19 November 2015
EMA/CHMP/738839/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the "Guideline on clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis"

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Medicine Evaluation Board (MEB), The Netherlands
2	Pediatric Rheumatology INternational Trials Organisation (PRINTO)
3	UCB Biopharma SPRL
4	EFPIA
5	PRINTO
6	IRCCS Ospedale Pediatrico Bambino Ges

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

1. Overarching comments

Stakeholder no.	General comment (if any)	Outcome (if applicable)
MEB	Newly introduced in this GL is that optimal use should be made from data available of the adult counterpart of the diverse diagnoses of juvenile arthritis (RA, PsA, spondyloarthrtis in adults versus polyarticular JIA (pJIA), jPsA, ERA in children). Extrapolation may occur by PK-PD data and a paediatric dose-finding study alone, and if further confirmation is needed, a randomised withdrawal study in initial responders. If extrapolation from adults is not justified –e.g. for systemic JIA, which is different from adult RA-, the proof of concept should be shown in a parallel randomised controlled trial, as a randomised withdrawal study does not provide unbiased evidence for the overall target population. This approach is encouraged, as in principle, optimal use should be made what is already known from a drug before the introduction to children , and often limited paediatric patients are available for trials, Extrapolation is further justified by the fact that several treatment options for Rheumatoid Arthritis and axial spondylarthritis in adults, like MTX, etanercept, adalimumab, abatacept and tocilizumab, have been shown effective with acceptable safety in their paediatric counterparts pJIA and ERA as well. Only for infliximab, the pJIA trial failed to meet its endpoint. Experts noted that the dose may not have been optimal in this trial, emphasizing the need for optimal dose assessment before a trial. To further emphasize this principle, some more specific criteria are suggested for this GL under which circumstances extrapolation of efficacy would be acceptable. See suggestions below for section 5.1, line 238	Partly accepted. Further clarification on extrapolation of efficacy has been included in section 6.1 (Extrapolation of efficacy) (see pages 28-30 of this Overview of Comments). Information regarding maintenance of efficacy and the search for lower maintenance has been retained in the corresponding sections, as this information is considered relevant for each section. The text has been partly modified based on comments from IRCCS Ospedale Pediatrico Bambino Ges and PRINTO (see pages 45-47). A list of abbreviations has been added.

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	As the child develops, the JIA symptoms may change and even become less. It is therefore supported that in the GL guidance is provided regarding maintenance of efficacy and the search for lower maintenance doses. Guidance regarding long-term treatment is now spread over different sections, which may be confusing. For clarity, a separate section is suggested, putting together information from line 347-349, 368-369 and 429-234 A list of abbreviation may be helpful	
UCB	UCB welcomes and supports the release of the guideline on the clinical investigation of medicinal products for the treatment of juvenile idiopathic arthritis (JIA). UCB believes that this guideline is a comprehensive document that collates the changes in clinical practice in JIA and recommends sound approaches to the clinical development in JIA.	Acknowledged.
EFPIA	EFPIA welcome the opportunity to provide comments on the draft revised JIA guideline. We have identified a few major comments we expect to be addressed in the forthcoming finalised guideline: **1. Targeted approach to therapy:** As EMA points out, the understanding of the pathophysiology of the different types of JIA has evolved greatly in the past few years, which has changed the recommendations for treatment. The currently recommended targeted approach to therapy now supports fewer categories of JIA being studied for new therapeutics such that fewer children would be unnecessarily exposed to inappropriate therapeutics. As an example, current data for systemic JIA strongly implicate the IL-1 and IL-6 pathways and targeted treatments have been recommended (Ringold, 2013). An additional example can be seen in the differences between the therapeutic responses to IL-17 inhibition of patients with psoriatic arthritis versus those with rheumatoid arthritis (Mease, 2014), consistent with a more	Partly accepted. The following text has been included in section 1 (Introduction), in line with the EFPIA comment and the paediatric regulation: *… 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**, 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**.* See also MEB comment “line 109” on page 11 and EFPIA comment “Lines 170-171” on page 16. Further guidance on patient populations to be studied has

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	prominent pathophysiologic role of the IL-17 pathway in psoriatic arthritis, and perhaps the broader seronegative spondyloarthropathy category (Fitzgerald, 2014). In order to prevent the exposure of a broad group of children to an experimental intervention where efficacy is not anticipated, the target paediatric population should be chosen based on: 1. The latest information regarding each JIA subset disease pathology 2. Response to treatment in the most closely analogous adult disorder Mease PJ, Genovese MC, Greenwald MW et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med* 2014; 370: 2295-306 Ringold S, Weiss PF, Beukelman T et al. Update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis. Arthritis Rheum 2013; 65:2499-251 Fitzgerald O and Winchester R. Emerging evidence for critical involvement of the Interleukin-17 pathway in both psoriasis and psoriatic arthritis. Arthritis Rheuma 2014; 66:1077-1080 **Examples of suggested revisions:** Lines 107-109: "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***, unless there is reason to believe that the product is likely to be ineffective or unsafe in part or all of the paediatric population, or*** there is evidence that the therapy would target a particular JIA subset" Lines 110-113: "Although the aetiology and pathogenesis of JIA are	been included in section 4.1. More detailed information related to cytokine profiles has been added in section 1: *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…* Proposed addition related to the adult counterparts of the JIA categories (*…i.e. if the adult indication is psoriatic arthritis the paediatric equivalent is juvenile psoriatic arthritis…*) is not accepted, as the adult counterparts are already mentioned in section 1 (Introduction). Proposed addition related to the registry versus OLE is not accepted, as both types of studies are important (see also PRINTO comment "Line 454" on page 58-59). The following text has been added in section 7.2 (Long-term safety): ***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).*

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	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 ***in different forms of JIA*** (e.g.interleukin-1ß ***and*** interleukin-6 ***in systemic JIA***, TNF-α ***in polyarticular JIA***) in conjunction with osteoclastic cell activation leads to degradation of adjacent cartilage and bone." Lines 172-173: "The ILAR category of each patient enrolled into trials needs to be defined ***(i.e. if the adult indication is psoriatic arthritis the paediatric equivalent is juvenile psoriatic arthritis). The subset*** ~~as this~~ is important for cross-trial comparisons." **2. Use of registries** Registries in some JIA populations will be very difficult if not impossible to enrol due to low prevalence of the disease. Disease-based registry may require cross-company collaboration, which may not be feasible. It should be clarified that an OLE is appropriate and sufficient for some indications. Detailed comments are also provided below in section 2 - "Specific Comments on the text".	
IRCCS Ospedale Pediatrico Bambino Ges	In the absence of an ideal solution for the study design an expert meeting might be envisaged. Bayesian designs and design based on responders/non responder identification also might be discussed	Partly accepted. A new expert meeting is not envisaged for this guideline. Paediatric Rheumatology Expert Group Meeting was held at EMA on 17 November 2010. See also PRINTO comment on page 48-50 and the response from EMA statisticians.

2. Major Comments on each Section

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 35	PRINTO	**Comment:** instead of “one disease” with multiple subtypes **Proposed change (if any):** Juvenile idiopathic arthritis consists of different diseases **Change: consists of** replaced with **is currently grouped in** **subtypes** replaced with **categories**	Accepted.
Executive summary Line 48-58	MEB 1	**Comment:** In these lines, the current treatment paradigm in JIA is shortly summarised. This information rather belongs to the introduction section, as it describes how JIA should be treated, which is not the subject of this guideline. Proposed change: transfer to section 1, introduction, e.g. after line 129	Partly accepted. Lines 48-49 have been moved to section 1 (Introduction). Lines 50-58 have been condensed and left within the Executive summary, to justify the update of the guideline and to present the current treatment options.
Line 49	PRINTO	**Inserted:** structural (joint damage)	Accepted.
Line 49	PRINTO	**Comment:** multi-disciplinary approach is advocated. To what extent have other disciplines than paediatric rheumatologists been involved in this guideline? Which patient representatives/parents have been involved and to what degree are they familiar with JIA? Clearly, the multi-disciplinary approach has to be specified. In how much does this affect this guideline? Not at all?	Not accepted. The text related to “multidisciplinary approach” is referring to optimal clinical care of JIA. For clarification, the text has been moved from the Executive summary to the corresponding paragraph in section 1 (see also MEB 1 comment above).
Line 50	PRINTO	**Inserted: most cases of**…newly	Accepted.
Line 51	PRINTO	**Change: instead of** followed by glucocorticosteroids (intra-articular or systemic), **proposed** - followed by	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		intra-articular glucocorticosteroids	
Line 51	PRINTO	**Comment:** 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). That statement does not apply to cases with polyarticular JIA with moderate to severe disease activity. **Proposed change (if any):** In contrast to adults, NSAIDs are considered as first–line treatment option in most cases with newly diagnosed JIA	Accepted.
Line 56	PRINTO	**Comment:** The sentence „the introduction of biological therapies has resulted in a significant advance in therapy for JIA." To my understanding it would be more appropriate to say that the introduction of biological therapies has resulted in new options and potential outcome improvement in therapy of JIA. To my knowledge there is no prospective study clearly showing that introduction of biologicals into treatment of JIA has improved overall outcome of the disease. Most of us paediatric rheumatologists are very satisfied with having more options than just Methotrexate but superiority of e.g. TNF blockage over Methotrexate has scientifically not been proven for most JIA subtypes. Blockage of Interleukin1 or Interleukin 6 gives us even more treatment options especially in sJIA but whether this is associated with an overall improved outcome is yet unclear	Not accepted. The phrase "significant advance" referring to biological therapies is considered appropriate and relevant for the Executive summary. This advance is among the reasons for the update of this guideline; the wording is also justified based on the (PRINTO) request to use more stringent primary endpoints "in this new biologic era" (see comment "Line 242" on page 32).
Line 61	PRINTO	**Comment:** Usually just one synthetic DMARD and no more than one biologic are being used: ",often using a	Accepted.

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		combination of a synthetic DMARD with a targeted biologic"	
Line 61	PRINTO	**Comment:** Targeted biological agents are to be used upfront in treatment of JIA along with synthetic DMARDs as per the EMA Guideline. But, it is very difficult to practice in developing countries like India due to economic constraint and restricted availability. **Proposed change (if any):** Reconsidering the possibilities of a trial of NSAID, corticosteroids and synthetic DMARDs before initiation of targeted biological agents.	Not accepted. The proposed wording represents clinical treatment guidance and not regulatory guideline.
Lines 60 - 62	PRINTO	**Comment:** Indeed, there are newer strategies with employing a more aggressive intervention in early disease. Again, the scientific evidence for the superiority of this approach to a conventional, less aggressive approach is not there. This needs to be stated. The study by Tynjälä from Finland has methodological flaws; moreover, a recent study of a more aggressive approach did not show a significant difference. (Wallace, 2012). I would prefer to say: "Therapeutic strategies are now employing more aggressive intervention in early disease. It is yet unclear, whether a more aggressive approach in children with JIA is more effective and associated with less side-effects than the conventional approach."	Not accepted. The proposed wording ("*It is yet unclear…*") is not considered relevant for this regulatory guideline. The paragraph within the Executive summary has been reworded mostly in line with PRINTO proposal (track changes version of the JIA guideline; Printo v2). It is however noted that PRINTO has also provided contradictory comments (see "Line 140 – 146" on page 14). The sentence "*…therapeutic strategies are now employing more aggressive intervention in early disease*" has been retained, as it holds true for both RA and JIA (recent references for JIA e.g. Wallace CA et al. J Rheumatol 2014 Dec 41(12) and J Rheumatol 2014 Jun 41(6)).
Line 65	PRINTO	**Comment:** More accurate: "when to deescalate treatment in responders and when to stop after achieving remission.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 75	PRINTO	**Added:** After (JCA)…and others not formally evaluated in children such as	Accepted.
Line 76	PRINTO	**Comment:** The ESSG classification has never been evaluated in children although it has been used extensively	Accepted.
Lines 79-85	EFPIA 1	**Comment:** This paragraph implies that all JIA is one disease, however the individual JIA categories describe diseases with differing pathogenesis and phenotypic features In addition, in ERA boys predominate; this should also be made clearer. **Proposed change (if any):** JIA refers to arthritis of at least 6 weeks duration of unknown aetiology that begins in children less than 16 years old. ***The International League of Associations for Rheumatology (ILAR) classification of JIA identifies the following 7 mutually exclusive categories: systemic arthritis, oligoarthritis (persistent or extended), rheumatoid factor [RF] negative polyarthritis, RF positive polyarthritis, psoriatic arthritis, ERA, and undifferentiated arthritis. Overall,*** 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	Partly accepted. The ILAR categories are already listed in section 1. The paragraph describing JIA has been moved further down within section 1. The predominance of ERA in boys has been added.

