NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Tocilizumab (RoActemra®) for the treatment of juvenile idiopathic polyarthritis

MTA Submission

17th March 2015

1. Executive Summary

1.1. Product characteristics, licence, existing SMC/NICE guidance in UK

Product

Tocilizumab (RoActemra®)

Licensed Indications

Juvenile idiopathic polyarthritis:
Tocilizumab (TCZ) in combination with methotrexate (MTX) is indicated for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative polyarticular juvenile idiopathic arthritis and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX (MTX-IR). TCZ can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Systemic juvenile idiopathic arthritis (sJIA):
TCZ is indicated for the treatment of active sJIA in patients 2 years of age and older, who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. TCZ can be given as monotherapy in case of intolerance to MTX or where treatment with MTX is inappropriate, or in combination with MTX.

Rheumatoid arthritis (RA):
TCZ in combination with MTX is indicated for the treatment of severe, active and progressive RA in adults not previously treated with MTX.

TCZ in combination with MTX is indicated for the treatment of moderate to severe active RA in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists.

TCZ can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. TCZ has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with MTX.

Mechanism of action

IL-6 has been implicated in the pathogenesis of inflammatory diseases. TCZ is a humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor, binding specifically to both soluble and membrane-bound IL-6 receptors, and thereby blocking the function of pleiotrophic cytokine IL-6.

Available formulations

Vial containing 80 mg of TCZ in 4 ml (20 mg/ml)
Vial containing 200 mg of TCZ in 10 ml (20 mg/ml)
Vial containing 400 mg of TCZ in 20 ml (20 mg/ml)

Current SMC guidance for TCZ in JIA

TCZ for the treatment of juvenile idiopathic polyarthritis (SMC No. 930/13):
TCZ is accepted for use within NHS Scotland, in combination with MTX for the treatment of juvenile idiopathic polyarthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with MTX. TCZ can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

TCZ has previously been accepted by SMC for treatment of adult RA and in active sJIA in patients from 2 years of age who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. TCZ can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate), or in combination with MTX.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of TCZ. This SMC advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower.

TCZ for the treatment of sJIA (SMC No. 754/12):
TCZ is accepted for use within NHS Scotland, for the treatment of active sJIA patients 2 years of age and older, who have responded inadequately to previous therapy with NSAIDs and

systemic corticosteroids. TCZ can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate), or in combination with MTX.

TCZ was superior to placebo in reducing disease activity and fever in patients with persistent active sJIA despite treatment with NSAIDs and corticosteroids.

This SMC advice takes account of the benefits of a PAS that improves the cost-effectiveness of TCZ. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland.

Current NICE guidance for TCZ in JIA

TCZ for the treatment of sJIA (TA238):
NICE technology appraisal guidance (TA238) recommends TCZ as a possible treatment for sJIA patients aged 2 years and older, whose disease has responded inadequately to NSAIDs, systemic corticosteroids and MTX, provided there is an available PAS.

Children and young people currently receiving TCZ for the treatment of sJIA who do not meet the criteria above should have the option to continue treatment until it is considered appropriate to stop. This decision should be made jointly by the clinicians, and the child or young person and/or their parents or carers.

NICE does not recommend TCZ for sJIA in children and young people aged 2 years and older whose disease is improving with methotrexate treatment, or who have not yet been treated with methotrexate.

1.2. Overview and submission focus

This submission focuses on providing data on the clinical and cost-effectiveness of TCZ for the treatment of patients with juvenile idiopathic polyarthritis as per licence, a term which encompasses rheumatoid factor positive and negative polyarticular juvenile idiopathic arthritis (pJIA) and extended oligoarthritis (EO).

We present results from the CHERISH study [Brunner et al, 2014], a Phase III, three-part, randomised, placebo-controlled , double-blind withdrawal study which evaluated the safety and efficacy of TCZ in patients with active pJIA (≥6 months) who had an inadequate response or were intolerant to MTX (patients who had previously been treated with a biologic were permitted). Long-term efficacy and safety, exploratory endpoints in growth and radiographic progression up to Week 104 are also summarised.

The submission also summarises the clinical effectiveness and safety data for TCZ in 19 pJIA patients from a Japanese study [Imagawa et al, 2012].

1.3. The role of biologics in pJIA and EO

JIA is a relatively rare disease, with an estimated incidence in the UK of 10 per 100,000 children, and a prevalence rate of 1 per 1000 [McCann et al, 2006]. In a recent UK analysis of 507 children with inflammatory arthritis, 15.8% were classified into the pJIA subtype (13.4% RF-negative; 2.4% RF-positive), and 46% oligoarthritis (children were not yet assigned to persistent or extended oligoarthritis) [Adib et al, 2008].

The aim of treatment is to suppress inflammation, decrease the number of actively affected joints, prevent joint damage, long-term disability and improve quality of life [Hayward and Wallace, 2009]. Attention is required not only on the affected joints, but also the complications of both disease and treatment, and the psycho-social effects of the illness to both the child and family.

There are no head-to-head studies comparing the safety and efficacy between two biologics for the treatment of pJIA or EO, therefore we cannot generate conclusions on whether a particular biologic exhibits greater efficacy in these patient populations.

A recent systematic review looked at the clinical efficacy and safety of biologics in pJIA. The literature search was limited to randomised controlled trials (RCTs), non-randomised comparative studies, and non-comparative observational cohort studies, published between January 2000 to September 2012. Eligible studies had to have at least 20 patients with JIA, the majority of whom had pJIA. The biologics evaluated included etanercept, infliximab, adalimumab, abatacept, anakinra, and ritixumab. Evidence reviewed from RCTs and observational studies demonstrated that biologics improved the disease in 80% pJIA patients who had an inadequate response

to conventional non-biologic disease-modifying antirheumatic drugs (DMARDs). Long-term effectiveness data is limited and does not address switches between biologics, handling patients that achieve disease remission, and long-term safety [Ungar et al, 2013].

Please note, the CHERISH study was not published until 2014 and therefore could not have been included in this systematic review. In the CHERISH study, we present long-term efficacy and safety data up to Week 104.

Although patients with pJIA may respond to biologic agents, an observational prospective cohort study has shown 26% may require a switch to a second biologic [Otten et al, 2013]. ACR 2011 guidelines on the initiation and safe monitoring of drug treatments in JIA, recommend switching TNFα inhibitors if there is an inadequate response (moderate to severe disease activity or intolerance) after four months of treatment [Beukelman et al, 2011].

1.4. The role of TCZ in pJIA and EO

Interleukin-6 (IL-6) is increased in the serum and synovial compartments of patients with pJIA and oligoarticular-JIA [Macaubas et al, 2009]. IL-6 concentrations are positively correlated with the severity of joint involvement and with C-reactive protein (CRP) levels [De Benedetti et al, 1992]. Elevated IL-6 levels are also associated with lower growth velocity, and it has been suggested that IL-6 could be an essential link between inflammation and stunted growth. TCZ is a humanised, monoclonal, antihuman IL-6 receptor (IL-6R) antibody that binds to membrane and soluble IL-6R, inhibiting IL-6–mediated signalling [Nishimoto and Kishimoto, 2008].

TCZ is licenced in the UK in pJIA and EO patients two years of age and older, who have not responded adequately to treatment with MTX. It is licenced to be used in combination with MTX, or as monotherapy if intolerant to MTX or where MTX treatment is inappropriate.

Currently, TCZ is recommended by SMC for the same licenced indication, on the condition there is a PAS available with the drug.

1.5. Efficacy data for TCZ in pJIA and EO

The CHERISH trial was a Phase III, three-part, randomised , placebo controlled , double blind withdrawal study which evaluated the safety and efficacy of TCZ in patients aged 2-17 years with active pJIA (≥6 months) who had failed treatment or were intolerant to MTX [Brunner et al, 2014].

The CHERISH trial was conducted in three consecutive parts: Part 1, a Lead-in period where patients received open-label TCZ IV 8mg/kg or 10mg/kg every 4 weeks for 16 weeks (8mg/kg was used if body weight ≥30kg and 10mg/kg if body weight <30kg); Part 2 Double-blind/Withdrawal Phase from Week 16-40 where patients with a juvenile idiopathic arthritis American College of Rheumatology (JIA ACR) 30 response or better, were randomly assigned to receive placebo or continue TCZ at the same dose. Patients who did not achieve ≥JIA ACR30 were withdrawn from the study; Part 3 Open-label Extension Phase from Week 40-104, where patients whom completed Part 2 or experienced a flare received TCZ at the same dose as received in Part 1.

The study met the primary endpoint with TCZ-treated patients experiencing significantly fewer JIA ACR30 flares compared to placebo-treated patients at Week 40 relative to Week 16 (25.6% versus 48.1%, respectively; p=0.0024). A rapid response to TCZ was also observed with 50% of patients achieving JIA ACR30 at week 2. Secondary endpoints of JIA ACR 30/50/70/90 responses at Week 40 relative to Day 0 were significantly higher in the TCZ-treated group. Patients who received TCZ for 40 weeks experienced marked improvement in all JIA ACR CRVs such as active joints, joints with limitation in range of movement, patient and physician-assessed global assessment of well-being, Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) and erythrocyte sedimentation rate (ESR) from baseline [Brunner et al, 2014].

One hundred and fifty-five patients (82%) completed 104 weeks of treatment. At Week 104, JIA ACR70 and JIA ACR90 were achieved by 70.4% and 48.1% of patients with previous biologic use, respectively. In patients with background MTX use, 88.1% achieved JIA ACR70 and 76.1% achieved JIA ACR90 [Brunner et al, 2013].

In the exploratory analysis on growth in the CHERISH study, the mean height standard deviation score (SDS) of patients with pJIA was below normal at baseline. The majority of patients who were Tanner stage <4 at baseline (71.8%) had an increased height SDS at the end of study (Week 104). First-year height velocity during treatment with TCZ was related to glucocorticoid dose and patient age at baseline. For patients with available data at year 2

(n = 103), the mean ± SD daily oral glucocorticoid dose decreased from baseline (0.05 ± 0.08 mg/kg) to year 2 (0.02 ± 0.05 mg/kg) [Bharucha et al, 2014].

Based on smallest detectable difference (SDD) analysis of adapted Sharp/van der Heijde and Poznanski scores to analyse radiographic progression, the results show that the large majority of pJIA patients receiving TCZ experienced no radiographic progression after 2 years of treatment [Ravelli et al, 2014].

Imagawa et al. conducted an open-label, multi-centre study which evaluated the safety and efficacy of TCZ in nineteen paediatric patients with pJIA whom had an inadequate response or were intolerant to other medications including MTX [Imagawa et al, 2012]. Patients received TCZ 8 mg/kg every 4 weeks in both the initial study (to Week 12) and the extension study (at least 48 weeks). Concomitant therapy with anti-TNFs, DMARDs, including MTX or immunosuppressants was not allowed.

The primary endpoint, ACR Pedi 30 response rate at Week 12 and at the end of the extension phase was met; ACR Pedi 30 increased over time in the initial study, reaching 94.7% (18/19) at Week 12, and 100% (19/19) at Week 48.

ACR Pedi 50/70/90 response rates, respectively, were 94.7%, 57.9% and 10.5% at Week 12, and 94.1%, 88.2% and 64.7% at Week 48 in the extension study. The mean DAS28 score remained lower than 2.6 from week 24 through week 48 (n=17).

1.6. Economic model

The economic model was designed to demonstrate the cost-effectiveness of tocilizumab when used in patients with pJIA who had an inadequate response to DMARDs. The structure of the model is developed to closely reflect clinical practice and the availability of the evidence. The model structure is consistent with the approach adopted in the NICE sJIA appraisal of tocilizumab [TA238].

Patients entering the model have active disease and have previously experienced an inadequate response to, or were intolerant of, methotrexate (MTX). This assumption is in line with the CHERISH trial population.

Etanercept, adalimumab, abatacept, and tocilizumab are the only treatments licensed within pJIA. As the licence of tocilizumab is for patients 'who have responded inadequately to previous therapy with MTX', our intention was to compare tocilizumab to the most appropriate DMARD-IR comparators. In line with expert clinical opinion, the most appropriate comparators are adalimumab, etanercept, and abatacept. Best supportive care, or re-challenging of MTX was not considered a relevant comparator as it did not reflect clinical practice in the UK.

Due to the differences in trial design, an indirect comparison was only possible with adalimumab. The results of this analysis indicate that tocilizumab and adalimumab have similar outcomes in the treatment of pJIA, however, tocilizumab is a less expensive alternative.

Both treatments significantly improve the outcomes of patients with pJIA. The results of the analysis are below in Table 1 and Table 2:

Table 1. Results: combination therapy (with PAS)

	Adalimumab + MTX	Tocilizumab + MTX	Incremental Difference	ICER (£ per QALY)
Total QALYs	18.76	18.72	(0.0303)	
Total Cost	£81,827	£70,707	(£11,120)	SWC

Table 2. Results: monotherapy

	Adalimumab	Tocilizumab	Incremental Difference	ICER (£ per QALY)
Total QALYs	18.65	18.7	0.0455	
Total Cost	£74,576	£68,560	(£6,015)	Dominant

2. Context

2.1. Classification of JIA

Several changes in the terminology of juvenile arthritis have been seen in the past. The older terms ‘juvenile rheumatoid arthritis’ and ‘juvenile chronic arthritis’ were commonly used in the US and Europe, respectively. These terms were replaced by the term ‘juvenile idiopathic arthritis’ in 1994 by the International League of Associations for Rheumatology (ILAR) committee. JIA encompasses all forms of arthritis that begin before the age of 16 years, persist for more than six weeks, and are of unknown cause [Petty et al, 2004]. The ILAR classification of JIA categorise seven subgroups: systemic arthritis, oligoarthritis, RF-positive polyarthritis, RF-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis, each with a specific clinical profile.

The objective of the ILAR classification was to classify chronic idiopathic childhood arthritides in a more homogeneous manner, and allow better evaluation of newer therapies [Ruth and Passo, 2012]. While this system is now used the most widely in rheumatologic literature, it must be remembered that each category most likely represents more than a single distinct disease.

For the purpose of this document, we will be focusing on the unmet need in the treatment of juvenile idiopathic polyarthritis (RF-positive or RF-negative pJIA and extended oligoarthritis).

2.2. Current management of pJIA and EO

JIA has an estimated incidence in the UK of 10 per 100,000 children, and a prevalence rate of 1 per 1000 [McCann et al, 2006]. In a recent UK analysis of 507 children with inflammatory arthritis, 15.8% were classified into the pJIA subtype (13.4% RF-negative; 2.4% RF-positive), and 46% oligoarthritis (children were not yet assigned to persistent or extended oligoarthritis) [Adib et al, 2008]. There is currently no cure for pJIA or EO. The aim of treatment is to suppress inflammation, decrease the number of actively affected joints, prevent joint damage, long-term disability and improve quality of life [Hayward and Wallace, 2009]. Attention is required not only on the affected joints, but also the complications of both disease and treatment, and the psycho-social effects of the illness to both the child and family.

