutic benefit in children.

Although the aetiology and pathogenesis of JIA are not fully understood, it is known that JIA shares many of the pathological abnormalities that have been identified in RA. At the same time multiple differing pathogenesis and phenotypic features exist between the JIA categories. Increased production of cytokines in different forms of JIA (e.g.interleukin-1ß and interleukin-6 in sJIA, tumor necrosis factor-alpha (TNF-α) in polyarticular JIA) in conjunction with osteoclastic cell activation leads to degradation of adjacent cartilage and bone. Increased knowledge of these factors including understanding their genetic background 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. Long-term complications resulting from longstanding inflammation and glucocorticoid therapy can include joint erosions and deformities, 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. In addition, specific types of JIA may be accompanied by chronic anterior iridocyclitis/uveitis particularly in anti-nuclear antibody (ANA) positive females with oligoarthritis. Early ophthalmology referral, early diagnosis and treatment are the major determinants of prognosis in uveitis associated with JIA.

Additional non-articular features of sJIA may include rash, fever, serositis and macrophage activation syndrome (MAS).

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.

A multidisciplinary approach is advocated for optimal long-term care of JIA including patient engagement and with focus on functional and structural outcomes (joint damage, vision) and psychosocial outcomes. In addition to suppressing signs and symptoms of arthritis, the ultimate goal of treatment of JIA in all categories should be the induction of clinical remission 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, treatment of uveitis, prevention and treatment of MAS and reduction of glucocorticoid 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, clinical remission on and 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 marketing authorisation applications for new products being developed for the treatment of JIA.

The guideline addresses specific issues related to the design of clinical studies, 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 to the following:

- 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 the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99)

- Guideline on Clinical Trials in Small Populations (CHMP/EWP/83561/2005)

- Guideline on Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1).

4. Patients characteristics and selection of patients

4.1. Patient populations to be studied

JIA is rare in children below 1 year of age. The clinical development program 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, or unless there is evidence that the product is not likely to be effective or beneficial in certain age groups.

In general patients with moderate to severe disease activity e.g. based on juvenile arthritis disease activity score (JADAS) should be included to enable demonstration of sufficient treatment response. Specific criteria for the different JIA categories should however be identified.

The ILAR category of each patient enrolled into trials needs to be defined as this is important for cross-trial comparisons. The evaluation of safety and efficacy in JIA categories should be proposed where feasible, and the rational to include or exclude any specific category in the development program should be adequately documented. In order to facilitate translation of clinical trial results into routine clinical care, the ACR has identified the following target JIA treatment groups with distinctive clinical courses and therapeutic approaches:

- History of arthritis of 4 or fewer joints (this will include those with 4 of fewer joints in the ILAR categories of persistent oligoarthritis, PsA, ERA 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, PsA, ERA, and undifferentiated arthritis).

- Active sacroiliac arthritis (ILAR categories ERA and PsA)

- 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. Based on the outcome of this expert meeting, patients can be grouped into the following treatment groups:

a) Polyarticular course JIA (patients with history of involvement of more than 4 joints, no sJIA and no ERA)

b) Oligoarticular course JIA (patients with history of involvement of no more than 4 joints, no sJIA and no ERA)

c) sJIA (including both with and without current active systemic features)

d) ERA, as defined by ILAR criteria.

Each of the 4 target patient population groups have to be addressed with regards to the potential benefits and risks of the proposed treatment. A development program (clinical trial or extrapolation of efficacy analysis) should be proposed where the need exists and a therapeutic benefit for JIA as a group of diseases is expected. If appropriate, patients from different treatment groups may be merged into one clinical trial with subgroup analysis performed. For example patients with ERA can be studied together with patients with polyarthritis. Usually extrapolation of efficacy from polyarthritis is acceptable for persistent oligoarthritis, where systemic therapy is exceptionally indicated. SJIA should be studied separately, as background therapy and response to established DMARDs is different between systemic and non-systemic JIA.

The grouping of patients, in particular of those with sJIA, can be adjusted with appropriate scientific justification based on increasing knowledge of the pathophysiology and the subpopulations of the disease.

Age of the patients to be studied

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

• Systemic JIA : from 1 years

• Other JIA categories: from 2 years.

Specific studies in adult patients with JIA (where disease started before the 16th birthday) are not required, but these patients should nonetheless be considered in the development and labelling of new medicines by

• Extrapolation from children

• Extrapolation from RA

• Or where necessary inclusion into clinical studies.

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

Due to the particular rarity of JIA 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

Age of onset, duration of the disease, family history, presence/absence of ANA, extra-articular features such as uveitis, enthesitis, dactylitis and nail changes, MAS, disease activity and functional ability recorded according to a validated score, 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 (where appropriate) have to be carefully documented.

The previous and concomitant 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 (e.g. age group, ILAR classification) and exploratory analyses (e.g. genetics, pharmacodynamics markers) should be prospectively planned.

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 conditions should be documented and predefined where possible.

5. Methods to assess efficacy

5.1. 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 primary endpoint has historically been the change in ACR paediatric core set criteria.