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		some of the categories girls predominate ***whereas in ERA boys predominate,*** and there are racial differences in incidence and relative frequency of JIA subtypes.	
Line 96	PRINTO	**Comment:** 2 subcategories based on joint count beyond 6 months	Accepted
Lines 92-101	EFPIA 2	**Comment:** Suggest that the wording be changed to reflect that in the literature to clarify that the joint count that is used in the definition is the number of joints affected over the course of the disease rather than the number of affected joints at a particular time point. Ref: Petty RE et al.: International League of associations for rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001; J Rheumatol 2004; 31(2):390-392 **Proposed change:** "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 ***of arthritis affecting one to 4 joints during the first 6 months of disease*** ~~based on joint count after 6 months~~) • Persistent ***(affecting not more than 4 joints throughout the disease course*** ~~**not more than 4 joints**~~) • Extended (***affecting a total of more***	Partly accepted. See previous PRINTO comment. The ILAR classification provides detailed criteria for each category. In this guideline it is sufficient to mention these categories. Reference to the ILAR classification is included within the section "References".

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		than 4 joints after the first 6 months of disease ~~more than 4 joints~~) • Psoriatic arthritis (JIA-PsA) • Enthesitis related arthritis (ERA) • Undifferentiated arthritis"	
Line 103	PRINTO	**Comment:** RA, axial spondylarthritis and psoriatic arthritis correspond to individual categories of JIA. However, clearly, there are significant differences between a 16-year-old with Enthesitis-associated JIA (which, in some cases, is self-limiting) from a 60-year-old with HLHB27-positive spondylartropathy. I agree that the new drugs should also be investigated in pediatric population. However, a one-to-one extrapolation from adults with these subgroups of rheumatic diseases is as inappropriate as to summarize subtypes of JIA in one group. This calls for multi-disciplinary trials. In other areas of pediatrics, these multi-disciplinary trials are highly successful by an intense collaborative network (eg PENTA Network in HIV infected children, Oncology Trials). There are far fewer HIV-infected children or children with soft tissue tumors in Europe than there are children with a given JIA subtype. JIA children deserve to receive treatments in properly designed clinical trials without using inferior and inadequate company initiated designs such as the withdrawal design. An appropriate treatment design is absolutely essential if doing clinical investigations of medicinal products in children. To me it is unethical to use clinical trial designs that measure withdrawal and not efficacy. To my knowledge,	Partly accepted. Randomised placebo controlled withdrawal design is an option and there are several successful examples of its use. The advantages and the disadvantages have been discussed. Parallel group design is however the preferred option (see also PRINTO comment "Line 350" on pages 48-51).

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		pediatric rheumatology is the only field in Pediatrics that repeatedly employs such an inadequate trial design to test new drugs in children.	
Introduction , line 104	MEB 2	Proposed change: Please add to complete the information of the juvenile counterpart of the diverse adult arthritides: Still's Disease is considered the adult counterpart of systemic JIA.	Not accepted. This paragraph discusses the overarching condition "chronic idiopathic arthritis".
Introduction, line 109	MEB 3	Comment: Whether paediatric studies should be performed for newly developed products has to be decided by the PDCO, and cannot be formally addressed in tis CHMP guideline. Proposed change: replace: "is required" by "should be considered"	Not accepted. Based on EFPIA comment on page 3 and the Paediatric regulation, the following additional text has been included: *"…the inclusion of JIA in the development 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****."*
Line 112	PRINTO	**Comment:** -1ß	Accepted.
Lines 110-115	EFPIA 3	Comment: This paragraph suggests again that all JIA shares the same pathogenesis. This is clearly not the case if one looks at heredity and phenotypic manifestations. Proposed change (if any): Although the aetiology and pathogenesis of JIA are not fully understood, it is however known that some forms of JIA share many of the pathological abnormalities that have been identified in RA, but multiple differing pathogenesis and phenotypic features exist between JIA sub-categories. Increased production of cytokines (e.g.interleukin-1ß interleukin-6, TNF-α) in conjunction with osteoplastic cell activation leads to degradation of	Accepted. The paragraph has been amended in line with previous EFPIA comment (see pages 3-4): *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,*** *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,*

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		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.	*response to treatment, risk of relapse or prognosis.*
Line 116	PRINTO	**Comment:** or even preceded	Not accepted. (see next comment).
Lines 116-119	EFPIA 4	**Comment:** This is only true for specific types of JIA and is not true for ERA which has acute anterior uveitis as inclusion criteria for classification. Acute anterior uveitis is not ANA associated. **Proposed change (if any):** JIA is a major cause of disability in children. In addition ***specific types of*** JIA may be accompanied by chronic anterior iridocyclitis/uveitis particularly in anti-nuclear antibody (ANA) positive females**. *In ERA acute anterior uveitis prevalence is not associated with ANA status***. Early ophthalmology referral, early diagnosis and treatment are the major determinants of prognosis in uveitis associated with JIA.	Partly accepted. The wording "specific types" has been added while more detailed information on different JIA categories and uveitis is not considered relevant for this regulatory guideline: *In addition, **specific types of** JIA may be accompanied by iridocyclitis/uveitis ~~particularly in anti-nuclear antibody (ANA) positive females~~.*
Line 120	PRINTO	**Added:** After complications - in systemic JIA	Accepted.
Line 122	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** The term glucocorticoid should consistently be used (throughout the entire document) **Proposed change (if any):** steroid changed glucocorticoid	Accepted.
Line 124	PRINTO	**Added:** After metabolic complications - joint erosions	Accepted.

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Line 134	EFPIA 5	**Comment:** Suggest adding the word “prevention” to treatment so as not to imply that all drugs should be tested in children who already have macrophage activation syndrome. **Proposed change:** “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 ***or prevention*** of macrophage activation syndrome and reduction of corticosteroid dose.”	Accepted.
Line 140 - 146	PRINTO	**Comment:** 1) Scope (**line 59 to 65 and 140 to 146**) The intended guideline should solely provide framework conditions for investigation of medical products for the treatment of JIA. This particular scope has to be clearly differentiated from a guideline for the treatment of JIA. **We strongly recommend to delete line 59 to 65, as those statements do not belong here.** Further, the scope of the guideline should not cover statements how to merge/ extrapolate / interpret data from different studies to	Partly accepted. The paragraph has been condensed and reworded mostly in line with PRINTO proposal (track changes version of the JIA guideline; Printo v2) which is however contradictory to the current comment. Relevant parts the Executive Summary have been kept to justify the update of the guideline and to give an overall picture of the current treatment options for JIA.

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		establish treatment (guideline) of JIA. Interpretation of results of studies should be based on clearly defined level of scientific evidence as provided e.g. by Feldmann et al. It might be advisable to mention the discrepancies between German evidence and consensus based treatment guidelines (Dueckers et al.) and ACR treatment recommendations (Beukelmann et al.), as these discrepancies showed that currently there is broad variety on interpretation of data of studies. Hence, a guideline on investigation in medical products might help to overcome obstacle in data interpretation by standardizing study design and conduction. The interpretation, the weighting of data should be restricted to consensus conferences as a transparent platform for the development of treatment guidelines. **Corrected:** The guideline addresses specific issues related to the proper planning of efficacy/safety studies (possibly including extrapolation)… from	The proposed wording in section 2 (Scope) has modified: *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.*
Line 165	PRINTO	**Comment:** 4- Patients populations to be selected: I consider important different target JIA treatment group • History of monoarthritis (this will include those with persistent oligoarthritis, psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis, all of them with one joint affected • Juvenile spondyloarthropaties as a different category • Systemic arthritis with active systemic features (and without arthritis) as a separate category	Not accepted. The target JIA treatment groups are based on the recommendation by the ACR (Beukelman et al., 2011) and the expert paediatric meeting at the EMA in 2010 (EMA/836276/2010), as referred to in the guideline. These treatment groups represent the current regulatory thinking and have generally been included in the PIPs, with the aim to make studies in JIA more feasible. It should also be noted that around 20% of JIA patients are not correctly classified according to the ILAR classification, based on a large PRINTO dataset of over 12000 JIA patients (Consolaro et al., Ped Rheum 2014; 12(Suppl 1):P176) (see also comments on

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		Note ; SJIA could be consider not a unique category, because the spectrum of this category is extremely broad, from some patients in proximity to MAS and others with only rash, for example.	pages 16 and 17). The following sentence has been added in section 4.1: *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.***
Line 166	PRINTO	**Comment:** moderate to severe disease activity… I think the definition of severe or moderate disease activity have to be required**.** **Sentence changed:** In general patients with moderate to severe disease activity, for example based on JADAS levels, should be included to enable demonstration of a sufficient treatment response. Specific criteria for the different JIA categories should be however identified.	Accepted. See also PRINTO comment on page 17 “After line 171”.
Line 168	PRINTO	**Comment:** It is good to highlight the enrolment of patients below 1 year of age. For the completeness we recommend to mention that upper age limitation should be 16 years of age, according to ILAR criteria. In General we strongly recommend to keep following ILAR criteria as long as no other international, evidence based classification is provided. It remains unclear to us how treatment groups where identified by the ACR (line 177 to 186). Citation, Study, international consensus process? Otherwise it should at least be marked as experts consensus (= low grad	Not accepted. For age of the patients to be studied, please see comments on pages 22-25. The target JIA treatment groups are based on the recommendation by the ACR (Beukelman et al., 2011) and the expert paediatric meeting at the EMA in 2010 (EMA/836276/2010), as referred to in the guideline. These treatment groups represent the current regulatory thinking and have generally been included in the PIPs, with the aim to make studies in JIA more feasible. It should also be noted that around 20% of JIA patients are not correctly classified according to the ILAR classification, based on a large PRINTO

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		evidence). For further comment see Tim Niehues mail.	dataset of over 12000 JIA patients (Consolaro et al., Ped Rheum 2014; 12(Suppl 1):P176) (see also comments on pages 14-15 and 17). The following sentence has been added in section 4.1: *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.***
Line 169	PRINTO	**Comment:** Though, JIA is rare in children below 1 year of age, cases of systemic onset JIA are seen below 1 year age group. So, exclusion of JIA below 1 year is not rational. **Proposed change (if any):** Age group of JIA drug trial to be modified at least for sJIA. **Sentence changed:** The clinical development programme should include children as young as 2 year and older unless	Not accepted. For age of the patients to be studied, please see comments on pages 22-25.
Lines 170-171	EFPIA 6	**Comment:** It is stated that only the occurrence of "significant adverse events in animals or adults" could prevent the inclusion of children from the age of 1. Other reasons such as, mechanism of action, expected lack of benefits over existing treatments, can also be a justification for not including the younger age groups	Accepted. The following sentence has been added, in line with EFPIA comment on page 3-4, MEB comment on page 11, and the Paediatric regulation: *… the inclusion of JIA in the development 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***