Treatment of the complications of the disease such as chronic synovitis, osteoporosis and growth impairment, and uveitis is often required. A high proportion of affected children develop destructive joint disease, often requiring early joint replacement.

Growth impairment is a well-known complication in JIA patients, and reduced final height is one of the permanent consequences affecting about 10–20 % of these patients with sJIA and pJIA [Bechtold and Simon, 2014]. Early recognition of patients who develop prolonged growth and body composition disturbances is an important part of disease management as it contributes to long-term morbidity. TCZ and TNFα receptor antagonists have been shown to positively affect height development in patients with pJIA.

In comparison with other subtypes of JIA, oligoarticular-JIA have milder disease and require less corticosteroid medication, which is considered to be a major cause in growth impairment. However, in a recent retrospective study, 35.8% of patients with persistent oligoarticular-JIA receiving treatment with intra-articular corticosteroid injections or DMARDs still experienced abnormal growth [Padeh et al, 2011].

Patients with mild pJIA or EO are often treated first-line with non-steroidal anti-inflammatory drugs (NSAIDs) which reduce pain and joint swelling/inflammation [Ruperto et al, 2005]. These medications should reach full efficacy within two to three months, and usually a response assessment is carried out at this time point [Beukelman et al, 2011]. For moderate to severe forms of pJIA, NSAIDs are often used in combination with DMARDs and/or biologic agents [Oberle et al, 2014]. Although patients with pJIA may respond to biologic agents, an observational prospective cohort study has shown 26% may require a switch to a second biologic [Otten et al, 2013].

Patients with moderate to severe EO are treated with intra-articular glucocorticoid injections [Beukelman et al, 2011]. Those patients who do not respond, will likely to go on DMARD therapy. Biologic agents are occasionally used in patients with persistent EO or in those with uveitis. Intra-articular glucocorticoid injections can also be given as adjunct therapy for children with pJIA with a limited number of affected joints [Oberle et al, 2014]. 35.8% of patients with persistent oligoarticular-JIA experienced abnormal growth [Padeh et al, 2011].

Systemic glucocorticoids are not routinely recommended for treatment of pJIA, but it may have a role in early aggressive therapy for severe disease by providing symptomatic relief while other medications are initiated [Oberle et al, 2014]. Long-term use of systemic glucocorticoids also raises other considerations in the management of JIA, including reduced growth and bone health [Prince et al, 2010].

There are no head-to-head studies comparing the safety and efficacy between two biologics for the treatment of pJIA, therefore we cannot generate conclusions on which biologic exhibits greater efficacy in this patient population.

Physical activity has an important role in the management of JIA. It may improve exercise capacity, decrease disability in adulthood, improve quality of life and, and in some patients, decrease disease parameters [Long and Rouster-Stevens, 2010]. The limited movement of joints due to inflammation restricts the range of motion and stretching exercises, and therefore may have limited benefit in some patients.

3. Efficacy and safety

3.1. Overview of key literature for TCZ in pJIA and EO

This section summarises the most relevant literature on the use of TCZ in patients with pJIA and EO.

Study acronym (Study ID) n=no. of patients Key publication	Characteristic	Short description
CHERISH (WA19977) n=188 Brunner HI et al, 2014	**Design and Duration**	Phase III, three-part, double blind, randomised, placebo controlled trial Part 1: Initial lead-in period of 16 weeks Part 2: At Week 16, patients with ≥JIA ACR30 entered a 24-week DB phase Part 3: Patients who completed the 24-week DB phase then entered an open-label extension study
	Patient Population	MTX-IR or MTX-intolerant pJIA or EO
	Treatment Arms	Part 1: patients with body weight ≥30kg, received open-label TCZ IV 8mg/kg every 4 weeks; patients with body weight <30kg, were randomised to TCZ IV 8mg/kg or 10mg/kg every 4 weeks Part 2: Placebo or continue at the same dose Part 3: TCZ at same dose as in lead-in phase
	Primary Endpoints	JIA ACR30 flare at Week 40 relative to Week 16
	Key Secondary Endpoints	JIA ACR30/50/70/90 responses rates Change to from baseline in JIA core response variables (CRVs) Clinically inactive disease
	Key Exploratory Endpoints	Growth: height velocity and height standard deviation scores Radiographic progression rates
Japanese data n=19 Imagawa T et al, 2012	**Design and Duration**	Open-label, multi-centre trial compromised of the initial study (up to Week 12), and an extension study (at least 48 weeks)
	Patient Population	pJIA or EO intolerant or refractory to other medications including MTX
	Treatment Arms	TCZ 8 mg/kg every 4 weeks
	Primary Endpoints	ACR Pedi 30 response rate at Week 12 and at final visit in extension study
	Key Secondary Endpoints	ACR Paediatric 30/50/70 response rates

3.2. CHERISH trial

The CHERISH trial was a Phase III, three-part, randomised, placebo controlled, double blind withdrawal study which evaluated the safety and efficacy of TCZ in patients with active pJIA (≥6 months) who had an inadequate response or were intolerant to MTX.

For the purpose of this document, the following publications/analyses have been presented:

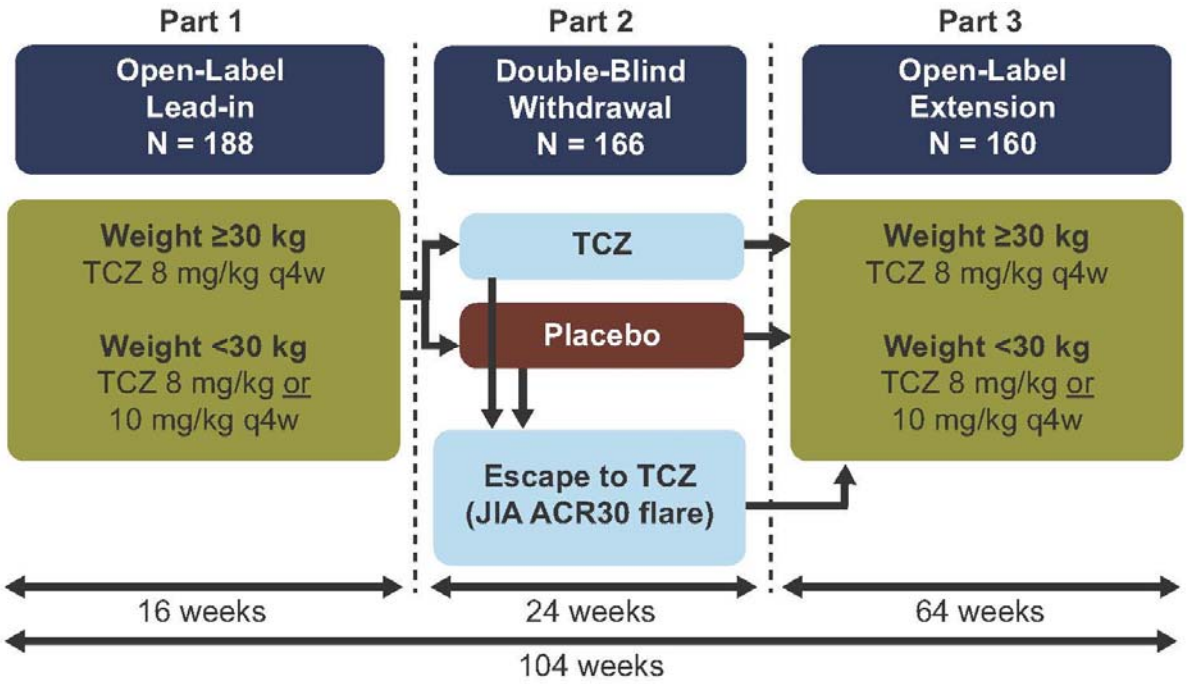
Efficacy and Safety Analysis at Week 40	Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of TCZ in patients with polyarticular-course juvenile idiopathic arthritis: results from a Phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis 2014;0:1–8 De Benedetti F, Ruperto N, Zuber Z, et al. Efficacy and safety of TCZ in patients with polyarticular juvenile idiopathic arthritis: data from a Phase 3 trial. Abstract #OP0060 and oral presentation presented at European League Against Rheumatism Annual Congress 2013 in Madrid, Spain; June 12-15, 2013 Baildam E, Ruperto N, Brunner H et al. Efficacy and safety of tocilizumab in polyarticular juvenile idiopathic arthritis (pJIA): CHERISH results at week 40. Abstract and oral presentation presented at British Society for Rheumatology Annual Meeting 2013 in Birmingham, UK; April 23-25, 2013
Efficacy and Safety Analysis at Week 104	Bunner HI, Ruperto N, Zuber Z et al. Efficacy and safety of Tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: 2-year data from CHERISH. Abstract and poster presented at American College of Rheumatology Pediatric Rheumatology Symposium 2014 in Florida, USA; April 3–6, 2014 Brunner HI, Ruperto N, Cuttica R et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: 2-year data from CHERISH. Abstract and oral presentation presented at British Society for Paediatric and Adolescent Rheumatology Annual Meeting 2013 in Dublin, Ireland; October 2-4, 2013
Growth Data at Week 104	Bharucha KN, Brunner HI, Ruperto N et al. Growth during tocilizumab therapy for polyarticular-course juvenile idiopathic arthritis: 2-year data from a phase 3 clinical trial. Poster presented at American College of Rheumatology Annual Scientific Meeting 2014 in Boston, USA; November 14-19, 2014
Radiographic Progression Data up to Week 104	Ravelli A, Ruperto N, Pederzoli S et al. Assessment of radiographic progression in patients with polyarticular-course juvenile idiopathic arthritis treated with tocilizumab 2-year data from CHERISH. Abstract and oral presentation presented at Paediatric Rheumatology European Society 21st Congress 2014 in Belgrade, Serbia; September 17-21, 2014

3.2.1. Study design

The CHERISH trial was conducted in three consecutive parts:

- Part 1 Lead-in Period: Patients received open-label TCZ every 4 weeks for 16 weeks.
    - Body weight ≥30 kg: TCZ 8 mg/kg IV
    - Body weight <30 kg: randomly assigned to receive 8 mg/kg IV or 10 mg/kg IV
- Part 2 Double-blind/Withdrawal Phase: At Week 16, patients with ≥JIA ACR30 entered a 24-week DB phase and were randomly assigned (1:1) to receive placebo or continue TCZ at the same dose. Patients who did not achieve ≥JIA ACR30 were withdrawn from the study.
- Part 3 Open-label Extension: Patients who completed the DB phase or experienced a flare were then entered into an open-label extension period in which they received TCZ at the same dose as in the lead-in phase.

Figure 1. Study design of CHERISH trial [De Benedetti et al, 2013]



The rationale for investigating the dose of 10mg/kg for patients weighing <30kg is based on pharmacokinetic modelling and simulation, where doses of 10 mg/kg for patients weighing < 30kg achieved similar TCZ exposure to 8 mg/kg for patients weighing ≥30kg.

Table 3. Key inclusion and exclusion criteria for CHERISH trial [De Benedetti et al, 2013]

Inclusion criteria	Exclusion criteria
• Age 2 to 17 years • RF-positive or RF-negative pJIA (ILAR criteria), or EO • JIA duration ≥6 months with ≥5 joints with active arthritis • Inadequate response to or inability to tolerate MTX therapy • MTX, oral corticosteroid (CS), NSAID at stable doses (if receiving) • Maximum stable oral CS dosage: 0.2mg/kg/day or 10 mg/day (whichever is lower)	• sJIA or other categories of JIA • Any other authoimmune or rheumatic diseases • History of significant or infusion reactions with prior biologic therapy • Active infection
Abbreviations: ILAR- International League of Associations for Rheumatology; RF- rheumatoid factor	

3.2.2. Outcome measures

Primary outcome measure was the percentage of patients with a JIA ACR30 flare in Part 2 of the study (Weeks 16-40) compared with the results at Week 16 [Brunner et al, 2014].

Secondary outcome measures at Week 40 included, but were not limited to, JIA ACR30/50/70/90 responses, change from baseline in JIA core response variables (CRVs) and clinically inactive disease [Bunner et al, 2014].

3.2.3. Statistical analysis

Sample size was calculated assuming JIA-flare rates of 35% for the TCZ groups and 65% for the placebo group in Part 2. Therefore, 60 patients had to be randomly assigned to each group in Part 2 to achieve more than 80% power to detect a significant difference in JIA-flare rates between groups using a two-sided significance test with $\alpha=0.05$. Based on an assumed JIA-ACR30 response rate of 65% in the TCZ group in Part 1, recruitment of 185 patients into Part 1 was planned to ensure that a sufficient number of patients were available for randomisation in Part 2 [Brunner et al, 2014].

To control for the type I error rate, secondary end points were tested in a hierarchical fixed-sequence approach provided the primary end point was found to be statistically significant.

Primary end point analysis was conducted with the Cochran–Mantel–Haenszel (CMH) test, adjusted for stratification factors (background use of MTX and oral glucocorticoids); patients who withdrew or for whom the end point could not be determined were considered to have experienced JIA-flare.