Paediatric JIA core set variables are:

- physician global assessment of disease activity
- parent/patient global assessment of overall well-being
- functional ability
- number of joints with active arthritis
- number of joints with limited range of motion
- laboratory marker of inflammation (erythrocyte sedimentation rate ESR or C-reactive protein CRP)

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

Definition of improvement: The ACR paediatric improvement criteria (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 ACR Pedi 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.). Demonstration of clinically highly relevant decrease in disease activity, such as ACR Pedi 70 response is expected.

With adequate justification, ACR Pedi 30 or 50 could be acceptable primary endpoints in hard-to-treat patients.

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.

Minimal disease activity and inactive disease / remission (treat to target approach):

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). Three versions of the JADAS were developed, which differ in the active joints count incorporated: JADAS10, JADAS27, and JADAS71. The JADAS components were selected from those included in the ACR paediatric core set and include the following four variables:

- physician global assessment of disease activity,

- parent/patient global assessment of well-being,

- active joint count,

- laboratory marker of inflammation (ESR or CRP).

Due to recent therapeutic advances, novel endpoints reflecting low disease activity and remission have become established treatment targets in the field and are the preferred primary endpoints. These endpoints include minimal disease activity and inactive disease based on the JADAS, and inactive disease / clinical remission (on and/or off treatment) based on the ACR. The cut-off values in the JADAS that correspond to various states of disease activity were recently developed. The ACR definition of inactive disease includes no arthritis, no systemic JIA signs/symptoms, no uveitis, normal markers of inflammation, normal physician's global assessment of disease activity, and absence of morning stiffness. When the definition of inactive disease status is met for 6 continuous months, the patient is considered to be in clinical remission on medication. When the inactive disease status is met for 12 months in the absence of any medication, the patient is classified as being in a state of clinical remission off medication.

Secondary and supportive endpoints

Suitable secondary and supportive endpoints include:

- ACR Pedi 30, 50, 70, 90, and 100

- Individual components of the ACR Pedi score

- Minimal disease activity and inactive disease / remission (if not chosen as the primary endpoint)

- Pain assessment by parent/patient 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 based on the JADAS. Additional disease activity assessment tools can be considered if sufficiently validated.Evidence of slowing/prevention of joint structural damage (see section 5.2)

- Quality of life with a validated tool, school attendance

- Functional ability with a validated tool

- Reduction/discontinuation in glucocorticoid use (particularly in sJIA)

- Reduction of systemic inflammation (particularly in sJIA)

- Tender entheseal score, overall back pain and nocturnal back pain, and modified Schober's test can be used in ERA as endpoints. Physician´s global assessment and psoriasis area and severity index (PASI) responses can be used for subjects with PsA.

- Other endpoints and indexes specifically validated in JIA categories at the time of planning of the clinical trial should also be considered.

Whenever appropriate specific trials should be performed in JIA associated uveitis. In clinical trials in JIA with the exception of systemic JIA, data should be collected on the incidence and severity of uveitis, including ANA status.

5.2. Assessment of structural damage

There is little experience on the prevention of structural joint damage in clinical trials in JIA. Particularly the novel endpoints reflecting low disease activity are expected to serve indirectly as an indicator for the prevention of structural damage. It is recommended to monitor structural damage routinely in long-term trials as a safety measure. If an additional claim to prevent structural damage is warranted randomised controlled studies should be performed. The modified van der Heijde score is a validated method for the assessment of structural damage in children by the evaluation of wrist and hand x-rays. Other validated measures can be considered when available to minimise exposure to radiation.

Preliminary validation of magnetic resonance imaging (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 use of ultrasound to evaluate tendonitis and synovial inflammation could also be considered. MRI and ultrasound assessments can be considered as exploratory endpoints since no final validation studies are currently available.

6. Strategy and design of clinical trials

6.1. Extrapolation of efficacy

The possibility of waiving efficacy studies in certain subgroups of children should be considered in order to spare children from unnecessary trials, when reasonably accurate information may be obtained by other means. This can be the case for example in well-studied pharmacological classes or when 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 children treated with the same medicinal product for other diseases (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). Pharmacokinetic

and dose finding studies in the target population are needed. In some instances the evidence from extrapolation may obviate the need for a formal efficacy trial. E.g. for medicines where a clear PK-PD (pharmacokinetic/ pharmacodynamic) relationship and therapeutic window has been established in adult arthritis models, PK and dose finding studies could potentially be supported by single arm studies. The results of the extrapolation analysis, if agreed and used for marketing authorisation, would have to be supported by post-marketing data.

6.2. Early studies in children

Pharmacokinetic aspects in different age ranges

The planning of the studies especially for PK should normally follow a staggered approach by providing proof of the proper dosing for the older children and then moving to the younger age groups. Usual measures to determine PK/PD properties (including immunogenicity where appropriate) have to be proposed for every new product. Age-specific and/or body weight related 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 PK parameters identified in adults e.g. most commonly AUC and C_{min} for chronic dosing. If a PD 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 individual dosing based on therapeutic drug monitoring may be necessary in some cases. The rational for the use of fixed dosing regimens instead of per kg or per m^2 dosing should be adequately explained.

