MCRN / Arthritis Research UK
Paediatric Rheumatology CSG

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National Institute for Health and
Clinical Excellence – Level 1A
City Tower, Piccadilly Plaza,
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23rd August 2011

Dear [redacted]

Re: Single Technology Appraisal for Tocilizimab for the treatment of Systemic Juvenile Idiopathic Arthritis

I am writing on behalf of [redacted] Arthritis Research UK to whom you had written to on 3rd August 2011 as a consultee for the above STA. I chair the Arthritis Research UK/NIHR MCRN Paediatric Rheumatology Clinical Studies Group (CSG). This is a National expert group of clinicians, clinical academics, multi-disciplinary Allied Health Professionals with a strong Consumer representation, supporting the development and conduct of a comprehensive portfolio of quality clinical studies and clinical trials in the field of paediatric rheumatology.

The CSG identified through both European and National consultation with all relevant stakeholders the strategic importance and priority of trials in systemic-onset juvenile idiopathic arthritis (sJIA). In particular, the CSG recognised the importance of a trial of tocilizimab in this disorder and from its outset has supported the conduct of such a trial at both the national and international level as one of the most important next-step studies.

Of note, it was especially in view of a very strong consumer call for this trial that the CSG has endeavored to do all it can to support the acquisition of a robust evidence base for the clinical and cost effectiveness of this treatment within the NHS. It is also important to acknowledge the severity of this condition in many patients and the previous requirement for complex multiple drug and intravenous immunoglobulin treatment regimes than many patients have required for very many years in order to be maintained in only partial remission. This is the most common paediatric rheumatological disorder referred for stem cell transplantation as a lost resort treatment. It is also a potentially life threatening disorder.

Therefore the published evidence and recent results of the TENDER trial, as well as the national and international clinical experience of the use of Tocilizimab in the management of severe systemic-onset JIA (sJIA) clearly support the highly significant benefit of tocilizumab for children. To this end, we are very supportive of the evidence that has been submitted to NICE and would strongly encourage NICE to approve the use of Tocilizimab in this disorder.

The CSG fully supports the previous submissions by the British Society of Paediatric and Adolescent Rheumatology (BSPAR) with whom it works in close collaboration, and that has been previously considered by NICE. In addition we are in agreement with the comments that BSPAR are due to submit in response to the August 2011 appraisal document, to be submitted by [redacted] on behalf of BSPAR. We cannot underestimate the importance of supporting integration of new, effective agents such as Tocilizimab for the treatment of sJIA within the NHS, encouraged by the very significant clinical data that has emerged as a result of recent trials. This is especially so in the context of so few alternative effective treatments, otherwise enormous steroid burden, and their associated cumulative adverse events.

The CSG also fully acknowledge the difficulty of applying an appropriate economic model in assessing the health impact of Tocilizimab in the treatment of sJIA.

We would like to address a few specific issues in the recent draft appraisal:

1. **Appropriate use of paediatric outcome measures and assessments of quality of life.**
   It is important, indeed critical, that NICE recognises that outcomes traditionally used for different diseases such as rheumatoid arthritis (RA) are inappropriate to be used as measures of outcome for juvenile idiopathic arthritis (JIA), and especially sJIA. sJIA has a debilitating systemic inflammatory component that has contributed to fatalities including from myocarditis and from secondary haemophagocytic lymphohistiocytosis in the children and young people, as well as longer term fatalities due to amyloidosis from uncontrolled disease as in the 1960s and 1970s. This is unlike adult RA.
   JIA is a spectrum of disorders and the vast majority (over 90%) of children do not have rheumatoid factor positive polyarthritis, CCP positive antibodies nor are they HLADR4 positive. Children with sJIA are both clinically and genetically different from RA. Therefore, it is imperative that NICE does not use the CHAQ alone, or out of context, simply because of the use of the adult "HAQ" (which has a very different utility and validation) in assessing clinical improvement or to define severity appropriate for the use of a therapeutic agent.
   CHAQ is a poor indicator of paediatric quality of life and there are separate tools for paediatric patients. Indeed, there is international consensus on the most appropriate way of assessing disease activity in JIA as stated below.
   The CHAQ is only used as one of six core set criteria which together inform the calculation of internationally approved and recognised measure of clinical improvement and disease activity for arthritis in children, but it is well documented that this does not fully reflect sJIA disease activity. The internationally approved American College of Rheumatology JIA paediatric outcome criteria that have been used in the TENDER trial and all current JIA trials are robustly validated. Both the FDA and the European Medicines Agency accept these as criteria for clinical effectiveness in JIA clinical trials. For sJIA, there are in addition clinical manifestations of systemic inflammation that are recognised and measured in all clinical trials of agents for this subtype, such as high quotidian fevers, serositis and macrophage activation, all of which necessitate hospitalisation. Therefore to use only the CHAQ in an economic model is entirely insufficient and inappropriate. Absence of systemic features, normal growth velocity and the ability to reduce corticosteroid use, are also important measures of outcome in sJIA.