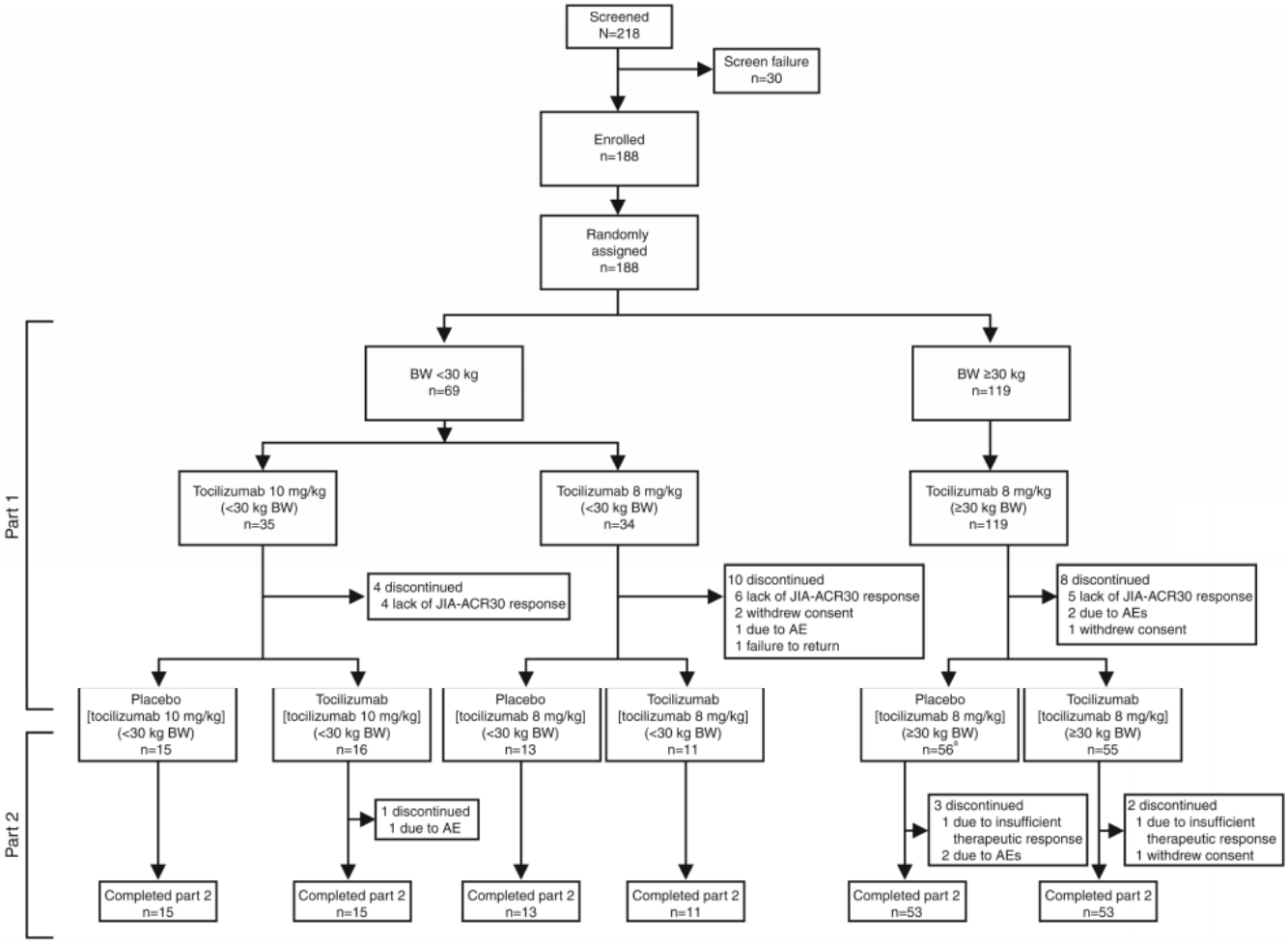
For secondary end points, the CMH test was used to determine statistical significance for differences in JIA-ACR30/50/70/90 responders at week 40 compared with baseline; patients who escaped or withdrew or for whom the end point could not be determined were considered non-responders.

Continuous variables were evaluated using analysis of variance, adjusted for baseline differences between groups and stratification variables. A last-observation-carried-forward approach was used for patients who withdrew or experienced flare and who escaped to open-label TCZ.

3.2.4. Patient disposition

188 patients were enrolled in Part 1 of the study and received at least one dose of TCZ. At the end of Week 16, twenty two patients had discontinued treatment. 166 patients were enrolled in Part 2 of the study, and during this time 6 patients discontinued treatment [Brunner et al, 2014]. At the end of Week 40, 160 patients entered in Part 3 of the study, with only 5 patients discontinuing treatment. At Week 104, one hundred and fifty five patients had completed the study.

Figure 2. Detailed summary of patient disposition from the CHERISH trial [Brunner et al, 2014]



[a]Three patients were not included in the ITT population for Part 2 because they discontinued before receiving a single dose of TCZ
Abbreviations: AE- adverse event; BW- body weight; JIA ACR- juvenile idiopathic arthritis American College of Rheumatology; ITT- intent-to-treat

3.2.5. Baseline characteristics

Baseline characteristics were generally similar across the three TCZ dosing groups.

Table 4. Patient's baseline characteristics from the CHERISH trial [Brunner et al, 2014]

Variable*	TCZ 8 mg/kg <30 kg n = 34	TCZ 10 mg/kg <30 kg n = 35	TCZ 8 mg/kg ≥30 kg n = 119	All TCZ n = 188**
Age, mean yrs	7.6±2.71	6.9±3.02	13.1±2.78	11.0±4.01
Females, n (%)	24 (71)	30 (86)	90 (76)	144 (77)
Disease duration, mean yrs	3.5±2.57	3.4±2.39	4.7±4.16	4.2±3.67
RF positive, n (%)	2 (6)	4 (11)	48 (40)	54 (29)
Previous DMARD use, n (%)	26 (76)	21 (60)	87 (73)	134 (71)
Previous biologic use, n (%)†	6 (18)	8 (23)	47 (39)	61 (32)
Number of active joints, mean	21.2±13.6	23.9±18.3	18.9±13.0	20.3±14.3
Number of LOM joints, mean	17.3±13.3	23.1±19.2	16.0±12.7	17.6±14.4
Physician global VAS (0-100mm), mean	64.7±18.5	64.7±20.5	59.4±21.3	61.4±20.7
Patient assessment of overall well-being VAS (0-100mm), mean	59.1±26.2	51.5±26.9	51.6±24.1	52.9±25.0
CRP (standard reference range: 0-10mg/L), mean mg/L	26.6±33.6	21.8±32.3	22.8±38.8	23.3±36.6
CHAQ-DI score (0-3), mean	1.8±0.68	1.7±0.71	1.2±0.69	1.4±0.74
ESR (standard reference range: 0-18mm/h), mean	36.6±23.0	35.1±24.1	34.2±26.7	34.8±25.5
Concurrent MTX, n (%) Mean MTX dose, mg/m^2/week	30 (88) 13.8±2.9	29 (83) 16.5±11.1	89 (75) 11.6±2.7	148 (79) 13.0±5.7
Concurrent oral CS, n (%)¶ Mean oral CS dose, mg/kg/day¶	18 (53) 0.15±0.038	15 (43) 0.15±0.033	54 (45) 0.12±0.052	87 (46) 0.13±0.048

*Values are mean ± standard deviation, unless otherwise stated
**Included all patients randomly assigned to receive TCZ 10mg/kg (weight <30kg), TCZ 8mg/kg (weight <30kg), or TCZ 8mg/kg (weight ≥30kg) in Part I
†Nine per cent of patients previously received three or more biological agents. TNF inhibitors were administered to 56 patients, anakinra to 5 patients, abatacept to 5 patients and canakinumab to 1 patient
¶ Measured in prednisolone equivalents

Abbreviations: CHAQ-DI- Childhood Health Assessment Questionnaire–Disability Index; CS- corticosteroid; ESR- erythrocyte sedimentation rate; LOM- limitation of motion; MTX- methotrexate; SD- standard deviation; TCZ- tocilizumab; VAS- visual analogue scale

3.2.6. Efficacy results at Week 16

At Week 16, the percentage of all TCZ-treated patients who achieved ACR 30/50/70/90 responses was 89.4%, 83%, 62.2%, and 26.1%, respectively [De Benedetti et al, 2013]. Improvements were seen across all CRVs. Efficacy endpoints for the initial lead-in period at Week 16 are presented in Table 5.

Table 5. Efficacy data at end of initial lead-in period at Week 16 from the CHERISH trial [De Benedetti et al, 2013]

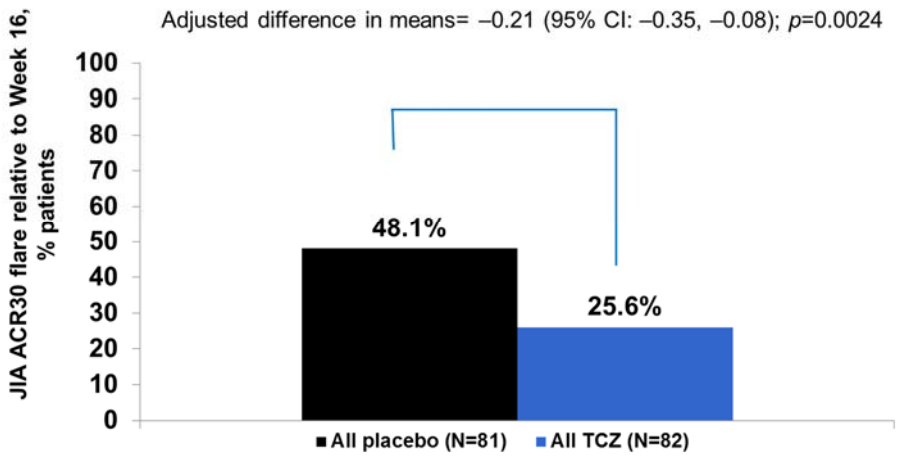
	TCZ 10 mg/kg IV <30 kg BW (n=35)	TCZ 8 mg/kg IV <30 kg BW (n=34)	TCZ 8 mg/kg IV ≥30 kg BW (n=119)	All TCZ IV (n=188)
JIA ACR Response*, n (%)				
JIA ACR30	31 (88.6)	26 (76.5)	111 (93.3)	168 (89.4)
JIA ACR50	28 (80)	24 (70.6)	104 (87.4)	156 (83)
JIA ACR70	22 (62.9)	14 (41.2)	81 (68.1)	117 (62.2)
JIA ACR90	11 (31.4)	8 (23.5)	30 (25.2)	49 (26.1)
JIA ACR Core Response Variables†, mean (%) change from baseline				
Active joints (range, 0-71)	-16.8 (-63.4)	-12.5 (-55.6)	-13 (-73)	-13.6 (-68.2)
Joints with LOM (range, 0-67)	-13.2 (-61.8)	-8.3 (-49.9)	-9.6 (-66)	-10.1 (-62.4)
Parent-rated patient global assessment of well-being (VAS range, 0-100mm)	-30.1 (-31.7)	-35.8 (-55.6)	-29.9 (-53.3)	-30.9 (-49.5)
Physician-rated global assessment of disease activity (VAS range, 0-100 mm)	-45.8 (-61.5)	-40.6 (-65.2)	-42.7 (-72.6)	-42.9 (-69.2)
CHAQ-DI (range, 0-3)	-0.892 (-54.5)	-0.827 (-46.2)	-0.621 (-49.1)	-0.708 (-49.6)
ESR (mm/h)	-26 (-71)	-17 (-21.8)	-26.8 (-70.9)	-25 (-62.5)

Notes: *Patients who withdrew or for whom the endpoint could not be determined were classified as non-responders; †Patients who withdrew before Week 16 were excluded.
Abbreviations: ACR- American College of Rheumatology; BW- body weight; CHAQ-DI- Childhood Health Assessment Questionnaire Disability Index; ESR- erythrocyte sedimentation rate; JIA- juvenile idiopathic arthritis; LOM- limitation of motion; VAS- visual analog scale

3.2.7. Efficacy results at Week 40

At Week 40, the primary endpoint of JIA ACR 30 flare was significantly lower in the TCZ group (25.6%) vs. placebo (48.1%; p=0.0024). Additionally the percent of patients who achieved JIA ACR 30/50/70 responses were significantly higher in the TCZ group vs. placebo [De Benedetti et al, 2013].

Figure 3. Percentages in JIA ACR30 flare at Week 40 relative to Week 16 in placebo-treated and TCZ-treated patients [De Benedetti et al, 2013]



Secondary endpoints of JIA ACR 30/50/70 responses at Week 40 relative to Day 0 were also significantly higher in the TCZ group, as summarised in Table 6 and JIA ACR core response variables at Week 40 for the ITT population are summarised in Table 7.

Table 6. Secondary endpoints at Week 40 from the CHERISH trial [De Benedetti et al, 2013]

Secondary endpoints at Week 40 relative to Day 0	All placebo n=81	All TCZ n=82	p value*
JIA ACR30, n (%)	44 (54.3%)	61 (74.4%)	0.0084
JIA ACR50, n (%)	42 (51.9%)	60 (73.2%)	0.0050
JIA ACR70, n (%)	34 (42%)	53 (64.6%)	0.0032
Notes: *Analysis adjusted for background methotrexate and/or corticosteroid therapy applied at Week 16. Abbreviations: ACR- American College of Rheumatology; JIA- juvenile idiopathic arthritis			

Improvement of all JIA-CRVs at the end of Part 2 Week 40 for the intention-to-treat population receiving TCZ in Parts 1 and 2 are shown in the table below.

Table 7. Ad-hoc analysis of JIA ACR core response variables at Week 40 for the ITT population receiving TCZ in both Part 1 and Part 2 (n=82) compared with baseline [Brunner et al, 2014]

JIA-ACR CRV, mean (SD)	Baseline	Week 40	Week 40 (change from baseline)†
Active joints (range, 0-71)	19.7 (13.95)	3.2 (8.06)	-14.5 (11.14)
Joints with LOM (range, 0-67)	16.5 (13.81)	3.9 (6.95)	-10.2 (8.97)
Parent-rated patient global assessment of well-being (VAS range, 0-100mm)	45.5 (23.11)	8.8 (16.12)	-31.1 (28.52)
Physician-rated global assessment of disease activity (VAS range, 0-100 mm)	57.8 (20.30)	6.2 (7.75)	-45.6 (21.47)
CHAQ-DI (range, 0-3)	1.216 (0.67)	0.333 (0.47)	-0.804 (0.65)
ESR (mm/h)	31.7 (22.88)	5.4 (6.08)	-25.2 (21.97)
†Change from baseline was calculated using last-observation-carried-forward imputation for mission values; in other columns, missing values were not imputed. Abbreviations: CHAQ-DI- Childhood Health Assessment Questionnaire-Disability Index; ESR- erythrocyte sedimentation rate; ITT- intent-to-treat; JIA-ACR- juvenile idiopathic arthritis-American College of Rheumatology; LOM- limitation of motion; SD- standard deviation; VAS- visual analogue scale			

3.2.8. Long-term efficacy results

One hundred and fifty-five patients (82%) completed 104 weeks of treatment. At Week 104, JIA ACR 70 response and JIA ACR 90 response were achieved by 70.4% and 48.1% of patients with previous biologic use, respectively [Brunner et al, 2013]. In patients with background MTX use, 88.1% achieved JIA ACR70 and 76.1% achieved JIA ACR90.

At Week 104, 73.2% of patients achieved Juvenile Arthritis Disease Activity Score-71 (JADAS-71) <3.8 (minimal disease activity), and 58.5% of patients achieved JADAS-71 <1 (inactive disease). Efficacy outcomes through Week 104 for the continuous TCZ group, based on previous biologic and MTX use, are summarised in Table 8 [Brunner et al, 2014].

Table 8. Efficacy outcomes through Week 104 from the CHERISH trial [Brunner et al, 2013]

	Continuous TCZ IV Week 40		Continuous TCZ IV Week 104	
	Previous Biologic Use (n=27)	**No Previous Biologic Use (n=55)**	**Previous Biologic Use (n=27)**	**No Previous Biologic Use (n=55)**
JIA ACR70 responders, n (%)	19 (70.4)	46 (83.6)	19 (70.4)	52 (94.5)
JIA ACR90 responders, n (%)	6 (22.2)	35 (63.6)	13 (48.1)	45 (81.8)
	Previous MTX Use (n=67)	**No Previous MTX Use (n=15)**	**Previous MTX Use (n=67)**	**No Previous MTX Use (n=15)**
JIA ACR70 responders, n (%)	54 (80.6)	11 (73.3)	59 (88.1)	12 (80.0)
JIA ACR90 responders, n (%)	36 (53.7)	5 (33.3)	51 (76.1)	7 (46.7)

Notes: Patients who withdrew due to nonsafety reasons are nonresponders and patients who withdrew due to safety reasons are included using last observation carried forward. JIA ACR 70/90 responders are patients who had response relative to baseline.