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			therapeutic benefit in children.
After Line 171	PRINTO	**Inserted:** Enrollment could now be based on the level of disease activity as measured by the JADAS (e.g. moderate to high level of disease activity).	Accepted. See also PRINTO comment on page 15 "line 166".
Lines 172-188	PRINTO/University of Nis Serbia	**Comment:** ACR recommended JIA groups to investigate allows overlaps and enrolment of different JIA subtypes in the same group, this is why I would suggest to insist on ILAR classification as only inclusion criteria and all studies in the future (like one did for etanercept) should clearly focus on separate JIA subtypes (long term outcome JIA studies have shown that almost 1/3 of JIA patients change JIA subtype over time ie. from oligo to poly or to psoriatic etc.).	Partly accepted (see also previous comments). The target JIA treatment groups are based on the recommendation by the ACR (Beukelman et al., 2011) and the expert paediatric meeting at the EMA in 2010 (EMA/836276/2010), as referred to in the guideline. These treatment groups represent the current regulatory thinking and have generally been included in the PIPs, with the aim to make studies in JIA more feasible. It should also be noted that around 20% of JIA patients are not correctly classified according to the ILAR classification, based on a large PRINTO dataset of over 12000 JIA patients (Consolaro et al., Ped Rheum 2014; 12(Suppl 1):P176). The following sentence has been added in section 4.1:: *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.***
Line 173	PRINTO	**Inserted:** Historically all trials with biologic agents (etanercept, infliximab, adalimumab, abatacept, tocilizumab, canakinumab) have use the concept of 'polyarticular course' JIA, an artificial category that lumps together all forms of JIA with more than five joints involved in the absence of systemic features (extended oligoarthritis, polyarthritis RF positive and	Partly accepted. The proposed text regarding historical trials with biologic agents is not considered relevant for this regulatory guideline. The proposed sentence: *The rational to include or exclude any specific JIA category should be adequately documented* has been included in section 4.1 (see also previous comments)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		negative, systemic arthritis without active systemic features in the prior 6 months. In some instances children with enthesitis related arthritis or psoriatic arthritis have been also considered. In all trials conducted children with oligoarthritis persistent have been excluded. The rational to include or exclude any specific JIA category should be adequately documented.	
Line 173	PRINTO	**Replaced: However** replaced with **In addition**	Partly accepted. "However" has been deleted. "In addition" has not been added (as not needed).
Lines 174 - 186	PRINTO	**Proposed change (if any):** rows 174 -186 should be deleted and replaced with ILAR classification criteria	Not accepted (see previous comments).
Line 178	PRINTO	**Comment:** The ACR grouping of JIA categories and presentations holds advantages, but also disadvantages. For example: patients with ERA with specific features, such as severe hip involvement or tarsitis, may better be allocated to the active sacroiliitis group than to the oligoarticular group	Acknowledged.
Line 178 and line 172	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** Enthesitis related arthropathy should be studied with group 3 (i.e. active sacroiliac arthritis) rather than being included (according to the number of joints involved) in group 1 (oligo) or group 2 (poly). ERA with or without axial involvement is to be considered the corresponding of adult spondiloarthropathies with or without peripheral arthritis. This group of disease might have significant differences in the pathogenic mechanisms and therefore in suitable therapeutic targets as demonstrated by recent experience with clinical trials:	Accepted. The target patient populations based on the Expert paediatric meeting at the EMA (EMA/836276/2010) have been added to the guideline. ERA is included as a separate target group.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		a) recent trials with 2 different IL-6 inhibitors showed lack efficacy in spondiloarthropathy underscoring the different role of IL-6 in RA, poly JIA versus spondiloarthrotpathies b) lack of efficacy of IL-17 inhibitors in RA compared to the efficacy in spondiloarthropathies and psoriatic arthritis in adults. Therefore, the inclusion of ERA in the poly or oligo group may hide potential beneficial effects or conversely dilute the efficacy of the reciprocal group. Proposed change (if any): delete "enthesitis related arthritis from line 178 and line 182	
Line 184	PRINTO	**Comment:** ...or history of intervertebral joint (i.e. axis) involvement	Not accepted. The treatment group "Active sacroiliac arthritis" requires active axis involvement.
Lines 185 - 188	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** The way systemic JIA is divided according to proposal from the ACR is not consistent with what happens in clinical practice. Indeed, most patients with a persistent disease course tend to have chronic synovitis with variable waxing and waning systemic features. This recommendation from ACR was provided in an "eminence" based process in order to discuss potential treatment algorithms and not with the goal of evaluating the efficacy and safety of novel treatments in a clinical trial setting. I strongly believe that separating sJIA in these two artificial groups should be discouraged, particularly in the setting of clinical trials. It might create confusion for the proper indication on the label. The present canakinumab label, indeed, does not restrict the use of the drug to patients with active systemic features, even if the pivotal trials (NEJM	Accepted. "*Systemic arthritis with and without active systemic features can be considered one group and studied together*" is already included in the guideline. In addition, the target patient populations based on the Expert paediatric meeting at the EMA (EMA/836276/2010) have been added to the guideline (see also comment on page 18). See also contradictory comments by PRINTO below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		2012) were conducted in patients with fever (at least 90%). In order to avoid potential future confusion based on the sJIA grouping suggested in the ACR treatment recommendations, I would much more strongly base the present guideline from the EMA on the expert paediatric 2010 meeting conclusion (line 187-188) **Proposed change (if any):** I would suggest that the guidelines for sJIA should read as follows "systemic JIA with or without systemic features can be considered one group and should be studied together	
Between Line 188 and 189	PRINTO	**Inserted:** However based on more recent finding for new drugs with different mechanism of action (e.g. drug different that anti IL6 or anti IL1) the scientific rational to study systemic JIA should be adequately documented. In general children with systemic JIA without active systemic symptoms could be lumped together with polyarticular course JIA. If the trial show a positive efficacy and safety profile in systemic JIA without active systemic symptoms (e.g. above 50-60% ACR 30-50 responders) then a trial with systemic JIA and active systemic symptoms could follow. Alternatively a proof of concept study dedicated to systemic JIA with or without active systemic symptoms and adequate stopping rule (e.g. disappearance of fever in 4/5 patients or above 50-60% ACR 30-50 responders for the children without active systemic symptoms) should preceed any implementation of a dedicated phase III confirmatory trial in systemic JIA. The experience gained with tocilizumab in systemic JIA	Partly accepted. A new paragraph has been added (see also comments above and below): *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.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		which showed that dosing and frequencies is higher in systemic JIA as compared to polyarticular course JIA underline the need that in all instances proper pk studies should provide adequate information on the correct dosing (same as polyarticular course JIA or higher). A consideration could be given to the potential enrollment of systemic JIA which, in the initial phase of the disease might lack the presence of arthritis. These children who could called with juvenile onset Still disease (as the analogous counterpart in the adult population) might be considered as well for enrollment.	
Line 188	PRINTO	**Comment:** From our point of view, the pooling of patients with systemic arthritis with and without systemic features should be reconsidered. Our growing experience with biologic drugs in systemic JIA points to differences in treatment response between both groups. Thus, a differentiation analogous to the ACR treatment groups seems meaningful.	Partly accepted. A new paragraph has been added (see previous comments): *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.*
Line 188	PRINTO	**Comment:** although the therapeutical approach is different in those two subgroups.	Partly accepted (see previous comments).
Lines 174 and 189	EFPIA 7	**Comment:** The guideline indicates the following: “The ACR has identified **five** target JIA treatment groups”. Then later on: “Each of the **4** target patient population groups”. It is unclear how many populations need to be studied separately, four or five? Please clarify.	Accepted. The ACR has identified five target JIA treatment groups. The Expert Paediatric Meeting (EMA/836276/2010) concluded that systemic arthritis with and without active systemic features can be considered one group and studied together, resulting in a total of four treatment groups. This has been made more clear by listing the four groups from “a” to “d”.
Lines 190 - 193	PRINTO/University of Nis	**Comment:** In accordance with previous comment (L188)	Partly accepted. “For JIA as a group of diseases” has been added within the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
	Serbia	**Proposed change (if any):** The development programme (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. (This sentence should be out: In most cases patients with ERA can be studied together with patients with polyarthritis and extrapolation of efficacy is acceptable for persistent oligoarthritis).	paragraph. The sentence regarding ERA and oligoarthritis has been modified but retained, as it represents current regulatory thinking and practice. Patients from different treatment groups can be merged into one clinical trial with subgroup analysis performed. ERA can also be studied separately but such studies may not be feasible and could lead to limitation to access. The text has been modified: ***For example*** ~~*In most cases*~~ *patients with ERA can be studied together with patients with polyarthritis.*
Line 193-194	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** for the reasons mentioned above I would not mention ERA in the sentence. Extrapolation to persistent oligoarticular on the other hand is definetively acceptable. **Proposed change (if any)**: delete ERA	Partly accepted (see previous comment).
Line 194	PRINTO	**Comment:** If cases with ERA are studied together with patients with polyarthritis, their specific features (enthesitis, back pain, etc.) have to be considered when it comes to efficacy assessments. Moreover ERA, being a spondyloarthritis, and polyarthritis are separate diseases with varying pathogenesis and should not be grouped together. Such lumping would mean that, translated to adult rheumatology, patients with RA and ankylosing spondylitis are being lumped together.	Acknowledged (see previous comments). ERA can also be studied separately but such studies may not be feasible and could lead to limitation to access.
Line 194	PRINTO	**Comment:** Extrapolation to persisten oligoarthritis is questionable since this form usually is not treated with biologic agents but rather with intraarticular corticosteroid injections. Only a limited portion of the	Accepted. Novel approved treatment options for difficult-to-treat persisten oligoarthritis are however welcome. The text has been modified:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		oligoarthritis persisten is treated with methotrexate or biologic agents.	***Usually*** *extrapolation of efficacy* ***from polyarthritis*** *is acceptable for persistent oligoarthritis,* ***where systemic therapy is exceptionally indicated****.*
After Line 196	PRINTO	**Inserted:** Which proper JIA category should be studied or excluded should be adequately documented in the PIP application. For example if a company has evidence that the experimental therapy has no effect on RA with positive rheumatoid factor that the corresponding JIA with polyarthritis RF positive could be excluded. Similarly if a company has evidence that a drug might work primarily in spondylorthropathies then the JIA related categories (ERA and Psa) could be the only one to be evaluated. The inclusion of persistent oligoarthritis, normally treated with intraarticular corticosteroid injections should be in general excluded. The only exception could be represented by the few patients who did not respond despite several courses of intraarticular corticosteroid injections	Accepted. The following sentence has been added (see previous comments): *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****.* With regard to the persistent oligoarthritis, the following sentence has been added (see also previous comment): ***Usually*** *extrapolation of efficacy* ***from polyarthritis*** *is acceptable for persistent oligoarthritis,* ***where systemic therapy is exceptionally indicated.***
Line 198	PRINTO	**Comment:** here, I would prefer 1 to less than 18 years	Partly accepted (see also comments below). The PDCO has granted a waiver in sJIA for children from birth to less than 1 year. A waiver is generally acceptable in other JIA categories up to 2 years (ref. Paediatric Rheumatology Expert Group Meeting, EMA/836276/2010).
Line 198	PRINTO/ University of Nis Serbia	**Comment:** There is necessity to rephrase this section defining age of JIA patients because JIA is not a disease that will “burn out” after the age of 18 years. In many countries, due to registration definition of upper age limit until 18 years, JIA patients in real life older than 18 years are not allowed to continue their	Partly accepted. The age groups for clinical trials or extrapolation analysis have been updated (sJIA from 1 year and other JIA categories from 2 years). A new paragraph on adult patients with JIA has been added:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medications. On the other hand, there are JIA subtypes which are specific for childhood onset and have no counterpart disease in adults. **Proposed change (if any):** That is why at the beginning of this section new sentence must be introduced: JIA registration studies can enroll only patients who are not older than 18 years. While following sentences should be rephrased as follows: Systemic JIA : from 1st year of life • Polyarthritis (RF pos and RF neg and extended oligoarthritis) from 2nd year of life • Oligoarticular arthritis (persistent and extended) from 2nd year of life • Enthesitis related arthritis and psoriatic arthritis from 6th year of life	*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.*
Line 201	PRINTO	**Comment:** Oligoarthritis often starts already at the beginning of the second year of life, so it should read: from 1 to less than 18 years of age	See previous comments
Line 201	PRINTO	**Comment:** Age of patients to be studied... I think for both from 1 to less... 18 years. I have seen patients with oligoarthritis from 6 months and psoritic arthritis as well.	See previous comments.
Line 202	PRINTO	**Comment:** Enthesitis related arthritis and psoriatic arthritis: from 12 to less than 18 years is probably not correct as many patients are seen with ERA below 12 years of age.Proposed change: Age group to be re-defined.	See previous comments.
Line 202	PRINTO	**Comment:** ERA and psoriatic arthritis may occur from the age of 6, therefore studies should include also	See previous comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		patients from 6 years of age **Proposed change (if any):** Enthesitis related arthritis and psoriatic arthritis: from 6 to less than 18 years	
Line 202	PRINTO	**Comment:** Since one of the criteria for the disease is age above 6 years of age, which corresponds to the age incidence of this disease form, the change of the age could be considered. „from 6 to less than 18 years"	See previous comments.
Line 202	PRINTO	**Comment:** or 8 Yrs old?	See previous comments.
Line 202	PRINTO	**Comment:** Enthesitis related arthritis and psoriatic arthritis: from 12 to less than 18 years (line 202) I do not understand why younger ERA and PsA patients should be excluded from clinical trials and in my opinion, if an age limit is introduced, it should be from 6 years.	See previous comments.
Line 202	PRINTO	**Comment:** here, I would prefer 6 to less than 18 years	See previous comments.
Line 202	PRINTO	**Comment:** why enthesitis related arthritis from 12 years on? I think the same as all the others from 2-18 years!	See previous comments.
Line 202	PRINTO	**Comment:** from 2 to less than 18	See previous comments.
Line 199 - 205	PRINTO	**Rephrased section:** Age of the patients to be studied • Systemic JIA : from 1 to less than 18 years • For all other JIA categories ages (oligoarthritis, polyarthritis RF positive or negative, ERA and PsA) could bePolyarthritis (RF pos and RF neg and extended oligoarthritis): from 2 to less than 18 years The planning of the study should follow in all instances	Partly accepted. See previous comments on the age groups. The sentence proposed has been added to section 6.2 (Early studies in children) instead of section 4.1. (Patient populations to be studied). It has been slightly modified, as this depends on the product and in well-known class might not be necessary:

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(especially for pk) a staggered approach by providing proof of the proper dosing for the older children and then moging to the younger age groups • Oligoarticular arthritis (persistent and extended): from 2 to less than 18 years • Enthesitis related arthritis and psoriatic arthritis: from to less than 18 years As reference for the age group please refer to ICH 11 guidelines and the 2008 version of the Ethical considerations for clinical trials on medicinal products conducted with the paediatric population Recommendations of the ad hoc group for the development of implementing Guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use). The recommendation distinguish the following age categories • preterm newborn infants • term newborn infants (0 to 27 days) • infants and toddlers (28 days to 23 months) • children (2 to 11 years) • adolescents 12 to 16-18 years (dependent on region) Long-term follow-up e.g. in registry type studies should include young adults as well. Undifferentiate arthritis should be excluded from clinical trials programmes	*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.* Reference to the ICH 11 guideline is included in section 3 (Legal basis and relevant guidelines). Quotation of the guideline and GCP practices is not needed within this guideline. The proposed text related to undifferentiated arthritis is not accepted. These patients should not be excluded from treatment groups. Due to classification there is large proportion of “undifferentiated” patients which might benefit from treatment, especially those with polyarticular course.
Section 4.1 , line 202	MEB4	Comment: The age range for ERA trial is set at minimal 12 years. Recently, adalimumab has been approved for ERA patienst from the age of 6 years	See previous comments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change :from 6 ~~12~~ to less than 18 years	
Line 210	PRINTO	**Comment**: Potential confounding factors Genetical analyses, immunogenicity..., I think should be recorded.	Accepted. "*Occurrence of antibodies to the drug*" is already mentioned in the second paragraph of section 4.2. "*Genetics*" has been added as an example of exploratory analysis in the fourth paragraph. "*Immunogenicity*" has been added in section 6.3.4 (*The following minimum set of data is recommended to be collected…)*
Line 213	PRINTO	**Comment:** 213 and 421: uveitis, enthesitis, dactylitis, nail changes, family history	Accepted.
Line 213	PRINTO	**Comment:** must be completed by enthesitis, dactilytis	Accepted.
Line 213	PRINTO	**Comment:** Disease activity and functional ability should be recorded according to validated, internationally accepted scores (e.g., JADAS, CHAQ) at baseline **Proposed change**: …disease activity through the Juvenile Arthritis Disease Activity Score (JADAS) and the presence of joint damage via wrist/hand xrays should all be fully documented at baseline and at regular follow up.	Partly accepted. *"Disease activity and functional ability recorded according to a validated score*" has been added. "Pain score" has been deleted from the next paragraph as being part of the previous scores. "*Wrist/hand x-ray*" has not been added, as methods other than x-ray for the assessment of the presence of joint damage can also be considered in children. "*…at regular follow up*" has not been added, as this paragraph discusses baseline factors.
Lines 215 - 216	PRINTO	**Comment:** (when available)	Partly accepted. Instead of "*when available*", the phrase "*when appropriate*" has been added (the guideline is not limited for biological therapies).
Line 221	PRINTO	**Inserted: exploratory** analyses	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			Genetics and pharmacodynamics markers have been included as examples of exploratory analyses.
Line 224	PRINTO	**Comment:** The predefinition, standardization or complete documentation of non-pharmacological treatment (e.g. physical therapy) is hardly feasible.	Accepted. The text has been modified (see also EFPIA comment "Lines 223-226" below): *Concomitant non-pharmacological treatment (e.g. physical therapy) and medication for diseases other than rheumatic conditions **should** be documented and predefined **where possible**.*
Lines 210 - 226	PRINTO	**Comment:** Potential confounding factors (line 210 to 226) It seems highly advisable to demand clear declaration of conflict of interest in each study. The declaration of conflict of interest is key in performing studies. Not only for the reader of the (resulting) manuscript but especially for the group itself. Many pediatric rheumatologists serve on advisory boards or are receiving funding from pharmaceutical companies regarding their research or registries. There is a clear conflict of interest, especially regarding the new, very expensive biological drugs. The prescription of drugs like anti-Il1 or –Il6 in a single patient concerns sums of 5 to 6-digit $ numbers. Although it will be very difficult to find leading pediatric rheumatologists that have not been involved with one or the other company it should be at least clear who is working with which company. Most importantly, this has to be made clear before studies are conducted.	Not accepted. Demand of declaration of CoI is not to be included in a regulatory guideline.
Lines 223-226	EFPIA 8	**Comment:** The draft guideline recommends that "Other treatment	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		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." The requirement that concomitant non-pharmacological treatment (e.g. physical therapy) must be documented completely may not be feasible since adequate records may not be available as non-pharmacological treatment is not usually done at the physicians' office. There is also no standardised and widely acceptable method to record non-pharmacological treatments in JIA patients. **Proposed change (if any):** Concomitant non-pharmacological treatment (e.g. physical therapy) and medication for diseases other than rheumatic disease ~~must~~ ***should*** be ~~completely~~ documented and ~~where possible it is recommended that these treatments are standardised and~~ predefined***, where possible.***	See PRINTO comment "Line 224" above.
Line 227 - 240	PRINTO	**Comment: Extrapolation of data** Extrapolation of data from studies on adults appears to be an elementary mistake and contradicts guidelines of good clinical practice respectively good scientific work to our point of view. PK studies (in vivo) in children are vital for safety reasons. We strongly disagree with the use of	Not accepted. The intention of this guideline is to provide guidance on the clinical development of medicinal products for the treatment of JIA. Analysis of extrapolation opportunities is an elementary part of this, with the rationale to avoid unnecessary (efficacy) studies in the paediatric population. PK

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		modelling or simulation approach (line 308 to 316).It is an open secret, that the growing child must not be regarded as a "little adult" at all. Extrapolation of adults data appears to be wrong. Pharmakokinetics in the growing child differs significantly form age group to age group. **Recommendations according to extrapolation**/ interpretation or even the merge of data of studies does not fit to the scope of this guideline. This guideline should strictly be limited to the guidance on how to conduct a valid and reliable investigation of medical products in JIA and thus, provide high level of evidence to use or not to use a medical product. **We recommend deleting lines 145 to 146 and 228 to 240.**	and dose finding studies are however required, and this has been stated more unambiguously: *Pharmacokinetic and dose finding studies in the target population are needed.*
Line 228	EFPIA 9	**Comment:** The title is not fully aligned with the content of the section : extrapolation is not restricted to efficacy. It is also successfully applied (as discussed in the Concept paper) for safety, and for PK and PD. **Proposed change (if any):** It is suggested to revisit the title, e.g. extrapolation ~~of efficacy~~ ***opportunities***.	Partly accepted. *Extrapolation of efficacy* has been moved to section 6 (Strategy and design of clinical trials) and in this context only extrapolation of efficacy is discussed.
Line 228	PRINTO	**Comment:** Because of new era of biosimilars we must additionally redefine and precise term extrapolation to avoid direct extrapolation of adult data on children (like it was done for child Crohn disease). According to Guideline on pharmaceutical development of medicines for paediatric use	Not accepted. The EU legislation and guidance for biosimilars is not within the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(EMA/CHMP/QWP/805880/2012 Rev. 2) and Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (EMEA/CHMP/EWP/147013/2004) and especially according to clinical experience and PK/PD specificities of biologics - extrapolation of efficacy and safety data obtained in studies perform in adults (RA, AS and/or PsA and IBD studies) cannot be extrapolated to children with JIA. Necessity to adjust dosing and perform dose finding studies for children population have been shown for several biologics (etanercept, adalimumab, tocilizumab) why it is rationale to request from any new biologic or biosimilar to perform this type of studies in JIA before obtaining approval for JIA indication. Since safety is as major concern in young age and regarding fact that even small changes in monoclonal antibodies molecule can induce change in immunogenicity and safety there is a necessity for short and long term (post-marketing) drug specific monitoring of biosimilars. **Proposed change (if any):** a) To achieve this, after the dose finding, safety and efficacy study performed, biosimilars for JIA should be registered as INN followed by brand name added as suffix. b) it is rationale to request from any new biologic or biosimilar to perform this type of studies in JIA before obtaining approval for JIA indication	
Line 229	PRINTO	**Comment:** Though the paediatric patient population with JIA is less, but extrapolation of data from adult	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		drug trial (regarding safety and efficacy) should not be copied in totality. **Proposed change (if any):** All attempts should be made to perform trial in JIA for most of the drugs used as far as practicable.	The circumstances under which extrapolation is possible and the extent of extrapolation opportunities have been explained in the guideline.
Line 238	PRINTO	**Comment:** explain the abbreviation?	Accepted.
Line 240	PRINTO	**Comment:** It should be considered that EMA withdraws a license if post marketing obligations are not met by the manufacturer	Acknowledged. This is part of the EU regulation but not to be included in the guideline.
Line 242	PRINTO	**Comment:** The limitation to the ACR ped criteria (especially the ACR ped 30) as primary outcome criterion does not appear to us contemporary. These criteria have never been validated in non-poly JIA and especially not in systemic JIA. Furthermore these criteria tend to show more easily a stronger improvement if the disease activity is higher at baseline. In addition, patients of recent past tend to receive treatment earlier and thus show less damage and less limitation of function. If the CHAQ is 0 at baseline (which is the case in more than one-third of the patients at disease onset), it cannot improve over time, but only worsen. In addition, if the ESR or the CRP is low at baseline, which occurs in a number of patients, it cannot improve but worsen only. The lower the disease activity, the easier a relative worsening. Generally speaking an pedACR 30 response is considered inacceptable for pediatric rheumatology! The mentioned secondary endpoints should rather be	Partly accepted. The first paragraph has been modified: *…the ~~recommended~~ primary endpoint ~~is~~**has historically been** the change in ACR paediatric core set criteria.* The following sentences have been added: *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.* The draft guideline stated that *"low disease activity, inactive disease or remission (on and/or off treatment) are alternative suitable primary endpoints)".* Due to recent advances and the comments received, a new paragraph entitled ***Minimal disease activity and inactive disease / remission (treat to target approach)*** has been added. This paragraph