2. **The challenge of treating children with sJIA cannot be understated.**
   The number of repeated hospital attendances and inpatient admissions due to systemic features in sJIA such as uncontrollable high fevers alone is costly to the health service in addition to loss of the ability to work fulltime for the carer. Developmental delay, growth retardation, osteoporosis and missed educational and employment opportunities all lead to poor quality adult life. Long term uncontrolled inflammation of the joints may lead to joint replacements in young teenagers after 10+ years of damage, and more subsequent operative procedures. Amyloidosis as a complication has already been mentioned. A drug that would prevent these problems, so costly to the individual, the family and the state, must suppress significantly disease activity using these appropriate outcome measures. Tocilizumab is the first therapeutic agent that is close to achieving this goal for sJIA.

3. **Cost comparisons to ineffective / partially effective alternatives**
   Using a costing model that compares Tocilizumab against ineffective/partially effective treatments with NSAIDs, corticosteroids and methotrexate, anti-TNF treatments, and / or Anakinra is clinically inappropriate. As outlined in the response from BSPAR, the very significant clinical data emerging from recent trials of Tocilizumab in sJIA have completely changed the expectation both of the child, family and clinician in what is a reasonable outcome for these children. It is no longer acceptable that children remain on long term cortosteroids, are poorly treated only with NSAIDs or even methotrexate. Although there is encouraging, yet to date very limited data of the probable effectiveness of Anakinra, use of anakinra is not standard practice in sJIA. It is clearly evident from the published literature that the anti-TNF agents are not good in treating sJIA (in contrast to their use in non-systemic, polyarticular-

course JIA). In contrast, there is now very strong evidence that Tocilizimab is of significant clinical benefit, far greater than any other agent to emerge in recent times. This must therefore be understood and contextualised in comparing its use within an economic model with traditional ineffective / partially effective treatment pathways.

4. **Differences in the biological basis of sJIA, supporting the use of Tocilizumab**
   It is very important to recognise that the international paediatric rheumatology community consensus, and the published data to date, makes a very strong case that the biological basis of sJIA is distinct from that of the other sub-categories of JIA. This is of particular relevance when it comes to the appropriate use of anti-TNF therapy. Many of the recent trials of biologics in JIA have actually excluded sJIA, or sJIA with systemic features from their inclusion criteria. Thus, the few that were included as polyarticular-course JIA do not constitute statistically significant evidence for its effectiveness in sJIA. Therefore, although there may be some anecdotal evidence of the use of anti-TNF agents in sJIA, it would be very inappropriate for this to be compared in terms of its clinical and therefore cost effectiveness.
   There is ample peer-reviewed, published evidence focussing on the biological basis of JIA showing that the cytokines IL-6 and IL1beta are key in driving the inflammatory pathway leading to development of sJIA, in contrast to oligo- and polyarticular course JIA . Therefore the rationale for targeting these pathways, supported by the clinical evidence now available for Tocilizimab from the recent TENDER trial data, underline why even in economic models, direct comparison to corticosteroids, methotrexate, or anti-TNF agents gives only a partial, incomplete view of the importance of these recent data.

On behalf also of Arthritis Research UK, the NIHR MCRN / Arthritis Research UK Paediatric Rheumatology Clinical Studies Group welcomes the opportunity of discussion and dialogue with NICE as to the challenges of looking at economic models that assess the cost effectiveness, as well as the clinical effectiveness. This is an evolving arena of use of new biologics within the treatment of different sub types of JIA. Biologics will become an ever increasing, important therapeutic opportunity for clinicians within the NHS, both for JIA and other paediatric connective tissue disorders in which biologics are beginning to be used.

To this end, the CSG would propose working with NICE, along with all stakeholders including BSPAR, and Consumer representatives in hosting a consensus meeting of the use of biologics in paediatric rheumatic disorders. The challenges facing the NICE assessment for tocilizumab and using appropriate economic models applies to the increasing numbers of different biologics that are already being used in clinical practice today. The CSG would be well placed to help facilitate this type of initiative in partnership with NICE, if you thought that was a good way forward.

We recognise the difficulties and challenges that this process brings to all stakeholders. However, we are keenly aware, through the very proactive participation of Consumers within our CSG, of the importance of the Consumer voice, as well as that of all the patients and families we look after in our clinics across the UK affected by this life threatening condition. The CSG would therefore, strongly support the approval by NICE of Tocilizimab for the treatment of sJIA.

We would be happy to provide any further information or background as required.

Yours sincerely

[redacted], NIHR MCRN / Arthritis Research UK Paediatric Rheumatology CSG