Abbreviations: IV- intravenous; JIA ACR- Juvenile Idiopathic Arthritis American College of Rheumatology.

3.2.9. Growth data at Week 104

Mean height standard deviation scores (SDS) of patients with pJIA was below normal at baseline [Bharucha et al, 2014]. Most patients who were at Tanner stage <4 at baseline (71.8%) had an increased height SDS at the end of the study at Week 104. First-year height velocity during TCZ treatment was related to glucocorticoid dose and patient age at baseline.

For this exploratory analysis, growth was assessed in the growth population, which included all patients who received at least one dose of TCZ and whom did not receive growth hormone treatment during the study. Of the 188 patients in the CHERISH study, 187 patients made up the growth population (1 patient who received growth hormone therapy was excluded from analyses). In the CHERISH trial, stable doses of oral glucocorticoids were allowed (the lesser of ≤0.2 mg/kg/day or ≤10 mg/day). Glucocorticoids could be tapered in Part 3, the open-label extension phase. Growth measurements included height velocity and height standard deviation scores.

The relationship between height SDS at baseline and age or disease duration was evaluated using Spearman rank correlation (*r*). The change in height SDS from baseline to Week 104 was assessed by paired *t* test.

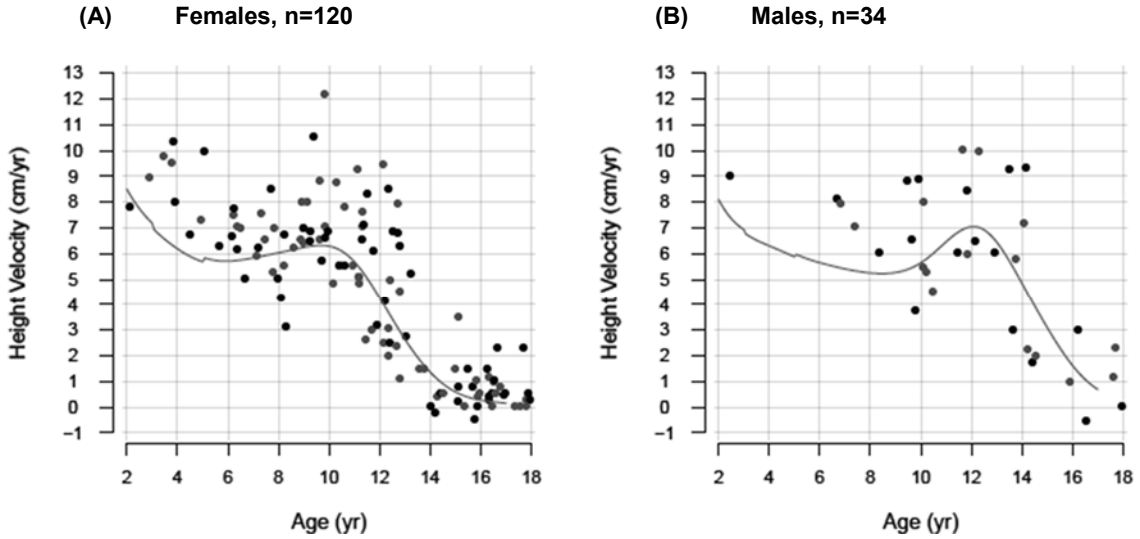
Mean height SDS of patients with pJIA was below normal at baseline. Baseline growth characteristics are summarised in the following table.

Table 9. Baseline growth characteristics of the growth population in the CHERISH trial [Bharucha et al, 2013]

Baseline Growth Characteristics	Growth Population n=187
Female, n (%)	143 (76)
Age, mean years	11.0±4.0
Tanner stage <4, n (%)	123 (65)
Duration since pJIA diagnosis, mean years	4.2±3.7
Mean height SD score (WHO)	-0.5±1.2
Mean BMI SD score (WHO)	0.05±0.11
Abbreviations: WHO- World Health Organisation	

Most patients in the growth population experienced greater than normal height velocities during two years of TCZ treatment. No evident difference was observed in patients receiving placebo in Part 2. Mean change in height SDS from baseline to Week 104 was 0.25±0.54 (from 154 patients of the growth population with height SDS data at both time points).

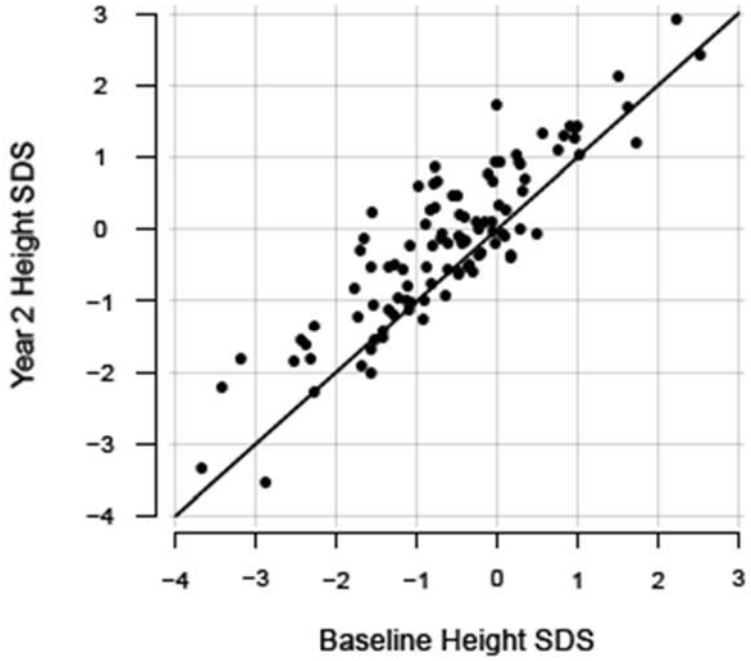
Figure 4. Height velocity at Week 104 versus baseline age in (A) females and (B) males* [Bharucha et al, 2013]



*Solid black curves represent the expected height velocity based on WHO norms for height for the mean observation time. 84 patients were randomly assigned to receive placebo treatment during Part 2; fewer than half the patients received placebo through the entire 24 weeks of Part 2 because most escaped to TCZ before Week 40.

Patients with Tanner stage <4 at baseline, represented the subset of patients with the highest growth potential. Of the 123 patients who were at Tanner stage <4 at baseline, 103 patients had height SDS data at baseline and Week 104. The majority of patients who were at Tanner stage <4 at baseline (71.8%) had an increased height SDS at Week 104. Mean height SDS was -0.68±1.23 at baseline, and -0.19±1.14 at Week 104 ($p<0.001$).

Figure 5. Baseline height SDS versus height SDS at Week 104 in patients with Tanner stage <4 at baseline (n=103)* [Bharucha et al, 2013]



*Black line represents no change in height SDS. Population presented is all patients who were at Tanner stage <4 baseline. A similar pattern was observed if the patients randomly assigned to receive placebo treatment during Part 2 were excluded (not shown). 84 patients were randomly assigned to receive placebo treatment during Part 2; fewer than half the patients received placebo through the entire 24 weeks of Part 2 because most escaped to TCZ before Week 40.

103 patients had glucocorticoid treatment data available at Week 104. The mean daily oral glucocorticoid dose decreased from baseline to Week 104, 0.05±0.08mg/kg to 0.02±0.05mg/kg, respectively. In a multiple linear regression analysis, height velocity at Week 52 was related to baseline age ($p<0.001$) and oral glucocorticoid use at the end of Week 52 ($p=0.0002$).

3.2.10. Radiographic progression data up to Week 104

The primary radiographic endpoint was the proportion of patients with no radiographic progression in the hand/wrist radiographs from baseline to Week 52 and Week 104 [Ravelli et al, 2014]. Radiographic progression was defined as a positive change in adapted Sharp/van der Heijde score (aSH) and/or a negative change in Poznanski score.

Baseline and ≥1 post-baseline adapted Sharp/van der Heijde scores and Poznanski scores were available for 45 and 35 patients, respectively, in the continuous TCZ population. Baseline and ≥1 post-baseline adapted Sharp/van der Heijde scores and Poznanski scores were available for 87 and 61 patients, respectively, in the total population. Early withdrawal, no consent, or unreadable radiographs (because of advanced damage resulting in unreliable measurements or growth plate fusion in post-pubertal children), preventing assessment of Poznanski scores, were reasons for missing data.

For the purpose of this exploratory analysis, the continuous TCZ population are patients who received TCZ in all three parts of the study and received baseline and at least 1 post-baseline adapated Sharp/van der Heijde or Poznanski scores, and the total radiographic population are patients who received baseline and at least 1 post-baseline adapted Sharp/van der Heijde or Poznanski scores (regardless of TCZ therapy).

Baseline characteristics were balanced for aSH and Poznanski populations and were similar to those for the full study population, see Table 10.

Table 10. Baseline characteristics [Ravelli et al, 2014]

Variables	Continuous TCZ population		Total CHERISH Population n=188
	Adapted Sharp/ van der Heijde n = 45	Poznanski n = 35	
Age, years	10.8 (3.71)	9.9 (3.29)	11.0 (4.0)
Female, n (%)	34 (76)	27 (77)	144 (77)
Weight, kg	39.3 (16.32)	36.3 (14.66)	39.6 (17.3)
Disease duration, years	3.9 (3.29)	3.2 (2.39)	4.2 (3.7)
Active joints[a]	20.9 (13.73)	21.7 (14.45)	20.3 (14.3)
Joints with LOM[b]	14.8 (11.95)	16.3 (12.99)	17.6 (14.4)
CHAQ-DI score (0-3)	1.3 (0.61)	1.3 (0.53)	1.4 (0.74)
ESR, mm/h	29.9 (22.28)	30.9 (21.91)	34.8 (25.5)
Previous DMARDs use, n (%)	31 (69)	20 (57)	134 (71)
Previous biologics use, n (%)	9 (20)	7 (20)	61 (32)
Background MTX use, n (%)	39 (87)	30 (86)	148 (79)
MTX dosage, mg/m^2/week	12.5 (3.29)	12.7 (3.32)	13.0 (5.75)
Background oral CS use, n (%)	19 (42)	15 (43)	86 (46)
CS dosage, mg/kg/day[c]	0.13 (0.053)	0.14 (0.046)	0.13 (0.048)

[a]71-joint count
[b]67-joint count
[c]Prednisone equivalent

Abbreviations: CHAQ-DI- Childhood Health Assessment Questionnaire–Disability Index; CS- corticosteroid; DMARDs- disease-modifying anti-rheumatic drugs; ESR- erythrocyte sedimentation rate; LOM- limitation of motion; MTX- methotrexate

Median changes from baseline to Week 52 and Week 104 in aSH and Poznanski scores indicated a lack of radiographic progression.

Table 11. Change in scores from baseline to Week 52 and Week 104 in the continuous TCZ population* [Ravelli et al, 2014]

	Week 52			Week 104		
Measure	**n**	**Median (IQR)**	**p-value**	**n**	**Median (IQR)**	**p-value**
Adapted Sharp/van der Heijde score	40	0.50 (–7.25, 4.50)	0.700	35	–1.00 (–6.50, 2.50)	0.109
Erosion score	40	0.00 (–1.50, 1.50)	0.819	36	0.00 (–2.75, 0.75)	0.402
JSN score	40	0.25 (–5.25, 3.50)	0.614	35	–1.00 (–3.50, 1.50)	0.109
Poznanski score	31	0.26 (–0.34, 0.91)	0.077	25	0.55 (0.04, 0.92)	0.004

*Missing individual joints within an x-ray segment were imputed, subject to the availability of a minimum number of adequate joints within the segment, for adapted Sharp/van der Heijde score data. No imputation was used for missing Poznanski score data. The Wilcoxon signed rank test was used to analyse change from baseline.

Abbreviations: IQR- interquartile range

With a cut-off of the smallest detectable difference, no radiographic progression was seen in 87.5% and 97.1% of patients based on aSH scoring, and 93.5% and 96.0% of patients based on Poznanski scoring at Weeks 52 and 104, respectively. Comparable proportions of the total radiographic population remained radiographic progression-free at Week 104 in both adapted Sharp/van der Heijde and Poznanski analyses.

Mean annualised progression rates from baseline to Week 104 show lack of radiographic progression over the two year period.

Table 12. Annualised progression rates from baseline to Week 104 in the all TCZ population* [Ravelli et al, 2014]

	Adapted Sharp/van der Heijde score	Erosion score	JSN score	Poznanski score
n	70	71	70	44
Mean	–0.75	0.31	–0.95	0.19
*The annualised progression rate between baseline and Week 104 is calculated as the change in adapted Sharp/van der Heijde or Poznanski score between the 2 assessments, divided by the time period in days, multiplied by 365.25. Missing individual joints within an x-ray segment are imputed, subject to the availability of a minimum number of adequate joints within the segment.				

3.3. Safety results at Week 40

Here, we report safety results to the data cut of 184.4 patient-years (PY) of TCZ exposure. Adverse events (AEs) and serious adverse events (SAEs) for the safety population (n=188) at the time of data cut are presented in this section. AEs occurred at a rate of 480/100 PY, and SAEs occurred at a rate of 12.5/100 PY. Infections were the most commonly reported AE and SAE, at 163.7/100 PY and 4.9/100 PY, respectively. The most frequently reported infection-related SAE (>1%) included pneumonia (2.1%), bronchitis (1.1%), and cellulitis (1.1%). All infection-related SAEs resolved without sequelae. There were no deaths during the study, and no malignancies were identified. Serious adverse events in the all-exposure safety population at Week 40 are summarised in the Table **13**.

Table 13. Serious adverse events in all-exposure safety population to Week 40 from CHERISH trial [Balidam et al, 2013]

Serious Adverse Events	SAE rate/100 PY
Overall SAE rate	**12.5**
Infections and infestations	4.9
Injury, poisoning, and procedural complications	1.6
Congenital, familial, and genetic disorders	1.1
Hepatobilliary disorders	1.1
Musculoskeletal and connective tissue disorders	1.1
Eye disorders	0.5
Gastrointestinal disorders	0.5
Nervous system disorders	0.5
Psychiatric disorders	0.5
Renal and urinary disorders	0.5
Abbreviations: PY- patient years; SAE- serious adverse event	

The most frequently reported adverse events (>10%) included nasopharyngitis (20.7%), headache (13.8%), and upper respiratory tract infection (10.1%). Results are summarised in Table 14.

Table 14. Adverse events in all-exposure safety population to Week 40 from the CHERISH trial [Balidam et al, 2013]

System Order Class	AE rate/100 PY
Overall AE rate	**480**
Infections and infestations	163.7
Gastrointestinal disorders	71.0
Musculoskeletal and connective tissue disorders	53.1
Respiratory, thoracic, and mediastinal disorders	36.9
Skin and subcutaneous tissue disorders	33.1
Nervous system disorders	28.7
Injury, poisoning, and procedural complications	22.2
Abbreviations: AE- adverse event; PY- patient years	

Other adverse events reported included: elevations of LDL-C ≥110 mg/dl (11.4%), elevations in total cholesterol ≥170 mg/dl (34.6%), neutropenia (3.7%), thrombocytopenia (1.1%), and elevations ≥3x ULN in ALT (3.7%) or AST (<1%). There were no reports of grade 3/4 elevations in serum bilirubin. No patients were treated with lipid lowering drugs. Laboratory abnormalities are summarised in Table 15.