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered primary endpoints: 1) Inactive disease or, if that cannot be reached, then at least 2) JADAS-minimal disease activity Such shortcomings may be avoided by using the JADAS as endpoint. Here, the number of patients achieving a “target to treat” can be used. A definition has been described for JADAS-remission, JADAS-minimal disease activity, JADAS acceptable disease state. Furthermore a definition of JADAS-improvement has been published in analogy to the DAS28 in adult RA defining the necessary decrease of the JADAS according to the value of the JADAS at baseline. The statistical performance of the JADAS-defined improvement was superior to that of the ACR ped criteria-defined improvement. (Ref. Horneff & Becker, Rheumatol 2014). This measure enables the implementation of a primary outcome criterion by analogy with the EULAR DAS28 improvement and definition of DAS28 remission.	describes assessment of disease activity based on the JADAS and the definitions for the above mentioned alternative primary endpoints (based on the JADAS/ACR).
Line 242	PRINTO	**Comment: 5.2- Primary endpoints** 253- For SJIA fever and ***rash*** should be added to the core set parameters 254- In this new biologic era it is undemanding to consider ACR ped 30 as an accepatable endpoint. For my consideration the first aceptable primary endpoint would be ACR ped 50 , so the patients at least experience 50% of improvement	Partly accepted. Inclusion of rash is not accepted, as only fever is included in the ACR paediatric core set criteria for sJIA. The following sentences have been added (see comments on pages 30-31): *Demonstration of clinically highly relevant decrease in disease activity, such as ACR Pedi 70 response is expected.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			With adequate justification, ACR Pedi 30 or 50 could be acceptable primary endpoints in hard-to-treat patients.
Lines 243-245	EFPIA 10	**Comment:** This may not be appropriate for types of JIA such as oligoarticular and ERA which have fewer active joints than polyarticular JIA. The likelihood of achieving a 30/50/70% change is dependent on the number of joints active at baseline. Additionally, different JIA types may have differing frequency of CRP or ESR elevation while still having active disease. An alternative endpoint, short of LDA or remission as noted to be acceptable below, should be recommended. Mean percent change from Baseline to Week 12 in the number of active joints with arthritis has also been accepted by the CHMP as the primary endpoint. **Proposed change (if any):** 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. **Other endpoints such as mean percent change from Baseline to Week 12 in the number of active joints with arthritis may also be justified.**	Partly accepted (see previous comments). The sentence proposed (*Other endpoints such as mean percent change from Baseline to Week 12 in the number of active joints with arthritis may also be justified*) is not accepted, as a validated composite endpoint should be used in pivotal studies.
Line 247	PRINTO	**Comment:** completed by and entheses	Not accepted. Entheses are not part of the JIA core set. Additional endpoints for ERA are listed within the secondary and supportive

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			endpoints (see also PRINTO comments “After Line 253” on pages 34-35 and “After Line 292” on page 41).
Line 247	PRINTO	**Comment:** joints and enthuses, Without these items we whould loose most of our ERA and PsA patients. Important because of the new “PsA specific” biologics.	Not accepted (see above).
Section 5.1, extrapolation of efficacy, after line 238	MEB5	Proposed change: Please add: In some instances the need for clinical trials might be limited to PK and dose finding studies, e.g. for medicines where a clear PK-PD relationship and therapeutic window has been established in adult arthritis models.	Accepted.
5.1. Extrapolation of efficacy	University of Nis Serbia	**Comment:** Because of new era of biosimilars we must additionally redefine and precise term extrapolation to avoid direct extrapolation of adult data on children (like it was done for child Crohn disease). According to Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) and Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (EMEA/CHMP/EWP/147013/2004) and especially according to clinical experience and PK/PD specificities of biologics - extrapolation of efficacy and safety data obtained in studies perform in adults (RA, AS and/or PsA and IBD studies) cannot be extrapolated to children with JIA. Necessity to adjust dosing and perform dose finding studies for children population have been shown for several biologics (etanercept, adalimumab, tocilizumab) why it is rationale to request	Not accepted (see also comment on page 29 “Line 228”). The EU legislation and guidance for biosimilars is not within the scope of this guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		from any new biologic or biosimilar to perform this type of studies in JIA before obtaining approval for JIA indication. Since safety is as major concern in young age and regarding fact that even small changes in monoclonal antibodies molecule can induce change in immunogenicity and safety there is a necessity for short and long term (post-marketing) drug specific monitoring of biosimilars. **Proposed change (if any):** a) To achieve this, after the dose finding, safety and efficacy study performed, biosimilars for JIA should be registered as INN followed by brand name added as suffix. b) it is rationale to request from any new biologic or biosimilar to perform this type of studies in JIA before obtaining approval for JIA indication	
Line 253	PRINTO	**Comment:** If present all the other systemic features should be included	Not accepted (see also PRINTO comment “Line 242” on page 32). Only fever is included in the ACR paediatric core set criteria for sJIA.
After Line 253	PRINTO	**Inserted:** For PsA and enthesitis related arthritis specific indexes should be considered as well like. As a reference the following could be considered for enthesitis related arthritis: tender entheseal assessment; overall back pain and nocturnal back pain (0–100 mm VAS), completed by parents; modified Schober’s test, For PSA the extent of psoriasis with the psoriasis body surface area (BSA) and PGA of psoriasis (0–5), the Psoriasis Area and Severity Index (PASI),	Partly accepted (see also PRINTO comment “Line 247” on page 33). The use of several secondary endpoints is endorsed but only the most relevant ones will be mentioned in this guideline. “Overall back pain and nocturnal back pain” have been added as additional endpoints for ERA, and “PGA” as an additional endpoint for PsA, in line with a recent PRINTO trial in extended oligoarticular JIA, enthesitis-related arthritis and

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		dactylitis, DIP arthritis, nail changes and family history. Any other index past or future index specifically validated in these categories should be also considered at the time of the planning of the clinical trial.	PsA (Horneff G et al. Ann Rheum Dis 2014;73:1114–1122). The following bullet point has been added: • *Other endpoints and indexes specifically validated in JIA categories at the time of planning of the clinical trial should also be considered.*
Line 254 - 255	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** I believe that the ACR response should be called JIA ACR30, JIA ACR50 etc responses. They are indeed designed for JIA in an effert supported by the ACR. A similar set of response criteria has been designed for JDM and they are as pediatric ("pedi") as well. The use of pedi is too generic. The level of response JIA ACR20 should not be even mentioned: this is too of an achievement. In addition, JIA ACR100 should not be mentioned because its use should be discouraged. It gives the impression that the disease is in remission (100 % improvement): however, because of the definition, one can have a JIA ACR100 response with active joints and abnormal ESR. **Proposed change (if any):** delete JIA ACR20 and JIA ACR100 from the paragraph. Properly name the outcome ad JIA ACR20, JIA ACR50, JIA ACR70 and JIA ACR90.	Partly accepted. ACR Pedi 30/50/70/90/100 are improvement criteria to be reported in JIA clinical studies. It is agreed to delete ACR Pedi 20. Although there is variability in the spelling of the acronym, the version used in this guideline (e.g. ACR Pedi 30) is considered established within the EU context.
Line 254	PRINTO	**Comment:** Pedi20 is not an acceptable endpoint in pediatric rheumatology **Corrected:** JIA ACR *of improvement:* The JIA ACR criteria (JIA ACR 30, JIA ACR 50, i JIA ACR 70, JIA ACR 90 and Pedi 100) are measures	Partly accepted (see above).
Lines 261 - 262	PRINTO	**Comment:** ACRPedi 30 usually is too low an	Accepted.

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		improvement to be meaningful especially for the lead in phase.	New wording (see also pages 30-32): *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.*
Line 264	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** In a future perspective, given the recognized important limitations of the ACR % response, it should be recognized that JIA ACR responses are far from ideal, and that in the future a continuous measure of disease activity might become the acceptable primary outcome. This concept should be included in this paragraph and JADAS should actually be listed as the first secondary endpoint. **Proposed change (if any):** include a sentence based on the above issues in line 264 that would provide a link to the mentioning of low disease activity (cut off from JADAS) inactive disease etc	Accepted (see comments above and below).
Lines 268-269	PRINTO	**Comment:** Treatment compliance should be checked beforehand before embarking on disease activity. **Proposed change:** Drug adherence should be checked and included in records before defining 'remission' & 'flare'.	Not accepted. Ensuring treatment compliance is essential in any trial. The proposed sentence is not considered needed within this regulatory guideline.
After Line 271	PRINTO	**Inserted:** 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).	Partly accepted. The text proposed by PRINTO has been condensed but mostly accepted (see also PRINTO comment "Line 242" on page 32): - Minimal disease activity and inactive disease / remission have been included as the preferred primary endpoints - The table proposed by PRINTO includes also data not related

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		Nowadays however with the availability of several therapeutic agents for the treatment of JIA other alternative and more demanding primary endpoints could be also considere such as minimal disease activity based on JADAS, ACR inactive disease or clinical remission (on and/or off treatment). Indeed the evaluation of the inactive disease status, (defined as no arthritis, no systemic JIA sign/symptoms, no uveitis, normal index of inflammation and normal physician's global assessment of disease activity, absence of morning stiffness) is an important outcome to be reported in JIA clinical trials. (Wallace et al, 2004, Wallace et al, 2011) When the definition of inactive disease status is met for 6 continuous months the patient is said to be in clinical remission on medication. When the inactive disease status is met for 12 months in the absence of any medication then the patient is classified as being in a state of clinical remission off medication. Criteria for the evaluation of the level of disease activity are now available through the Juvenile Arthritis Disease Activity Score (JADAS).(Consolaro et al, 2009, Consolaro et al, 2012, Consolaro et al, 2014a, Consolaro et al, 2014b) The JADAS components were selected from the 6 variables included in the ACR Pedi pediatric core set, and includes the following 4 measures: physician global assessment of disease activity, measured on a 10-cm visual analog scale (VAS); parent/patient global assessment of well-being; count of joints with active disease; and erythrocyte	to the primary endpoints (e.g. cut-off values for low-moderate-high disease activity) and is therefore not included. It is mentioned in the guideline that these cut-off values were recently developed, and the relevant references have been provided - It is not needed here to mention that the primary endpoint should be evaluated after an adequate course of treatment, and that sample size simulation should be provided. The relevant issues are discussed in section 6 (Strategy and design of clinical trials). - Individual components of the ACR Pedi score are already mentioned within the *Secondary and supportive endpoints*. Components for calculation of the JADAS are the same. The following text has been included in the paragraph "*Primary endpoints*": *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*