6.3. Therapeutic confirmatory studies

6.3.1. 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 and is the preferred design. Ideally, randomised placebo or active comparator controlled trials (RCT) should be conducted for efficacy evaluation and this is especially relevant 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 superiority study design (verum, active comparator or placebo) and a three-arm non-inferiority study design (verum, active comparator and placebo). Trials convincingly demonstrating superiority to placebo and non-inferiority or superiority to the active comparator are regarded as high-quality evidence. In order to minimize placebo exposure, unequal randomisation can be considered (e.g. verum placebo 2:1) and the placebo period can be kept short with patients switching in a blinded manner to the test and the active control arms. 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. Nevertheless in a paediatric study there may be ethical concerns about including a placebo-arm when safe and effective alternative medication is available. Two-arm non-inferiority studies without placebo-arm could be acceptable provided that the selected comparator can be justified on the basis of a well-established efficacy, and an appropriately justified non-inferiority margin can be predefined. Such comparative studies must have assay sensitivity (see Guideline on the choice of the non-inferiority margin, EMEA/CPMP/EWP/2158/99).

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 addition, escape rules for placebo-patients and criteria for discontinuation due to lack of efficacy should be predefined and reported.

It is important to explore the degree to which treatment effects are sustained in the long-term. An extension study is feasible to evaluate lower maintenance doses or dose-interruption after randomised and blinded withdrawal. These could also be studied post-approval.

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, small safety database and potential for rebound effect. However these shortcomings are expected to be balanced by the advantages of having a feasible size of population and short placebo exposure. 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 to evaluate safety in larger populations. To minimise exposure of children to ineffective treatments, a 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. Unequal randomisation could also be considered (e.g. verum placebo 2:1).

Particular attention should be devoted to the duration of the withdrawal part especially for drugs with long half-life or prolonged biologic effect. Trials with short duration of the withdrawal part carry a risk that the time could be too short to show a difference in the flare rate between the placebo and the new drug. In order to avoid this problem an event driven approach can be considered. This foresees that the withdrawal part is not necessarily fixed in terms of duration (e.g. 6 months) but driven by the number of events (number of flares) that should be observed before closing the withdrawal part.

Given the well-known bias of the withdrawal trial toward responders, every effort should be made to report a meaningful outcome over time such as ACR Pedi 70, 90, minimal disease activity or inactive disease / remission at 1 and 2 years.

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

Biological or environmental causes for response/resistance

The studies should actively analyse biological or environmental causes for treatment responsiveness or resistance in individual patients. This may include detailed individual exposure/response analysis and the use of biological samples to identify the genetic risks for and the underlying mechanisms of disease manifestation and treatment responses in individual JIA subtypes. It is strongly recommended to include studies on biomarkers in the development program, to predict response and to identify patients who will not relapse after treatment withdrawal.

6.3.2. 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 for non-responders 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.

6.3.3. Combination therapy

Treatment with a combination of different drugs/medicines is an option 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 or tolerability. 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 needs to be investigated. A careful evaluation of safety is needed. For guidance on fixed drug combinations see Guideline on Fixed Combination Medicinal Products (CPMP/EWP/240/95 Rev. 1).

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

6.3.4. 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, the nature and the magnitude of the effects, and the PK parameters including the half-life of the agent studied.

Anti-inflammatory effects, relief of symptoms such as pain or maintenance of symptomatic improvement should be evaluated e.g. for up to 12 weeks. The earliest time point of evaluation of

efficacy will be determined by the expected mechanism of action of the drug 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. 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.

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 e.g. in an open label extension study or in an observational registry-type of study.

The following minimum set of data is recommended to be collected (as appropriate to the specific disease being studied):

- Age, sex, ethnicity, country of residence

- JIA category, duration of the disease, family history, comorbidities

- Medication history (active and concomitant treatment, previous treatments – dosage and duration)

- Uveitis, enthesitis, dactylitis and nail changes

- MAS – presence, past, specific treatment

- Growth and maturation parameters (weight, height, Tanner score)

- JADAS over time

- Measures of activity and damage (number of active joints, joints with limited motion, damage index, X-ray or another validated method)

- Patient/parent reported outcome measures (patient's/parent's and physician's global score, quality of life score)

- Laboratory parameters (ESR, CRP, ANA)

- Immunogenicity data (when applicable)

- 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. Dose-reduction or dose-interruption and re-treatment at relapse should be addressed within the clinical programme. Controlled clinical study designs are preferred (see section 6.3.1). These data could also be provided post-authorisation.

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 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 or by studies in adults 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. This is particularly true for a drug with new mechanism of action to be tested in younger children (e.g. less than 6 years old) where adequate measures to evaluate the potential impact of the experimental therapy on vaccination should be implemented.

7.2. Long-term safety

The long-term evaluation of safety requires collection of data from larger number of patients for a longer period of time, potentially into adulthood. Long-term safety should be studied in open label extension studies and in the post-marketing observational registry-type studies (see section 6.3.4.). The protocols for such studies should define and record the identifiable or potential 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 a sufficient number of patients treated with different medicinal products. Extent of data and study protocol for fulfilment of post-marketing obligations needs to be agreed during authorisation.

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