Table 15. Laboratory abnormalities in TCZ-treated patients to Week 40 from the CHERISH trial [Balidam et al, 2013]

Laboratory Abnormalities	Common Toxicity Criteria Grade			
	1	2	3	4
ALT elevations (n=187)	27.8%	4.3%	0.5%	0%
AST elevations (n=187)	17.1%	1.1%	0.5%	0%
Bilirubin elevations (n=187)	7.5%	7.0%	0%	0%
Neutrophil decrease (n=188)	7.4%	20.7%	3.2%	0%

ALT elevation: Grade 1 (>ULN-2.5xULN); Grade 2 (>2.5-5xULN); Grade 3 (>5-20xULN); Grade 4 (>20xULN)
AST elevation: Grade 1 (>ULN-2.5xULN); Grade 2 (>2.5-5xULN); Grade 3 (>5-20xULN); Grade 4 (>20xULN)
Bilirubin elevation: Grade 1 (>ULN-1.5xULN); Grade 2 (>1.5-3xULN); Grade 3 (>3-10xULN); Grade 4 (>10xULN)
Neutrophil decrease: Grade 1 (<LLN-1.5 $x10^9$/L); Grade 2 (<1.5-1 $x10^9$/L); Grade 3 (<1-0.5 $x10^9$/L); Grade 4 (<0.5 $x10^9$/L)
Abbreviations: ALT- alanine aminotransferase; AST- aspartate aminotransferase; LLN- lower limit of normal; ULN- upper limit of normal

3.3.1. Long-term safety results

Here, we report safety results to the data cut of 307.0 PY of TCZ exposure. At Week 104, among 188 patients in the all-exposure population, adverse events occurred at a rate of 406.5/100 PY and SAEs occurred at a rate of 11.1/100 PY, with infections being the most common adverse event and SAE. Other adverse events observed included gastrointestinal disorders, neutropenia, thrombocytopenia, and elevations in liver enzymes and lipid levels. Adverse events (AEs) and serious adverse events (SAEs) for the safety population (n=188) at the time of data cut are presented in this section.

Table 16. Adverse events and serious adverse events in all-exposure safety population to Week 104 from the CHERISH trial [Brunner et al, 2014]

	Baseline to Week 40* All TCZ IV (n=188)	Baseline to Week 104 All TCZ IV (n=188)
Duration in study†, PY	184.4	307.0
Total Adverse Events, n (per 100 PY)	885 (479.8)	1,248 (406.5)
Infections and infestations	302 (163.7)	465 (151.4)
Musculoskeletal and connective tissue disorders‡	98 (53.1)	121 (39.4)
Gastrointestinal disorders	131 (71)	159 (51.8)
Total serious adverse events, n (per 100 PY)	23 (12.5)	34 (11.1)

Notes: Multiple occurrences of the same adverse event in one individual were counted; *Includes all data up to the time when the last patients in the study completed Week 40; †Duration in study (years)=[(date of last assessment-date of first TCZ dose +1)/365.25]-exposure to placebo treatment (years). ‡52 events were juvenile idiopathic arthritis
Abbreviations: IV- intravenous; PY- patient-years

A summary of all serious adverse events through Week 104 in the all-exposure population are presented in Table 17.

Table 17. Serious adverse events from all-exposure population through to Week 104 from the CHERISH trial [Brunner et al, 2013]

Serious Adverse Events	Baseline to Week 40* All TCZ IV (n=188)	Baseline to Week 104 All TCZ IV (n=188)
Total patients with ≥1 SAE, n (%)	**17 (9%)**	**26 (13.8%)**
Total SAEs, n	**22**	**33**
Infections (e.g. pneumonia, bronchitis)	9	16
Injury (e.g. fracture, synovial rupture)	3	3
Musculoskeletal and connective tissue (e.g. osteoporosis, back pain)	1	3
Uveitis	1	2
Sclerosing cholangitis	1	1
Hypertransaminasaemia	1	1
Familial Mediterranean fever	1	1
Constipation	1	1
Benign intercranial hypertension	1	1
Pregnancy	-	1
Psychosomatic disease	1	1
Urinary calculus	1	1
Asthmatic crisis	-	1

Notes: *Includes all data up to the time when the last patients in the study completed Week 40.
Abbreviations: IV- intravenous; SAE- serious adverse event.

Patients with worst Common Toxicity Criteria (CTC) Grades for key laboratory safety data through Week 104 are presented in Table 18.

Table 18. Patients with worst CTC grades for key laboratory safety data through to Week 104 from the CHERISH trial [Brunner et al, 2013]

Variable, n (%)	Baseline to Week 40* All TCZ IV (n=188)	Baseline to Week 104 All TCZ IV (n=188)
ALT ≥CTC Grade 3	1 (<1%)	4 (2%)
AST ≥CTC Grade 3	1 (<1%)	4 (2%)
Total bilirubin ≥CTC Grade 3	-	2 (1%)†
LDL-cholesterol ≥130 mg/dL	8 (4%)‡	10 (5%)
Total cholesterol ≥200 mg/dL	17 (9%)‡	22 (12%)
Neutrophil worst CTC Grade ≥3	7 (4%)§	11 (6%)
Neutrophil worst CTC Grade ≥4	1 (<1%)§	-
Platelet worst CTC Grade ≥3	2 (1%)	2 (1%)
Platelet worst CTC Grade ≥4	1 (<1%)	1 (<1%)

Notes: * Includes all data up to the time when the last patients in the study completed Week 40; †One patient with Grade 4 bilirubin elevation due to a data error; ‡Lipid data taken from May 3, 2012 datacut; §No Grade 4 neutrophil count; unit conversion error (corrected to a Grade 2 neutrophil count)
Abbreviations: ALT- alanine aminotransferase; AST- aspartate aminotransferase; CTC- common toxicity critera; IV- intravenous; LDL- low-density lipoprotein.

3.4. Japanese study on the use of TCZ in pJIA and EO

The Japanese study by Imagawa et al. met its primary endpoint, ACR Pedi 30 response rate increased over time to 94.7% (18/19) at Week 12, and 100% (17/17) at Week 48. Results for individual JIA core criteria, including pain and number of tender joints all progressively improved throughout the study [Imagawa et al, 2012]

Seventy-five adverse events were reported in the 19 patients during the 48-week study period. No patient was withdrawn from TCZ treatment due to adverse events, and there were no deaths.The most commonly reported events were nasopharyngitis (n=9), and upper respiratory tract infection (n=9). Other reported adverse events were insect bite (n=4), gastroenteritis (n=4), pharyngitis (n=3), abdominal pain (n=3), diarrhoea (n=3) and stomatitis (n=3). There were no reports of cardiac failure or malignancies. All laboratory abnormalities were mild; there were no serious abnormalities requiring urgent treatment. No patient had persistent elevation in autoantibodies (including antinuclear and anti-DNA antibodies).

This study was an open-label, multi-centre study which evaluated the safety and efficacy of TCZ in nineteen paediatric patients with pJIA whom had an inadequate response or were intolerant to other medications including MTX.

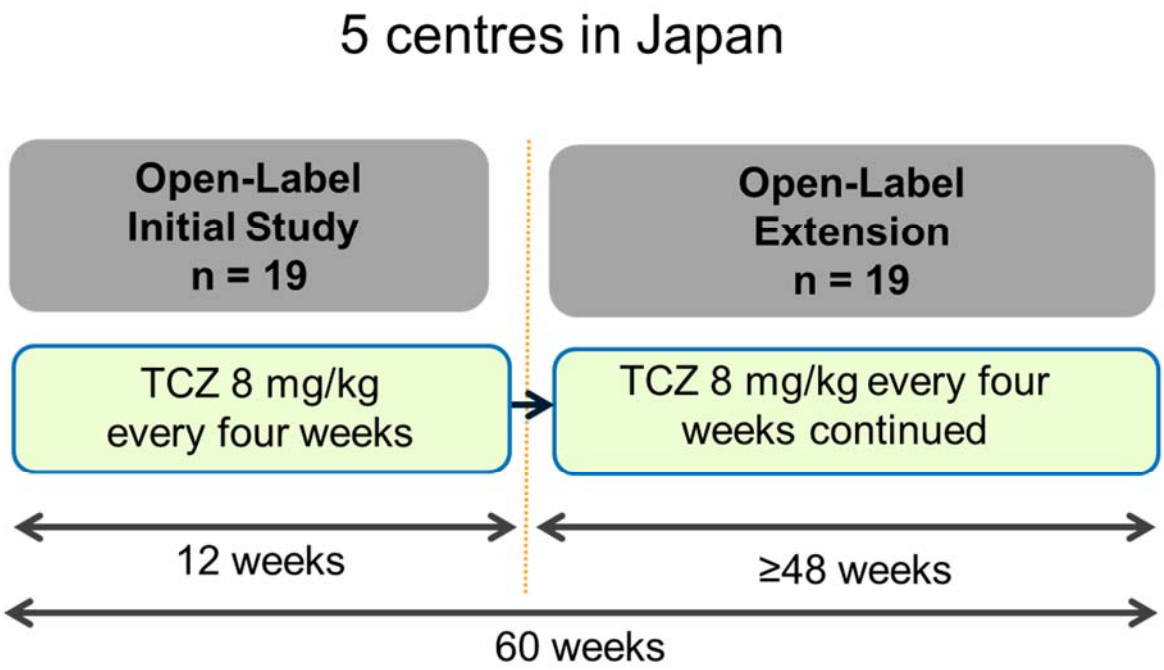
For the purpose of this document, the following publication has been summarised:

Efficacy and Safety Analysis at Week 12 and Week 48	Imagawa T, Yokato S, Mori M et al. Safety and efficacy of tocilizumab, an anti-IL-6-receptor monoclonal antibody, in patients with polyarticular-course juvenile idiopathic arthritis. Mod Rheumatol 2012;22:109–115

3.4.1. Study design

Patients received TCZ 8 mg/kg every 4 weeks in both the initial study (to Week 12) and the extension study (at least 48 weeks). Concomitant therapy with anti-TNFs, DMARDs, including MTX or immunosupressants was not allowed.

Figure 6. Study design of Imagawa et al. study [Imagawa et al, 2012]



The study population comprised of patients with RF-positive pJIA (n=9), RF-negative pJIA (n=8), and extended oligoarticular arthritis (n=2). Key inclusion and exclusion criteria are summarised in the table below.

Table 19. Key inclusion and exclusion criteria for Japanese study [Imagawa et al, 2012]

Inclusion criteria	Exclusion criteria
• Patients aged 2 to 19 years (when informed consent was obtained) who were diagnosed with pJIA or EO by the ILAR criteria • At least 3 tender joints with limited range of motion (of 74 joints observed) and at least 5 inflamed, swollen joints • Inflammation signs, including ESR ≥30 mm/h or CRP ≥1.0 mg/dL • Received no other biologic medication during the 3 months before baseline assessment • Practiced adequate contraception prior to enrolment and for women, tested negative for pregnancy at screening and first-line assessment after first menstruation	• Patients categorised as ACR Pedi functional class IV • Patients with any of the following: ALT >5 time or bilirubin >3 times normal for age, low white blood cell count (<3,500/μl), low neutrophil count (<1,000/μl), low platelet count (<10x10^4/μl), or low lymphocyte count(<500/μl) • Evidence of severe infection • History of allergic reaction to protein formulations e.g. immunoglobulins • Patients who received any DMARD, or intravenous or intra-articular corticosteroid injection, fourteen days prior to baseline assessment

3.4.2. Outcome measures

The primary endpoint was defined as the ACR Paediatric 30 response rate at Week 12 (initial study) and at the final visit in the extension study [Imagawa et al, 2012].

Other exploratory endpoints included ACR Paediatric 30/50/70 response rates at various time-points in the study.

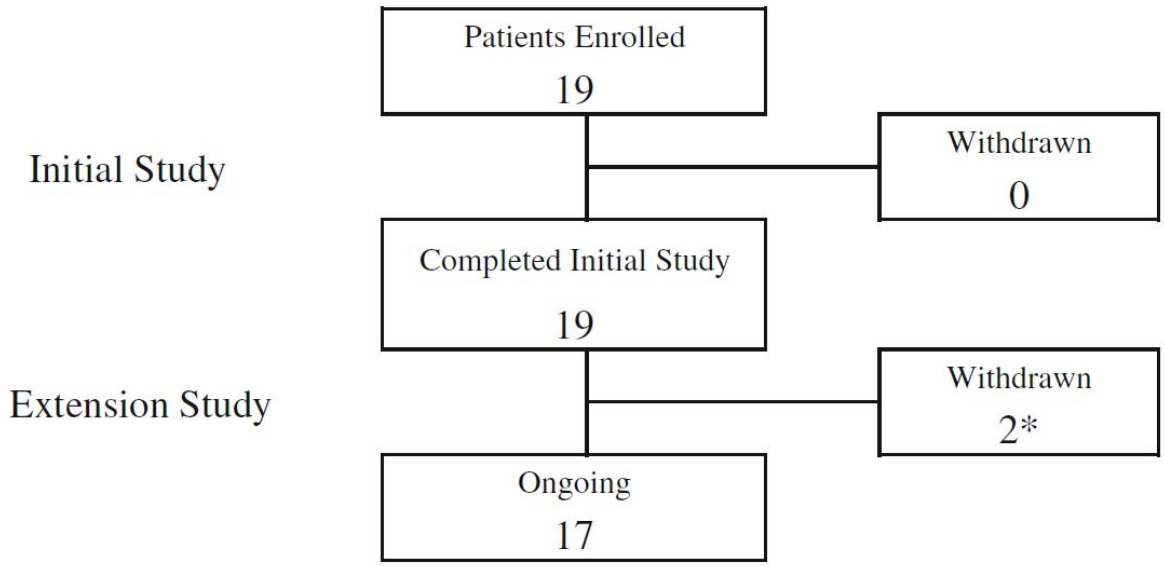
3.4.3. Statistical analysis

For each assessment time point, categorical data are expressed as number and percentage (%) of patients, and numerical data are expressed as mean and standard deviation. No other statistical analysis was described by the authors [Imagawa et al, 2012]

3.4.4. Patient disposition

Nineteen patients were enrolled in the initial study. At the end of Week 12, no patients had discontinued treatment. All nineteen patients went on to the extension study, and during this time 2 patients discontinued treatment. At Week 48, seventeen patients were still receiving treatment with TCZ [Imagawa et al, 2012].