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		sedimentation rate (ESR) or alternatively CRP,(Nordal et al, 2012) normalized to a 0 to 10 scale. Three versions of the JADAS were developed, which differ in the active joints count incorporated: JADAS10, JADAS27, and JADAS71. The total score is calculated as the simple sum of its components. The cutoff values in the JADAS that correspond to the states of inactive disease, minimal disease activity, parent/child acceptable symptom state and high disease activity were recently developed for all the original JADAS versions (Box 1). The use of the JADAS for minimal disease activity or the JIA ACR inactive disease/clinical remission criteria should foresee by definition the evaluation of the primary endpoint after an adequate course of treatment depending on the half life of the drug and the time to response as derived from studies in the adult counterpart. Table 1. Cutoffs for disease activity states in original and clinical JADAS version JADAS10/71 JADAS27 cJADAS10 Oligoarthritis Inactive disease ≤ 1 ≤ 1 ≤ 1 Low disease activity ≤ 2 ≤ 2 ≤ 1.5 Moderate disease activity 2.1 – 4.2 2.1 – 4.2 1.51 – 4 High disease activity > 4.2 > 4.2 > 4 Polyarthritis	*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 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.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Inactive disease ≤ 1 ≤ 1 ≤ 1 Low disease activity ≤ 3.8 ≤ 3.8 ≤ 2.5 Moderate disease activity 3.9 – 10.5 3.9 – 8.5 2.51 – 8.5 High disease activity > 10.5 > 8.5 > 8.5 Sample size simulation for all different primary endpoints should be provided in order to evaluate the most feasibile trial with the lower number of children to be enrooled. It is advisable that higher level of JIA ACR improvement (e.g. JIA ACR 50) or minimal disease activity/clinical remission should be more appropriate endpoints. The parameters for the calculation of the JIA ACR criteria, JADAS and inactive disease should be always reported	
Line 275	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** Remission is not defined. This could be clarified as indicated below. To the best of my knowledge, at present, there is no evidence that one is better than the other **Proposed change (if any):** remission as defined by Wallace's criteria or by JADAS validated cut-off (reference cited).	Accepted (see above).
Line 277	PRINTO	**Comment:** Pain assessment.... for children or for parents? I think have to be mentioned.	Accepted. “By parent/patient” has been added.
Line 281	EFPIA 11	**Comment:** The guidelines highlight the limitation of ACR and recommend the use of JADAS as a secondary endpoint.	Accepted (see above).

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		Could change in JADAS be used as a primary endpoint?	
Lines 281-285	PRINTO	**Deleted:** Lines 281-285	Partly accepted. Absolute disease activity (based on the JADAS) corresponding to minimal disease activity and inactive disease is discussed within the primary endpoints (see above). In addition, absolute disease activity should be measured within the secondary endpoints.
Line 287 5.3. Assessment of structural damage	PRINTO/ University of Nis Serbia	**Comment:** Muskulo-skeletal ultrasound (MSUS) may enable detection of active synovitis in the absence of clinical signs and symptoms and may aid in a further refinement of disease subtype or definition of remission in JIA. A. Consolaro, G. Negro, S. Lanni, N. Solari, A. Martini, A. Ravelli Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. Clin Exp Rheumatol 2012; 30 (Suppl. 73):S157-S162. Lanni S, Wood M, Ravelli A, Magni Manzoni S, Emery P, Wakefield RJ. Towards a role of ultrasound in children with juvenile idiopathic arthritis.Rheumatology (Oxford). 2013 Mar;52(3):413-20 Collado P, Jousse-Joulin S, Alcalde M, Naredo E, D'Agostino MA. Is ultrasound a validated imaging tool for the diagnosis and management of synovitis in juvenile idiopathic arthritis? A systematic literature review. Arthritis Care Res (Hoboken). 2012 Jul;64(7):1011-9 Roth J.et al. Definitions for the sonographic features of joints in healthy children Arthritis Care Res. 2014 in press Naredo E, Wakefield RJ, Iagnocco A, Terslev L,	Partly accepted. The use of ultrasound is mentioned within section 5.2 (Assessment of structural damage). As discussed in the pages below, MSUS is currently an exploratory measure. The wording suggested by PRINTO has been accepted with some modification (see “Line 301” page 43): *The use of MRI and ultrasounds can be considered as exploratory endpoints since no final validation studies are currently available.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Filippucci E, Gandjbakhch F, Aegerter P, Aydin S, Backhaus M, Balint PV, Bruyn GA, Collado P, Finzel S, Freeston JE, Gutierrez M, Joshua F, Jousse-Joulin S, Kane D, Keen HI, Moller I, Mandl P, Ohrndorf S, Pineda C, Schmidt WA, Szkudlarek M, Conaghan PG, D'Agostino MA. The OMERACT ultrasound task force--status and perspectives J Rheumatol. 2011 Sep;38(9):2063-7 **Proposed change (if any):** In this section it is necessary to add paragraph about ultrasound to be used as a tool in JIA studies: Muskulo-skeletal ultrasound (MSUS) may enable detection of active synovitis in the absence of clinical signs and symptoms and may aid in a further refinement of disease subtype or definition of remission in JIA. MSUS can be used as tool to estimate JIA disease activity and structural damage.	
Line 287	PRINTO	**Comment:** Secondary outcome parameters (such as quality of life, damage, pain, fatigue, morning stiffness) should be mentioned here, but not individual measures (i.e., CHQ, JAMAR) which are to be used. Mentioning that validated measures should be used is sufficient.	Accepted.
After Line 292	PRINTO	**Inserted**: • For psa and enthesitis related arthritis specific indexes should be considered as well like. As a reference the following could be considered for enthesitis related arthritis: tender entheseal assessment; overall back pain and nocturnal back pain (0–100 mm VAS), completed by parents; modified	Partly accepted (see also PRINTO comments “Line 247” and “after Line 253” on pages 33-35). The following changes have been included: • *Tender entheseal score, **overall back pain and nocturnal back pain**, and modified Schober’s test can be*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Schober's test, For PSA the extent of psoriasis with the psoriasis body surface area (BSA) and PGA of psoriasis (0–5), the Psoriasis Area and Severity Index (PASI), dactylitis, DIP arthritis, nail changes and family history. Any other index past or future index specifically validated in these categories should be also considered at the time of the planning of the clinical trial.	*used in ERA* ***as additional 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.***
Line 293	PRINTO	**Comment:** Only the van der Heijde score is mentioned here, even though there are several other validated measures for radiographic damage. **Proposed change:** Assessment of damage by X-ray, MRI or sonography is encouraged, however, validated scores should be used and minimal exposure to radiation sought.	Partly accepted. See below PRINTO and UCB comments.
After Line 293	PRINTO	**Inserted:** Assessment of structural damage should be a mandatory requirement for trials which foresee at least a 2 years extension phase Although tThe modified van der Heijde score is currently the only validated methods for the assessement of structural damage in children by the evaluation of wrist and hand xray. Other future validated measures could be considered when available	Partly accepted. There are ethical and practical issues against requiring a comparative assessment of structural damage in JIA. The following text has been added (see also comment below by UCB): *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*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			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 could be considered when available to minimise exposure to radiation.
294 - 295	UCB	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. Comment: In children the effect of age on bone images may induce more variability in images that in adults. Effect on growth plate should be captured, as JIA can lead to early closure and a shorter bone when affected joint is near growth plate. It also retards onset of puberty and retards closure generally due to systemic inflammatory mediators	Accepted (see previous comment).
Lines 294-301	PRINTO	**Comment:** Assessment of structural damage.... (Marco: non capisco cosa volesse modificare… ha scritto solo questo)	N/A
Line 301	PRINTO	**Comment:** The use of MRI for patients with ERA could be included in trial for detection of early sacroileitis, for structural damage or for remission. **Inserted:** The use of MRI and ultrasounds could be considered as secondary exploratory endpoint since no final validation studies are currently available.	Accepted. The text has been modified (see also PRINTO comment “Line 287” on page 40-41): *The use of MRI and ultrasounds can be considered as exploratory endpoints since no final validation studies are currently available.*
Line 305	PRINTO	**Comment: PD -** explain the abreviation?	Accepted.

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Line 306	EFPIA 12	**Comment:** Add “or body weight related” after age-specific **Proposed change (if any):** Age-specific ***and/or body weight related*** changes...	Accepted.
Lines 308 - 316	PRINTO	**Comment:** We strongly disagree with the use of modelling or simulation approach.	Not accepted. Modelling and simulation is part of modern drug development but applicability of the results needs to be confirmed in each case.
Line 316	PRINTO	**Comment:** The limitations related to the amount collected blood per unit of time and age of patient should be particularly considered in children studies. I do not have major comments to the document.	Accepted (see next comment).
After Line 316	PRINTO	**Inserted:** The rational for the potential use of fixed dosing regimens, instead of x kg or m2 dosing should be adequately explained. In all instances the protocol should specify that the amount of blood to be undertaken is in line with international recommendation (e.g. See 2008 version of the Ethical considerations for clinical trials on medicinal products conducted with the paediatric population Recommendations of the ad hoc group for the development of implementing Guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use). In all case a proper pK and dose ranging studies should be performed prior to the implementation of	Partly accepted. The proposed first paragraph is accepted: *The rational for the use of fixed dosing regimens instead of per kg or per m^2 dosing should be adequately explained.* Reference to the most relevant guidelines is found in section 3 (Legal basis and relevant guidelines) (see also PRINTO comment “Line 199 – 205” on pages 24-25). Last paragraph proposed *(In all case a proper PK and dose ranging studies should be performed prior to the implementation of any phase III clinical trial*) is not accepted. As mentioned in the previous paragraph, modelling and simulation can be used and “*where appropriate, well-planned dose ranging studies should be carried out*”.