Figure 7. Summary of patient disposition from Imagawa et al. study [Imagawa et al, 2012]



*One patient withdrawn because of insufficient response to treatment, and another patient withdrawn due to development of neutralising antibodies to TCZ

3.4.5. Baseline characteristics

All nineteen patients had active arthritis at enrolment. Serum IL-6 was elevated at baseline in seventeen patients. Nine patients had been diagnosed with RF-positive pJIA and eight with RF-negative pJIA during the first 6 months of their disease. The remaining two patients had been diagnosed with extended oligoarticular arthritis before enrolment in this study.

Table 20. Baseline characteristics of patients from Japanese study [Imagawa et al, 2012]

Variable	TCZ 8 mg/kg n = 19
Age, median years (range)	12 (3-9)†
Age group, n (%)	
2-5 years	3 (15.8)
6-10 years	5 (26.3)
11-15 years	4 (21.1)
16-19 years	7 (36.8)
Females, n (%)	15 (78.9)
Age at disease onset, median years (range)	7 (0-14)
Interleukin-6 levels in pg/mL, median (range)	18.9 (3.2-187)
Disease duration, median years (range)*	4.7 (1-17)
Patients with previous treatments with DMARDs or immunosuppressants, n (%**)	19 (100)
Prednisolone-equivalent corticosteroid dose at study entry in mg/kg/day, median (range)	0.16 (0.02-0.30)

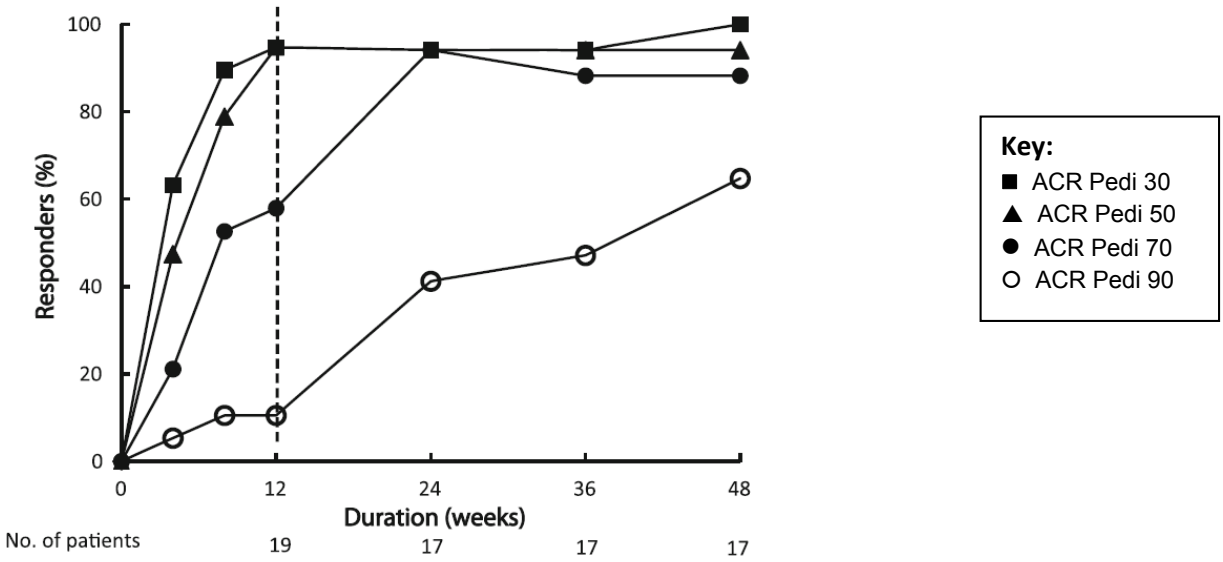
†Range published in journal was 3-9 but we suspect this may be a printing error and should be 3-19 as the age data splits the group up to 19 years of age
*All patients developed the disease before their 16th birthday
**Percentage of patients with past treatments

3.4.6. Efficacy

The primary endpoint, ACR Pedi 30 response rate, increased over time in the initial study, reaching 94.7% (18/19) at Week 12, and reached 100% (17/17) at Week 48 [Imagawa et al, 2012].

ACR Pedi 50 response rate was 78.9% (15/19) and 94.7% (18/19) at Week 8 and 12, respectively, and reached 94.1% (16/17) at Week 48. ACR Pedi 70 response rate was 52.6% (10/19) and 57.9% (11/19) at Week 8 and 12, respectively, and reached 94.1% (16/17) at Week 24 and reached 88.2% (15/17) at Week 48. The ACR Pedi 90 response rate was only 10.5% (2/19) at Week 12, and steadily increased to reach 64.7% (11/17) at Week 48.

Figure 8. ACR Paediatric 30/50/70/90 response rates over time throughout the Japanese study [Imagawa et al, 2012]



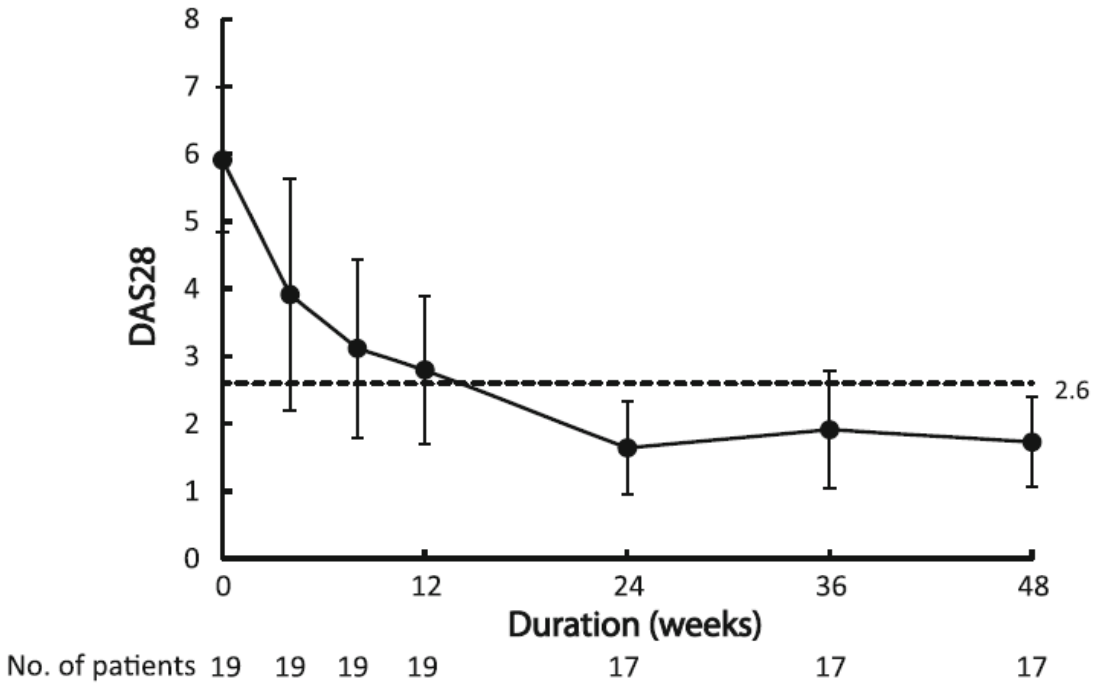
Results for individual JIA core criteria, including pain and number of tender joints all progressively improved throughout the study. The table below summarises other core indicators of JIA disease activity measured in the study.

Figure 9. Indicators of JIA disease activity throughout the Japanese study [Imagawa et al, 2012]

Parameter, median (range)	Initial study n=19				Extension study n=19
	Baseline	Week 4	Week 8	Week 12	Week 48
Number of active joints	13 (5-43)	5 (0-36)	3 (0-27)	2 (0-12)	1 (0-10)
Number of joints with limited motion	9 (1-21)	6 (0-35)	4 (0-18)	4 (0-16)	2 (0-21)
Number of tender joints	13 (2-44)	3 (0-32)	2 (0-22)	2 (0-4)	0 (0-5)
Physician's global assessment of disease severity[a]	67 (19-91)	29 (4-47)	16 (1-52)	12 (1-36)	9 (0-30)
Patient's or parent's global assessment of well-being[a]	65 (9-100)	44 (0-81)	42 (1-74)	27 (1-80)	5 (0-58)
CHAQ score[a]	1.25 (0-2.88)	0.88 (0-3.00)	0.75 (0-2.88)	0.63 (0-3.00)	0.13 (0-2.50)
Pain[b]	68 (6-100)	35 (6-91)	32 (0-93)	21 (0-100)	6 (0-55)
CRP, mg/dl	1.95 (0.06-8.20)	0.20 (0-4.90)	0.05 (0-4.00)	0.05 (0-5.78)	0.03 (0-0.05)
ESR, mm/h	43 (18-83)	10 (1-55)	7 (2-75)	9 (2-79)	6 (2-12)

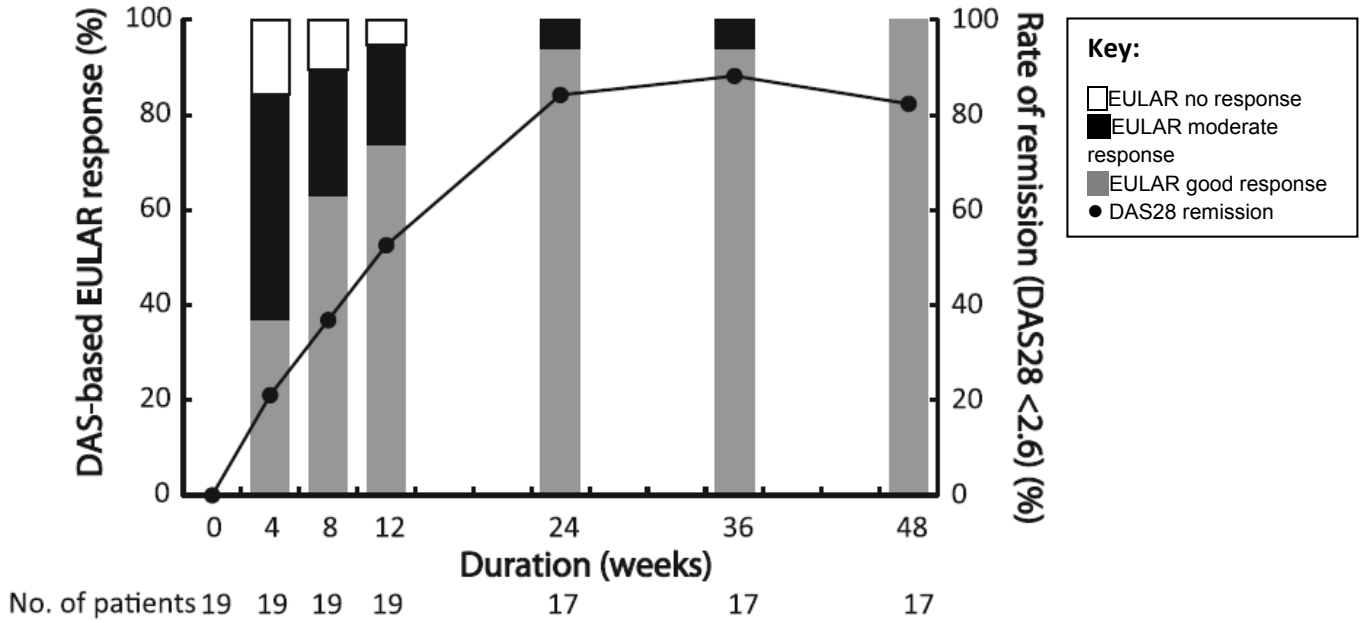
Abbreviations: CHAQ- Childhood Health Assessment Questionnaire; ESR- erythrocyte sedimentation rate, CRP- C-reactive protein
[a]Japanese CHAQ, range: 0 (best) to 3 (worst)
[b]Score on a visual analogue scale, range: 0 (best) to 100 (worst)

Figure 10. Mean DAS28 scores throughout the Japanese study [Imagawa et al, 2012]



DAS28 remission was defined as DAS28 score <2.6. The number of patients who achieved remission increased over time with 10 patients achieving DAS28 remission at Week 12, and 14 patients at Week 48. Using the EULAR response criteria, 73.7% (14/19) patients exhibited a good response at Week 12, and 94.1% (16/17) at Week 24. By Week 48, all the remaining patients 100% (17/17) exhibited a good response.

Figure 11. DAS28 remission rate and EULAR DAS28 response rates throughout the study [Imagawa et al, 2012]



3.4.7. Safety

Seventy-five adverse events were reported in the 19 patients during the 48-week study period. No patient was withdrawn from TCZ treatment due to adverse events, and there were no deaths [Imagawa et al, 2012].

The most commonly reported events were nasopharyngitis (n=9), and upper respiratory tract infection (n=9). Other reported adverse events were insect bite (n=4), gastroenteritis (n=4), pharyngitis (n=3), abdominal pain (n=3), diarrhoea (n=3) and stomatitis (n=3). There were no reports of cardiac failure or malignancies.

All laboratory abnormalities were mild; there were no serious abnormalities requiring urgent treatment. No patient had persistent elevation in autoantibodies (including antinuclear and anti-DNA antibodies).

Four patients required hospitalisation due to gastroenteritis (n=2), pneumonia (n=1), and sensory disturbance (n=1). One of the two patients with gastroenteritis tested positive for campylobacter, and the infection resolved with antibiotic therapy. Mycoplasma was detected in the patient with pneumonia, and the infection was also resolved with antibiotic treatment. There were no reports of tuberculosis or pneumocystis pneumonia. There were no neurological findings or abnormal electroencephalograms (EEG) or imaging test results for the patient with sensory disturbance, and the event was diagnosed as a psychogenic reaction related to hospitalisation.

4. Discussion on clinical evidence

The collective clinical literature suggests that TCZ is an effective treatment of pJIA, with a safety profile in this patient population consistent with the known safety profile of TCZ. The results from the CHERISH trial demonstrated that response to treatment with TCZ was both rapid (50% of patients achieved JIA ACR30 at week 2) and sustained up to week 104. Patients in the CHERISH Trial also experienced improvements in growth and the majority of radiographic patients (92.9%) experienced no progression at week 104.

Results from the CHERISH trial demonstrate that administration of TCZ 10 mg/kg IV every four weeks in patients <30 kg and TCZ 8 mg/kg IV every 4 weeks in patients ≥30 kg is effective for the management of pJIA. The primary end point at Week 40 was met; fewer patients treated with TCZ (21/82; 25.6%) experienced a JIA ACR30 flare at Week 40, compared to placebo-treated patients (39/81; 48.1%) (p=0.0024) [Brunner et al, 2014]. Patients who received TCZ for 40 weeks experienced marked improvement in all JIA ACR CRVs (active joints, joints with limitation in range of movement, patient and physician-assessed global assessment of well-being, CHAQ-DI and ESR) from baseline. At Week 104, JIA ACR70 and JIA ACR90 were achieved by 70.4% and 48.1% of patients with previous biologic use, respectively. In patients with background MTX use, 88.1% achieved JIA ACR70 and 76.1% achieved JIA ACR90.