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		any phase III clinical trial.	
Line 318	PRINTO	**Comments:** Studies head to head Some selected group of patients, might not be necessary to start with DMARDs	Acknowledged.
Line 319	PRINTO	**Comment:** Patient number in non-inferiority trials tend to be higher than realistic for studies in childhood. Thus solutions have to be found to overcome this. Otherwise further improvement of the treatment strategies in children will be impossible. All options have to be discussed. Also the mathematical border of a p of 0.05 is a historical agreement and can be a matter of discussion. Why not 0.1? This would markedly lower the number of participants. Every agreement has to live with the risk of error.	Response from EMA statisticians: We could consider that NI trials are feasible. Consider common assumptions of one-sided alpha 2.5%, power 90%, and response rate for both arms (investigational treatment and active control) of 70% or 75% in a non-inferiority (NI) setting. NI margin 5%, total N (both arms) = 3532 (response 70%) or 3154 (response 75%) NI margin 10%, total N = 884 or 790 NI margin 15%, total N =394 or 352 NI margin 20%, total N =222 or 198 The last presented margin (20%) may be unreasonably high, but one has to consider to the expected placebo response rate is much lower, so a NI margin larger than 5% or 10% could be up for discussion. Allowing for less power (e.g. 80%) could help too. All in all, the number of patients needed may be more in the order of hundreds than thousands.
Line 319	IRCCS Ospedale Pediatrico Bambino Ges	**Comment**: in the whole paragraph there is no mention of early escape to minimize placebo exposure. I believe that this is a key point and the sentence below should be added at the beginning of the 2nd paragraph (ln 327)	Accepted. The following text has been included: *In addition, escape rules for placebo-patients and criteria for*

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		Proposed change (if any): In order to reduce placebo exposure, use of predefined escape rules is encouraged	*discontinuation due to lack of efficacy should be predefined and reported.*
Line 332	PRINTO	**Comment:** Those ethical concerns can be solved by switching the placebo patients to other arms (verum/active comparator) after a reasonable time (e.g. 12 weeks or earlier when life-threathening events are ocurring).	Accepted. The following text has been included: *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.* Note: comments proposed in PRINTO v2 (lines 333-341; no justification provided) have not been implemented. It is normally not justified to perform an equivalence trial in JIA due to large sample size requirement. Also, the proposed addition at the end of the paragraph (*This last study design might have the limitation of being not applicable in case the add-on with foresees the addition of a biologic agent over another biologic agent*) is not considered relevant, as it is already mentioned that "*Add-on placebo therapy may be used when study design requires placebo and allows for combination with other effective treatment*".
Line 347-349	PRINTO	**Deleted**	Partly accepted (see comments below).
Line 347-349	IRCCS Ospedale Pediatrico	**Comment:** The objective of this sentence is not clear in the setting of chronic inflammatory diseases such as the various JIA forms. While blinded tapering and	Accepted. The paragraph has been amended (see also PRINTO comment

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	Bambino Ges	withdrawal is the best reasonable approach to define a maintenance dose or even identify the patients who may withdraw treatment after long-lasting remission, efficacy measure after a parallel arm study evaluated by withdrawing an efficacious treatment appears to be unnecessary (efficacy having been demonstrated already in the previous controlled parallel arm phase) and potentially unethical. **Proposed change (if any):** I would clarify the sentence to clearly state the objective of this withdrawal phase (as stated in line 368-369)	below "After Line 349"): *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.*
After Line 349	PRINTO	**Inserted:** The major problem with formal active comparator (either as superiority or non-inferiority) is the problem of the sample size. A suitable alternative could be a randomized open-label trials against active comparator. Children are randomized in an open fashion to an active drug (e.g. methotrexate or an anti-TNF for polyarticular course JIA or anti-IL1 or anti IL6 for systemic JIA) or to the verum. Both groups have the same inclusion criteria. The primary endopoints (JIA ACR criteria or JADAS minimal disease activity or inactive disease/clinical remission) will be evaluated after a proper follow up period which will depend from the half-life of the drug and its biologic effect (e.g. 6 or 12 months). The comparison of the verum versus the active comparator will be done by comparing the lower bound of the 95% CI interval of the most active drug with the upper bound of the 95% CI interval of the lower effective drug. An overlap of the confidence interval of verum and active comparator will be the criteria to judge about the	Partly accepted. The paragraph starting with "*The major problem…*" is not accepted. Acceptance of open label data for marketing authorisation should remain exceptional (subject to case-by-case assessment and based on an analysis of extrapolation opportunities). See also UCB comment "Lines 318 – 374" on pages 47-48 and PRINTO comment "After Line 374" on pages 52-54. <u>Response from EMA statisticians:</u> We fail to see how an open label design answers the problem of sample size. It makes no difference and is not an appropriate solution. <u>Other changes proposed by PRINTO (v2) for section 6.3.1:</u> The paragraph related to discontinuation (*In addition*

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		efficacy of the verum. In this hypothesis the active comparator and the experimental therapy should have a 95% CI quite narrow, e.g. with a pre-specified error (standard error x a constant equal to about 10-15% of the point estimate). For example for an active comparator which at 1-2 years has shown an ACR 70 equal to 70%, the CI intervals will be 63-77% in the hypothesis of error equal to 10% of the point estimate. An experimental therapy in which the error will be similarly equal to 10% of the point estimate will be equivalent in case its upper bound will overlap with the lower bound of the active comparator. Such example would require a sample size of 150 patients per arm. In addition appropriate criteria to drop out patients must be clearly reported. For example a trial in systemic JIA might foresee that if a child has persistent fever after 3 days despite verum, active comparator or placebo, the child should be dropped, considered as a non-responder and treated with the alternative method available. Similarly a in polyarticular JIA a child not reaching at least a JIA ACR pediatric 30 level of improvement or minimal disease activity by JADAS within 2-3 months should be treated in the same fashion. In order to explore the degree to which treatment effects are sustained in the long-term (e.g at least 2 years better 5 years), a study design in which efficacy measures are observed after randomised and blinded withdrawal is recommended. In order to further minimize placebo exposure an unequal randomization could also be considered (e.g.	*appropriate criteria to drop out patients must be clearly reported…*) has been partly accepted. The text proposed is considered too detailed and does take into account e.g. the potential to increase the dose in non-responders. The following sentence has been added: *… criteria for discontinuation due to lack of efficacy should be predefined and reported.* PRINTO proposes to delete the following sentence: *In all of these designs current ideas favouring early treatment should also be taken into account.* The sentence has been retained. The concept of early treatment is established (see also comments on page 8), and the duration of placebo treatment should be kept minimal. The changes proposed within the paragraph: *In order to explore the degree to which treatment effects are sustained in the long-term…* are partly accepted. It is not considered appropriate to state the duration of "at least 2 years better 5 years". In fact, these effects have often been studied at an earlier time point. The paragraph has been amended: *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.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		verum placebo 2:1)	The following sentence proposed has been accepted: *In order to further minimize placebo exposure, unequal randomisation could also be considered (e.g. verum placebo 2:1)…*
318 - 374	UCB	Section 6.2.1. Study design Comment: For products where efficacy and safety have been established in adults, the draft guidance only mentions the randomised placebo controlled withdrawal design trials. In cases where products of the same pharmacological class have already been approved and where similarities between the adult RA and the JIA population were shown in the placebo-controlled clinical studies with respect to efficacy, safety and dosing, an alternative to the randomised placebo controlled withdrawal design trials could be open-label design. In this context, extrapolation of efficacy data could be made to the intended JIA population if similar results are obtained for PK and safety in JIA as seen for adult RA. The rationale for open-label studies includes ethical concerns associated with denying active treatment to a population of patients that cannot make their own fully-informed choices about healthcare, the enrolment difficulties commonly encountered for placebo-controlled paediatric studies, and the limited size of the patient population from which to recruit. Proposed change (if any): new text	Partly accepted. Please see also PRINTO comment above “After Line 349” and PRINTO comment “After Line 374” on pages 52-54. Acceptance of open label data for marketing authorisation should remain exceptional (subject to case-by-case assessment and based on an analysis of extrapolation opportunities). The following text has been included in section 6.1 Extrapolation of efficacy: *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-*

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		Open label design **For products where efficacy and safety have been established in adults and in cases where product of the same pharmacological class have already been approved and where similarities between the adult RA and the JIA population were shown in the placebo-controlled clinical studies with respect to efficacy, safety and dosing, open-label design could be used.**	*marketing data.*
Line 350	PRINTO	**Comment:** The time to leave the withdrawal study design has come. Drugs are used to improve the situation of patients. The withdrawal design does not measure improvement but deterioration. Alternative study designs should be allowed: e.g., flexible-adaptive study designs with population enrichment, studies with several primary outcomes (e.g. efficacy and safety), Bayesian statistics.	Not accepted. Randomised placebo controlled withdrawal design is an option and there are several successful examples of its use. The advantages and the disadvantages have been discussed. Parallel group design is however the preferred option. See also PRINTO comment "Line 103" on pages 10-11. Response from EMA statisticians: The use of **Bayesian** methods may help to understand the benefits of a treatment, but should always be presented alongside a traditional frequentist analysis, so that the actual contribution of the data generated in the trial can be assessed and understood. If substantial differences between the two approaches are apparent, the results will be heavily influenced by the choice of prior and so may not be considered sufficiently robust. **Adaptive** study designs can be considered, for population enrichment and/or selection of the best dose. This can be

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			done under both frequentist and Bayesian frameworks. Some methods can be used to change the randomisation allocation and therefore decrease the overall number of patients needed. Studies with **several primary outcomes** (e.g. efficacy and safety): Are you thinking about a combined "benefit-risk" type endpoint making studies more ethical to run if one uses a much lower dose as an active comparator? Or did you consider co-primary endpoints? But for the latter, it can only increase the sample size if one of the two co-primary endpoint requires more patients and it will decrease power for sure. So it is difficult to see an advantage in co-primary endpoints here. If you consider **uncontrolled** clinical trials, the guideline could refer to ICH E10 and the EMA/CHMP guideline on clinical trials in small populations. Both documents talk extensively about aspects concerning historical (or external) controls. The EMA guideline states "The ideal is a comparative trial using an internal control group, as there are several well-known problems inherent with historical (or other external) controls".
Line 350	PRINTO	**Comment:** The preference of a "parallel group design" over a "randomised placebo controlled withdrawal design" should be stated.	Accepted. The following has been added in section 6.3.1 (Study 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****.*
Line 351	IRCCS Ospedale Pediatrico	**Comment:** The fact that this design has been accepted for many authorization studies does not represent a proper rational for choosing this design	Not accepted (see comments above and below).

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	Bambino Ges	**Proposed change (if any):** delete the sentence	
Lines 354-358	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** I believe that the pros and cons of the randomized placebo withdrawal design should be discussed in more detail. 1) An additional disadvantage is represented by the unknown safety risks linked to a potentially dangerous acute flare of the underlying disease: a rebound effect of a yet unknown novel inhibited mechanism by a novel target cannot be excluded a priori and therefore this should be added among the potential disadvantages 2) Among the presently listed potential advantages - there is no evidence demonstrating that this design is associated with short placebo exposure compared to a randomized parallel design with early escape based on non-response/flare. Therefore short placebo exposure should be removed - regarding the acceptability of patients and parents; again there is no evidence of a better acceptability. Actually, it is my personal experience as well as that of a number of other clinicians that the withdrawal of an efficacious treatment in a blinded manner is far from being easily accepted even in the setting of control trial. Moreover, a major conceptual disadvantage, that must be taken into account and discussed in this document, is represented by the fact that the length of the randomized withdrawal phase might be difficult to pre-define while designing the study. The recent example	Partly accepted. 1. "Potential for rebound" has been added (instead of "unknown safety risk of potential acute flares"): *The disadvantages of such a study design are non-conventional efficacy demonstration, bias towards responders and, small safety database* ***and potential for rebound effect****.* 2. The "short placebo exposure" is mentioned e.g. in the ICH E10 (Choice of control group and related issues in clinical trials) and the corresponding text has therefore not been deleted. 3. "Better acceptability of patients, parents and health care professionals" has been deleted as suggested, as there is no direct evidence for the claim. *4.* A paragraph on the duration of the withdrawal part has been added, as proposed by PRINTO "After Line 374" on pages 52-54.