In the exploratory analysis on growth in the CHERISH study, the mean height SDS of patients with pJIA was below normal at baseline [Bharucha et al, 2014]. The majority of patients who were Tanner stage <4 at baseline (71.8%) had an increased height SDS at the end of study (Week 104). First-year height velocity during treatment with TCZ was related to glucocorticoid dose and patient age at baseline.

Based on SDD analysis of adapted Sharp/van der Heijde and Poznanski scores to analyse radiographic progression, the results show that the large majority of pJIA patients receiving TCZ experienced no radiographic progression after 2 years of treatment [Ravelli et al, 2014]. Only a small proportion of patients were available for radiographic analysis which is a limitation of the CHERISH study.

At Week 104, among 188 patients in the all-exposure population, adverse events occurred at a rate of 406.5/100 PY and SAEs occurred at a rate of 11.1/100 PY, with infections being the most common adverse event and SAE [Brunner et al, 2013; Brunner et al, 2014]. AE/SAE rates were similar to those at Week 40, and there were no new or unexpected safety concerns; the safety profile was consistent to what was seen previously in TCZ treated patients. No deaths were reported.

The withdrawal design of the CHERISH study was valuable in minimising placebo treatment in children with pJIA. Limitations to the CHERISH study include, withdrawing patients who did not achieve JIA ACR30 response in Part 2, limiting long-term information about dose responsiveness. The ability to determine differences in safety and efficacy over Part 2 in placebo-treated patients previously treated with TCZ in Part 1 was limited, as it might have taken time for TCZ to clear from the system prior to receiving placebo.

Results from the Japanese study published by Imagawa et al. showed that TCZ monotherapy demonstrated efficacy in the treatment of 19 patients with refractory pJIA over the total extension study period of 48 weeks, and an acceptable safety profile [Imagawa et al, 2012]. ACR Pedi 30/50/70/90 response rates, respectively, were 94.7%, 94.7%, 57.9% and 10.5% at Week 12, and 100%, 94.1%, 88.2% and 64.7% at Week 48 in the extension study. The mean DAS28 score remained lower than 2.6 from Week 24 through to Week 48 (n=17). No patient was withdrawn due to adverse events, and there were no serious infections or deaths. All laboratory abnormalities were mild and required no urgent treatment.

5. Economic Section

5.1. Introduction

The purpose of the economic analysis has been to determine the cost-effectiveness of tocilizumab in the treatment of pJIA when added to the current treatment paradigm.

5.2. Perspective

All relevant healthcare costs are considered from an NHS and personal social services (PSS) perspective.

5.3. Time horizon

The economic evaluation estimates costs and health benefits over a 25 year time frame. This reflects the chronic nature of the disease, and allows for all relevant costs and benefits to be included in our analysis.

As discussed at the Stakeholder Engagement meeting, there is no clinical evidence in JIA for patients 18 years and older , compared to patients less than 18 years. Expert clinical opinion was sought on whether the treatment or outcomes were likely to be different to inform the length of our time horizon. Expert clinical opinion was that the treatment should not change as patients enter adulthood, and the expert's experience there is no difference in outcomes for patients with JIA 18 years and older.

5.4. Cycle length

The model implements a 6 month cycle length, which is in line with timing of available efficacy evidence (ACR data).

5.5. Half-cycle correction

Half-cycle correction is applied in the model

5.6. Discounting

Discounting of 3.5% per annum according to NICE guidelines for both costs and effects has been applied in the model.

5.7. Patient Characteristics

Patients entering the model have active disease and have previously experienced an inadequate response to, or were intolerant of, methotrexate (MTX). This modelled patient population is in line with the CHERISH trial population.

The base case analysis assumes the starting age is 11 years based on the mean age for patients on TCZ in CHERISH. Data from the British Society for Paediatric and Adolescent Rheumatology (BSPAR) national Biologics and New Drugs Registry (BNDR) report a median starting age for a first biologic therapy of 12 years [Southwood et al., 2011].

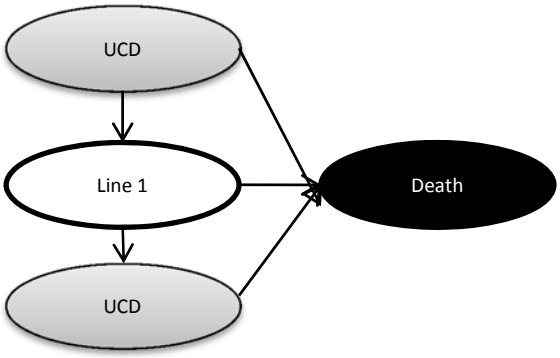
5.8. Model structure

The structure of the model is developed to closely reflect clinical practice and the availability of the evidence. The design allows the comparison of two clinical pathways for a cohort of patients with pJIA.

The model structure is consistent with the approach adopted in the sJIA [TA238], and rheumatoid arthritis appraisals of tocilizumab [TA247].

A diagrammatic representation of the model is presented in Figure 12

Figure 12. Economic model



The model contains three health states:

- Uncontrolled disease (UCD) or off-treatment
- On treatment
- Dead

Patients start with uncontrolled disease at cycle 0 then move to first line treatment. Once all lines of treatment are exhausted, patients move into UCD health state. Death is an absorbing health state.

5.9. Comparators

In the NHS patients with pJIA are treated with MTX, systemic corticosteroids, and non-steroidal anti-inflammatory drugs, although none of these treatments are licensed for pJIA. These treatments do, however, represent first line therapy.

Etanercept, adalimumab, abatacept, and tocilizumab are the only treatments licensed within pJIA (some slight differences in the licenses exist). As the licence of tocilizumab is for patients 'who have responded inadequately to previous therapy with MTX', our intention was to compare tocilizumab to the most appropriate DMARD-IR comparators.

Biologics are the current standard of care in the UK for patients who have had an inadequate response to DMARDs, we have therefore sought to compare tocilizumab where possible with etanercept, adalimumab, and abatacept.

We note, the expert clinical opinion disagreed with the premise that a relevant comparator to the products being evaluated as part of this review would be best supportive care. According to the clinical expert, it would be completely unrealistic to assume in this rare paediatric setting that patients would receive no therapy. It is also unlikely that patients who have already had an inadequate response to MTX would be re-challenged with the same treatment.

We have therefore completed our economic analysis as a comparison of tocilizumab to the other biologics which have formed part of the standard of care in the NHS since 2002 [TA35].

5.10. Indirect Comparisons

There are no biologic head to head studies in juvenile arthritis. A systematic literature review was completed to develop an indirect comparison between tocilizumab and other biologics in the treatment of pJIA.

Given similarities in terms of trial design, patients, methods of imputation and quality, only adalimumab and tocilizumab could be compared via indirect comparison.

We therefore do not have evidence of the comparative effectiveness of tocilizumab with the NICE approved etanercept, or with abatacept. The challenges for comparing biologics in pJIA was noted as a significant limitation at the NICE scoping meeting, although we believe the indirect treatment analysis we have completed for tocilizumab and adalimumab is robust when considered in light of the paediatric setting.

As etanercept is the only NICE approved biologic in this setting, we have provided an exploratory analysis comparing tocilizumab with etanercept (See Exploratory Results 5.17). This analysis is only illustrative as it assumes etanercept is as effective as adalimumab. In general, expert clinical opinion is that all biologics offer similar outcomes, therefore this assumption – while not back by robust evidence – is supported by clinical experience.

A comparison with abatacept was also not possible due to the difference in trial design. We have chosen not to conduct an exploratory analysis primarily because it is not approved by NICE but also because of the slight difference in the licence with tocilizumab (treatment of patients aged 6 years or above, and must be given with MTX).

Results from each study were combined by means of a hierarchical Bayesian indirect treatment comparison using an ordered probit model to estimate relative treatment effects and probabilities of achieving different levels of ACR response.

The model was implemented in WinBUGS version 1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK) with non-informative priors and followed the methods described by Dias [Dias et al, 2013].

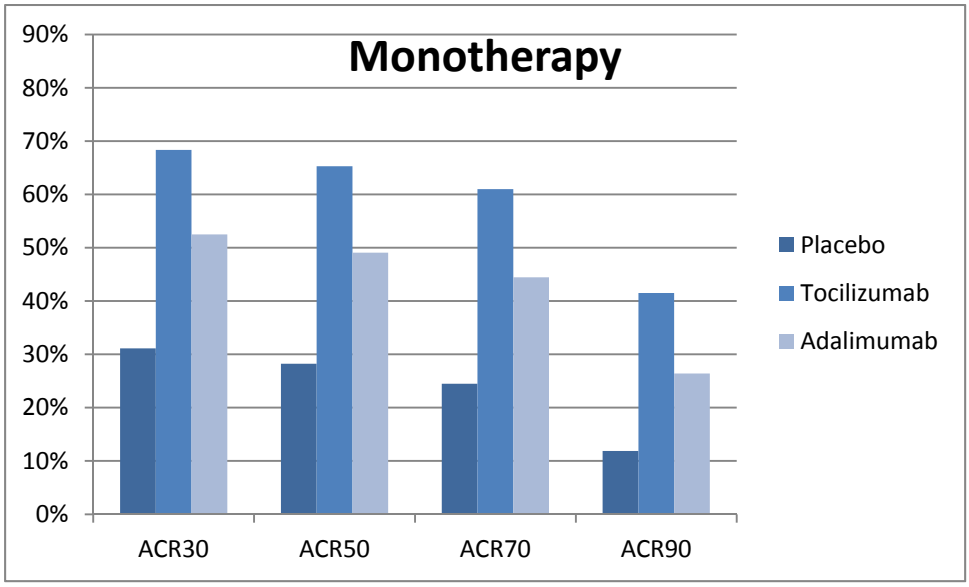
The adjusted response rates used in the base case analysis from the indirect comparison are shown in Table 21.

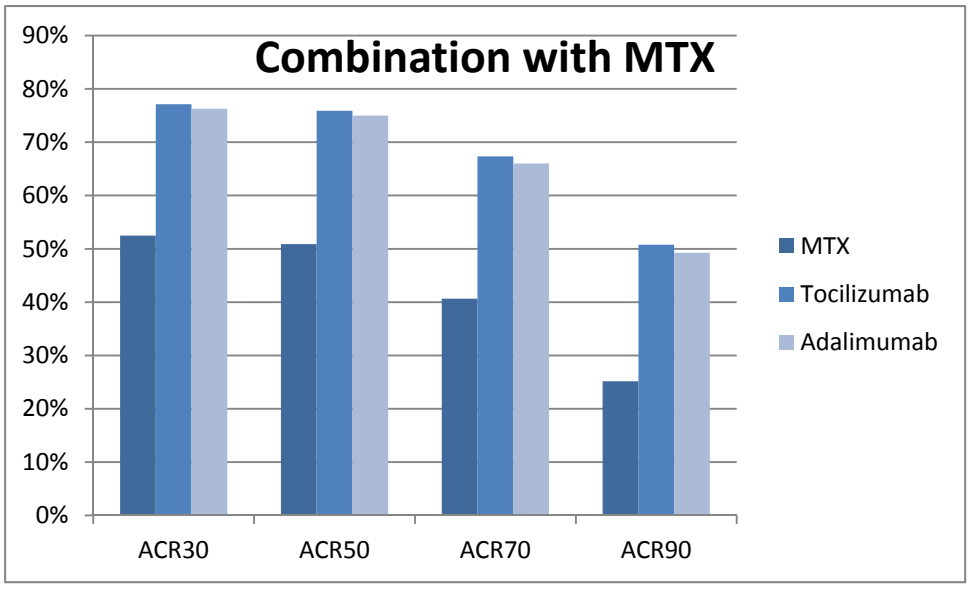
Table 21. ACR overlapping response rates

		JIA ACR30	JIA ACR50	JIA ACR70	JIA ACR90
Without MTX	Placebo	31%	28%	25%	12%
	Tocilizumab	62%	59%	54%	35%
	Adalimumab	52%	49%	44%	26%
With MTX	MTX	52%	51%	41%	25%
	Tocilizumab	72%	70%	61%	44%
	Adalimumab	76%	75%	66%	49%

The response rates for each combined health state are shown in Figure 13

Figure 13. ACR overlapping response rates used in the model





5.11. Discontinuation

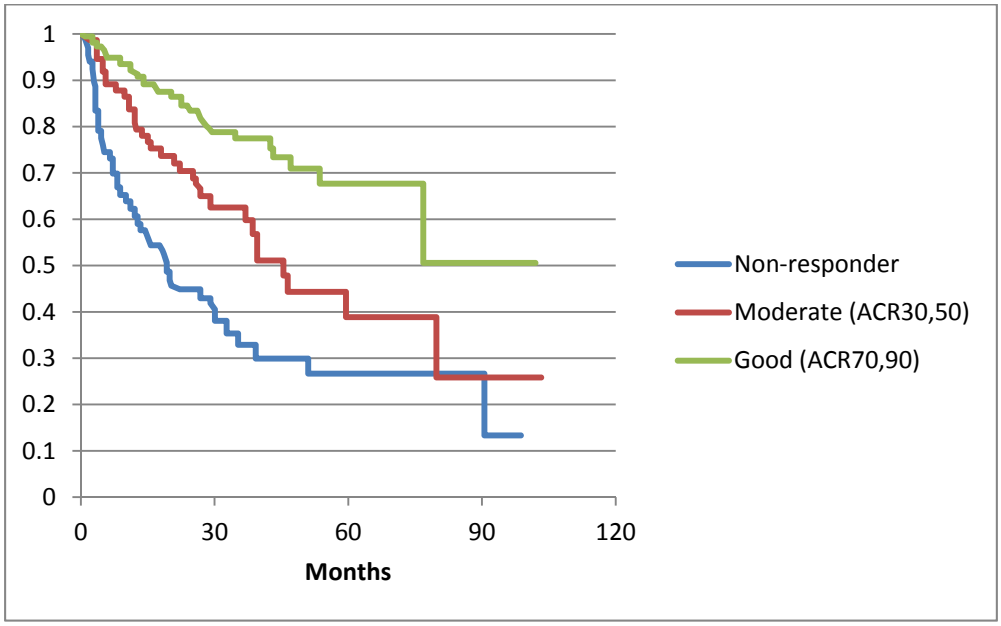
The model assumes that patients discontinue treatment at a rate dependent on their response to that treatment. The discontinuation rate is based on survival data reported for etanercept patients in the Dutch Arthritis and Biologicals in Children (ABC) Register. The model assumes the discontinuation rate is dependent on treatment response only, and is therefore the same for all biologics.

Analysis of the ABC registry data found no statistically significant difference in drug survival for each JIA ACR category. However, discontinuation rates were significantly different when the response categories were merged to form combined health states

- No response (JIA ACR response <30)
- Moderate response (JIA ACR response >30 and <70)
- Good response (JIA ACR response ≥70)

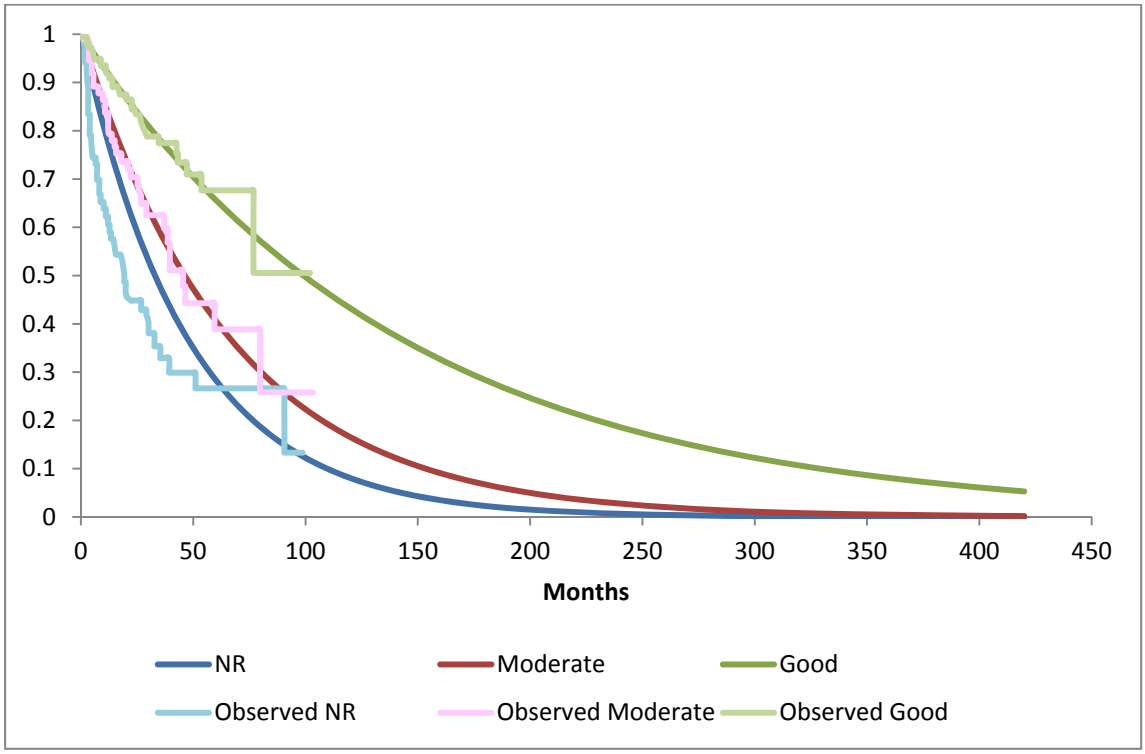
Drug survival for these merged response categories are shown in Figure 14.

Figure 14. Drug survival for merged response categories from ABC registry



The 6 month discontinuation rate was estimated from an exponential parameterisation of the Kaplan-Meier curve. This model had a good fit for all three of the response groups (Figure 15).

Figure 15. Model fit based on visual inspection



The 6-month discontinuation rates used in the model are shown in Table 22.

Table 22. Discontinuation rate

	6-month rate
No response	0.1260
Moderate	0.09
Good	0.0420

5.12. Mortality rates

A literature review was conducted to find mortality rates for pJIA. The literature indicates that the overall mortality for JIA is low (1-4%), and that most mortality occurs among systemic-JIA [Stoeber 1981; Weiss 2005].

Calabro [1983] reported the mortality rate in juvenile chronic polyarthritis to be 2-4%. Due to the significant uncertainty in the mortality evidence, we have chosen the conservative 2% annual mortality rate to reflect the likely improvement in outcomes for pJIA patients over the last 30 years.

This has been converted into a 1% 6-month mortality rate in the model. Mortality is assumed to be the same across all treatment strategies.

5.13. Adverse Events

A systematic literature review of adverse events (AEs) with biologics was conducted to identify the most relevant events. Kemper et al. [2012] conducted a systematic review of DMARDs in JIA, however the authors only reported very rare serious events such as death and cancer, with no details provided on more common adverse events. This review did not therefore contain sufficient data for our model.

A recently published economic analysis in pJIA [Ungar et al. 2011] included adverse events in the form of serious infections on the basis that these are the most common adverse events associated with biologics alongside injection site reactions. Serious infection rates of 4% for etanercept and adalimumab, and 2% for abatacept were used in the model, which the author state was based on data from the paediatric RCTs, and adult meta analyses. However, no details are given on the methods used to obtain these rates.

Ungar et al.'s [2011] decision to include serious infections in the economic model is supported by a review of the safety profile of biologic therapies for JIA conducted by Hashkes et al. [2010], who reported the most common AEs were infections and infusion/injection site reactions.

Hashkes et al. [2010] reported the total number of serious infections reported in clinical studies of each of the biologic agents for JIA, along with patient-years of exposure where available. Unfortunately, patient-years of exposure are only reported for adalimumab and infliximab so it is only possible to calculate the annual rate of serious infections for these therapies (Table 23). The annual rate of serious infections was also obtained from the CHERISH trial.

Although data on adverse events are available from some of the clinical trials, indirect comparison of safety is not possible since there is no common comparator or control. A simple average annual rate of serious infections was therefore calculated across all biologics using the data in Table 23. This method resulted in an annual rate of serious infection of 4.366%, or 2.18% over a 6-month period. Note that the model input for AEs is a 6-monthly risk (probability); not a rate, as in the parameters presented above.

Since patients in the control arm of each of the trials had prior exposure to biologic therapy, any adverse events experienced by these patients may be due to a residual effect of the biologic. It is therefore not appropriate to use adverse event rates from the control arm for either methotrexate or placebo. The model therefore assumes that the AE risk for MTX and placebo is 0% in the base case.

Table 23. Annual rate of serious infections pJIA

	ADA [Lovell et al. 2008]	INF [Ruperto et al. 2007]	TCZ [CHERISH]
Total N	171	122	188
Patient years of exposure	310	101	n/a
Serious infections	7	6	9
Annual rate of serious infections	2.3%	5.9%	4.9%

5.14. Health related quality of life

A literature review identified one study [Prince et al., 2011] that reported utility values suitable for use in the model. Prince et al. [2011] reported utility scores obtained by administering the HUI3 questionnaire to JIA patients starting treatment with etanercept in the Dutch Arthritis and Biologicals in Children (ABC) Register. The questionnaire was given before treatment started, and then 3, 15 and 27 months after initiation of therapy. The utility score at 12 months was estimated from the 3 and 15 month values using linear interpolation.

Utility values at each of timepoint are shown in Table 24.

Table 24. HUI3 based utility values

Months	Mean utility value	SEM
0	0.53	0.04
3	0.69	0.05
12*	0.7275	0.0575
15	0.74	0.06
27	0.78	0.07

*estimate

It is important to note that the 3, 12, 15 and 27 month utility values presented in Table 24 represent all patients on treatment, regardless of their response to that treatment. The utility value at month 0 may be assumed to be representative of patients not receiving treatment.

The annual utility values used in the model are summarised below:

- On treatment (No response, moderate response, good response): 0.7275
- Off treatment (Uncontrolled disease): 0.53
- Dead: 0.00

The model assumes that the on-treatment utility value already takes any disutility associated with adverse events into account, so does not include this separately.

5.15. Costs

Health state costs

The cost associated with each health state is obtained from Prince et al. [2011] who report cost data from the Dutch ABC Register. Costs were reported for the year prior to starting etanercept, and for 1 year (months 3-15) after the start of etanercept treatment. As with the utility values, costs were not reported by response rate, so the model applies off treatment costs to the uncontrolled disease health state, and on treatment costs to all other health states. Etanercept therapy costs were excluded from the health state costs since these are estimated separately in the model.

The costs used in the model are reported in Table 25.

Table 25. Model inputs - health state costs

	Off treatment	**On treatment**
Consultation PR at outpatient clinic	£422.21	£231.05
Telephonic consultation PR	£29.86	£16.34
Consultation other specialists	£80.52	£36.28
Hospital admissions	£824.83	£189.03
Physiotherapy	£337.07	£267.67
Other paramedical care	£188.00	£92.50
Other medication	£701.52	£612.53
Laboratory	£233.70	£71.80
X-ray	£305.07	£223.17
DEXA scan	£26.10	£73.08
US	£16.17	£3.94
MRI	£17.80	£7.27
Total 12 month HS cost	**£3,182.87**	**£1,824.66**
Total 6 month HS cost	**£1,591.43**	**£912.33**

Treatment acquisition costs

Drug acquisition costs used in the model are outlined in Table 26.

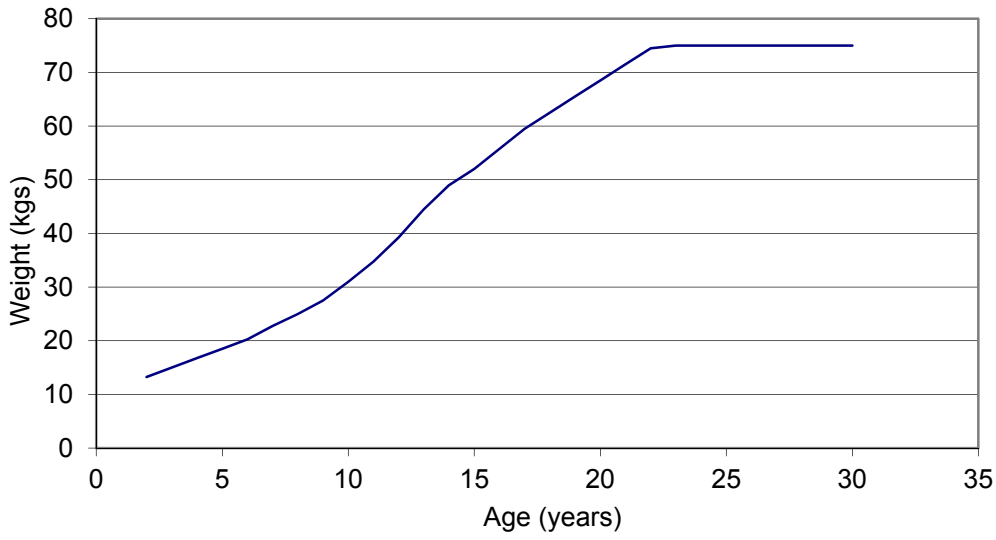
Table 26. Drug acquisition costs

Treatment	Dose1	Frequency	Unit cost (list price)
Adalimumab (40mg)	40 mg (assume wastage and all children receive 40mg vial)	Every 2 weeks	£352.14
Etanercept (10mg)	0.4mg/kg (max 25mg)	Twice a week	£35.75
Etanercept (25mg)			£89.38
Methotrexate (10mg, oral)	10mg	Every week	£0.56
Tocilizumab (80mg)	10 mg/kg for patients < 30 kg;	Every 4 weeks	£102.40*
Tocilizumab (200mg)	8 mg/kg for patients ≥ 30 kg)		£256.00*
Tocilizumab (400mg)			£512.00*

*Tocilizumab is provided with a confidential discount.

Patient weight was obtained from the NICE etanercept rapid review [2002], and can be seen in Figure 16.

Figure 16. Patient weight



Administration cost

The model includes costs for both IV infusion, and for subcutaneous injection. It is assumed that nurse assistance is required for 20% children (<10 years of age) and 10% young adults (≥ 10 years of age). The costs associated with each method of administration are outlined in Table 27.

Table 27. Drug administration costs

	Value	Source
Administration cost of infusion (per admin)	£152.24	Barton et al. [2004] cost per administration; inflated from 2003/2004 price
Nurse visit cost (per visit)	£30.50	PSSRU [2012] Community nurse (includes district nursing sister, district nurse): £61 (without qualifications) per hour of home visiting (including travel), assume 30 minutes per visit including travel
Proportion of children requiring assistance	20%	Personal contact: Dr. Westhovens
Proportion of young person's requiring assistance	10%	Personal contact: Dr. Westhovens
Young person age	10	Assumption

The cost per administration for each treatment is outlined in Table 28.

Table 28. Cost per administration

	Description	Unit cost per administration - child	Unit cost per administration - young person
Adalimumab	Subcutaneous injection	£6.10	£3.05
Tocilizumab	IV infusion	£152.24	£152.24

Adverse event costs

The model includes the risk of patients experiencing a serious infection. Harris et al. [2011] report the results of routine resource use data collection in the North of England Community Acquired Pneumonia (CAP) study. This study collected preadmission GP visits, antibiotics prescribed in the community and in hospital, and number of days of hospital care including any intensive care

These costs are outlined in Table 29.

Table 29. Cost of adverse events

	Cost per event
Average cost per admitted patient	£3273
Mean cost per severe case	£4025
Mean cost per mild case	£1041

5.16. Results for tocilizumab with PAS

The base case analysis compares tocilizumab in patients with pJIA who have had an inadequate response to DMARDs (including MTX). Due to the limited evidence in this paediatric indication, it was difficult to compare tocilizumab to all the biologics licensed for use in pJIA following an inadequate response to DMARDs.

Our base case analysis compares tocilizumab with adalimumab, and the results indicate that both treatments are of similar clinical and cost effectiveness whether used in combination with MTX or as monotherapy. The absolute differences in the QALY estimates should be interpreted with caution, as we would consider the results indicate that both therapies are of similar effectiveness. Importantly, tocilizumab is less expensive , and therefore represents better value to the NHS.

We would conclude that in this rare paediatric setting, for patients who have had an inadequate response to DMARDs, tocilizumab represents a cost-effective therapy which greatly improves the outcomes of patients with pJIA.

Table 30. Results: combination therapy

	Adalimumab + MTX	Tocilizumab + MTX	Incremental Difference	ICER (£ per QALY)
Total QALYs	18.76	18.72	(0.0303)	
Total Cost	£81,827	£70,707	(£11,120)	SWC

Table 31. Results: monotherapy

	Adalimumab	Tocilizumab	Incremental Difference	ICER (£ per QALY)
Total QALYs	18.65	18.7	0.0455	
Total Cost	£74,576	£68,560	(£6,015)	Dominant

5.17. Exploratory Analysis with Etanercept

We have undertaken an additional analysis which assumes class effect across TNFs in pJIA. This allows us to compare tocilizumab with etanercept, based on the indirect comparison with adalimumab. When applying the cost of etanercept to our model, the result were similar to the base case that tocilizumab was as effective but at a lower overall cost to the NHS.

While only illustrative due to the limitations in the evidence, we believe there is enough reason to conclude that tocilizumab represents a cost-effective alternative to the NICE approved pJIA treatment, etanercept.

Table 32. Results: combination therapy

	Etanercept + MTX	Tocilizumab + MTX	Incremental Difference	ICER (£ per QALY)
Total QALYs	18.76	18.72	(0.0303)	
Total Cost	£79,189	£70,707	(£8,483)	SWC

Table 33. Results: monotherapy

	Etanercept	Tocilizumab	Incremental Difference	ICER (£ per QALY)
Total QALYs	18.65	18.72	0.0455	
Total Cost	£71,911	£68,560	(£3,350)	Dominant

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