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		of golimumab failing the primary outcome in the pivotal JIA phase III randomized withdrawal trial (most probably because of its long half-life, in spite of apparently very good data in the lead-in open phase) underscores this additional conceptual disadvantage (in addition to non-conventional efficacy measures and bias towards responders) and should dampen the enthusiasm on the randomized withdrawal design Proposed change (if any) - add to ln. 355: “unknown safety risk of potential acute flares” - rephrase ln 355 to 358 as follows: “The mean practical advantage of this design is the possible reduced population size that may allow for an easier feasibility” deleting “short placebo exposure” and better acceptability of patients, parents and health care professionals” - add in line 358: particular attention should be devoted to the design of the length of the withdrawal phase that has to be balanced between minimizing placebo exposure and allow sufficient time (based on drug efficacy and half-life) for sufficient number of flares to occur.	
Lines 368 - 369	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** In order to obtain better information from this withdrawal phase in established remission, the following sentence should be added. **Proposed change (if any):** Withdrawal should be performed together with biomarkers studies aimed at identifying patients who will not relapse after withdrawal	Accepted. A new subtitle has been added in Section 6.3.1 and the proposed text has been modified: *Biological or environmental causes for response/resistance* *…/…* *It is strongly recommended to include studies on biomarkers in the development program, to predict response and to*

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			identify patients who will not relapse after treatment withdrawal.
Lines 370 - 374	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** Would it be possible to make biomarker studies for the identification of responders compulsory? With the absence of such a study being justified in an appropriate waiver section? Moreover, it should be made clear that this paragraph concerns all study design and not necessarily the randomized placebo withdrawal design **Proposed change (if any):** dedicated paragraph to the issue of biomarker. Possibly including the previous sentences and its corresponding comment (at line 368-369)	Accepted (see above).
After Line 374	PRINTO	**Inserted**: A particular attention should be devoted to the duration of the withdrawal part especially for drugs with a long half-life or a prolonged biologic efficacy. Recent evidence (e.g. canakinumab, golimumab) showed that withdrawal trials with shorter duration of the withdrawal part could be a potential risk since the time could be too short to show a difference in the flare rate toward placebo for a possible prolonged biologic effect in children. In order to avoid this problem an event driven approach could be considered: this foresee that the duration of the withdrawal part is not necessarily fixed in term 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 (see canakinumab phase III experience). In order to further minimize placebo exposure an unequal randomization could be	Partly accepted (see also IRCCS Ospedale comment “Lines 354-358” on pages 50-52). The text proposed by PRINTO has been condensed and the detailed examples have been removed: *Particular attention should be devoted to the duration of the withdrawal part especially for drugs with long half-life or prolonged biologic efficacy. 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.*

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		considered as well (e.g. verum placebo 2:1). Given the well know bias of the withdrawal trial toward responders every effort should be put to report more meaningful outcome over time such as ACR 50, 70, 90, minimal disease activity or inactive disease at 1 and 2 years with the related 95% CI. **Alternative study design** Alternative study design could be also considered for example for drugs within the same class of action (e.g. another anti-TNF, another anti IL1 or anti IL6 generically called me too drugs). If for these drugs safety data primarily and efficacy also are convincing in the corresponding adult population then a proper pk (and if appropriate dose ranging study) should be performed and once the dose is establish a proper open label long term extension for safety (primarily) but also for efficacy (e.g. up to 2 years) should be implemented. A similar simplified approach could be considered for biosimilars when adequate safety and efficacy data are available from the adult counterpart. **Trials in uveitis** Whenever appropriate specific trials should be performed in JIA associated uveitis or the reasons for exclusion adequately documented. In all instances collection of data about the occurrence of uveitis (e.g. slit lamp examination, related therapies) ANA status should be collected as part of any clinical trials in JIA with the exception of systemic JIA.	The sentence on unequal randomisation has been added. The proposed paragraph *Given the well know bias of the withdrawal trial toward responders…* has been included and modified in line with the recommended primary endpoints: *Given the well-known bias of the withdrawal trial toward responders, every effort should be made to report a more meaningful outcome over time such as ACR Pedi 70, 90, minimal disease activity or inactive disease / remission at 1 and 2 years*. The proposed paragraph "Alternative study design" is not accepted (see also PRINTO comment "After Line 349" on page 46-47 and UCB comment "Lines 318-374" on pages 48-49). The proposed paragraph on uveitis has been modified and moved to section 5.1 (Assessment of symptoms and disease activity): *Whenever appropriate specific trials should be performed in JIA associated uveitis. In clinical trials in JIA with the exception of sJIA, data should be collected on the incidence and severity of uveitis, including ANA status.* A sentence proposed in PRINTO v2 under subtitle "Randomised placebo controlled withdrawal design" (*The disadvantages of such a study design are non-conventional*

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			efficacy demonstration ***(based mainly in open label and extension phase without a control)****, bias towards responders and a small safety database*) is not accepted, as the placebo controlled withdrawal period is an essential part of efficacy demonstration in this design.
Line 390	PRINTO	**Comment:** And to improve tolerability of biologics.	Accepted.
After Line 395	PRINTO	**Inserted:** However a careful evaluation should be considered for safety especially when combination foresee the use of 2 or more biologic agents at the same time.	Partly accepted. Combining multiple biologicals is generally not feasible due to safety risks. The proposed text in section 6.3.3 (Combination therapy) has been modified: *A careful evaluation of safety is needed.*
Line 400	PRINTO	**Comment:** And pharmacokinetic parameters including half-life.	Accepted.
Line 402	PRINTO	**Comment:** Why is the evaluation of anti-inflammatory effects, relief of symptoms such as pain or maintenance of symptomatic improvement limited to 12 weeks	Accepted. "E.g." has been added not to restrict the evaluation to 12 weeks: *Anti-inflammatory effects, relief of symptoms such as pain or maintenance of symptomatic improvement should be evaluated* ***e.g.*** *for up to 12 weeks.*
Line 408	IRCCS Ospedale Pediatrico Bambino Ges	**Comment:** 6 months is too short of a time interval to evaluate evidence supportive of a positive effect on joint structure **Proposed change (if any):** I would delete the 6 and just leave the 12 month time interval	Not accepted. Demonstration of structural damage is challenging; the placebo control needs to be kept short for ethical reasons and there is no established active control. The current wording (6-12 months) allows more flexibility in producing evidence supportive of a positive effect on joint structure.
Line 411-412	PRINTO	**Comment:** We have concerns in terms of	Acknowledged.

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		extrapolating safety results from adults to children. The risk profile in children is quite different from that in adults. There are risks that are higher and other risks that are lower in children than in adults. Examples are: the risk of myocardial infarctions or of infections. While children tend to have simple infections like common cold at higher frequencies, the rate of serious infections seems to be lower than in adults.	See previous comments on extrapolation.
Lines 414 to 416 and lines 452 to 459	EFPIA 13	**Comment:** The proposed draft revised guideline recommends conducting post-authorisation efficacy and safety observational registry studies in a systematic manner. The guideline should be clear that this is the case when only short term data is available from clinical trials and should recognise that there are different methods to assess the long-term efficacy and safety of a product that must be discussed and evaluated on a case by case basis. **Proposed change (if any):** Lines 414 to 416: "Because the marketing authorisation ~~would be~~ ***is*** 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*** the observational registry-type of study." Lines 453 to 459: The long-term evaluation of safety requires collection	Partly accepted. "*…e.g. in an open label extension study…*" has been added in section 6.3.4 (Study duration). The proposed change ("*Observational registry-type studies may be one approach to the collection of such data"*) has not been accepted, as these studies are generally required post-approval. The following text has been added into section 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.).*

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		of data from larger number of patients for a longer period of time, potentially into adulthood. Therefore safety data should also be collectedin the post-marketing ~~observational registry-type studies~~ ***period*** (see section 6.2.4.). ***Observational registry-type studies may be one approach to the collection of such data.*** 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 ***a sufficient number of*** 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.	
Line 417	EFPIA 14	**Comment:** "The following minimum set of data is recommended to be collected ***(as appropriate to the specific disease(s) being studied)***:..." To add consistency throughout the document.	Accepted.
Line 421	PRINTO	**Comment:** 213 and 421: uveitis, enthesitis, dactylitis, nail changes, family history	Accepted.
Between Line 422 and Line 423	PRINTO	**Inserted:** JADAS over time	Accepted.
Line 429	PRINTO	**Comment:** "However, once the patients are stabilized in remission lower maintenance dosages and even drug withdrawal may be appropriate. It is expected that options of dose-reduction and dose-interruption	Partly accepted (see also previous comments and the comments below). The last paragraph in section 6.3.4. (Study duration) has

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		and retreatment at relapse are addressed which could be performed in a randomized withdrawal phase (see section 6.2.1-)" This statement is in our view too passive. Protocols evaluating these issues in long-term follow-up clearly need to be prioritized. EMA might consider to require mandatory extension phases after phase III trials addressing these crucial questions which are more relevant in the pediatric population than in adults.	been modified (and further guidance related to study design is found in section 6.3.1): *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.*
Lines 431 to 434	EFPIA 15	**Comment:** "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.)". While treatment interruption is part of the randomized withdrawal study design, and re-treatment is often available outside of the study (e.g. in an open-label extension study) assessment of dose reduction would add another dimension to this randomised withdrawal trial design. It will not always be possible and relevant to study both dose-reduction and dose-interruption in the same paediatric trial. The guideline should state that at least one of these options, i.e. dose-reduction or dose-interruption, should be studied. **Proposed change (if any):** "It is expected that options of dose-reduction ~~**and**~~ **or** dose-interruption and re-treatment at relapse are addressed which could be performed in a randomised withdrawal phase (see section 6.2.1.)".	Accepted (see previous comment).

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431 - 434	UCB	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.). Comment: Assuming an open label study design is acceptable (see above), this dose-reduction/dose-interruption could also be handled within that study design. Proposed change (if any): 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 **or open-label** withdrawal phase (see section 6.2.1).	Not accepted. See previous comments. Acceptance of open label data for marketing authorisation should remain exceptional (subject to case-by-case assessment and based on an analysis of extrapolation opportunities).
Lines 449-451	EFPIA 16	**Comment:** It is unclear if this statement refers to effects on the immune system that are specific to children and cannot be addressed in adults. **Proposed change:** ***It would be preferable to address as many of these questions in adults and only conduct studies in children when necessary.***	Accepted. "*…or by studies in adults…*" has been added in section 7.1 (Specific adverse events to be monitored): *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 ….*
After Line 451	PRINTO	**Inserted:** This is particularly true for drug with new	Accepted (see also comment above).

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		mechanism of action to be tested in younger children (e.g. less than 6 years of age) where adequate measure to evaluate the potential impact of the experimental therapy on vaccination should be implement.	
Line 454	PRINTO	**Comment:** A comment should be added that "open-label extension studies" are the preferred study type over "registry-type studies"	Partly accepted. Both types of studies are important. The following text has been added in section 7.2 (Long-term safety) (see also EFPIA comment on pages 3-4): ***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).*
After Line 459	PRINTO	**Inserted:** **7. Miscellaneous** **7.1 Consent/assent forms** Language for consent and assent form should be prepared in a format understandable to children of different age groups and parents with difference cultural background. **7.2 Drug provision** Participation to industry trials from low-income countries is becoming more and more important for successful completion of enrolment in a timely fashion (Ruperto N, et al. The impact of the European paediatric legislation in pediatric rheumatology: past	Not accepted. Quotation of GCP and general trial practices is not needed in this regulatory guideline. Relevant references are found in section 3 (Legal basis and relevant guidelines).

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		present and future. Ann Rheum Dis 2013; 72:1893–189.). Pharmaceutical companies should secure a written commitment in the final protocol, to provide the drug until its approval for JIA in the participating country or until until there is a clinical benefit for the child (whichever come last). **7.3 Study reporting** Clinical trials study report, either for the primary short term outcome than for the long term outcome (e.g. 1-2 years and later) should follow the recommendation of the CONSORT treatment with particular emphasis on the intention-to-treat approach with all patients enrolled/randomized considered in the denominator and the dropped/lost to follow up considered as non-reponders from that point onward. Results of technically negative trials should be reported as well.	