Common Drug Review
Clinical Review Report

August 2014

Drug	tocilizumab (Actemra, intravenous)
Indication	For the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis in patients two years of age and older who have responded inadequately to previous therapy with disease-modifying antirheumatic drugs and systemic corticosteroids.
Listing request	For the treatment of active polyarticular juvenile idiopathic arthritis in patients two years of age and older who are intolerant to, or have had an inadequate response to, one or more disease-modifying antirheumatic drugs.
Manufacturer	Hoffmann-La Roche Limited

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
CHAQ	Childhood Health Assessment Questionnaire
CHAQ-DI	Childhood Health Assessment Questionnaire-Disability Index
CI	confidence interval
CDR	Common Drug Review
CSR	Clinical Study Report
DB	double blind
DMARD	disease-modifying antirheumatic drugs
IL-6	Interleukin-6
ITC	indirect treatment comparison
ILAR	International League of Associations for Rheumatology
ITT	intention-to-treat
IV	intravenous
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
LOCF	last observation carried forward
MCID	minimally clinically important difference
MCII	minimally clinically important improvement
NSAIDs	nonsteroidal anti-inflammatory drugs
O/L	open-label
pJIA	polyarticular juvenile idiopathic arthritis
PY	patient-year
RCT	randomized controlled trial
RF	rheumatoid factor
RR	relative risk
SAE	serious adverse event
SD	standard deviation
TCZ	tocilizumab
TNF	tumour necrosis factor
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Polyarticular juvenile idiopathic arthritis (pJIA) is a chronic rheumatic disorder defined as arthritis of unknown etiology in children 16 years of age or younger persisting for at least six weeks with exclusion of other known conditions. Clinical manifestations of pJIA include joint effusion, joint-line warmth and tenderness, and limitation of movement. Inadequately controlled disease may lead to abnormalities of growth such as short stature, localized bone overgrowth or premature fusion, and alteration of limb length. The goal of therapy is to target the underlying inflammation and prevent complications associated with the condition. Commonly used therapies for JIA include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologic agents such as the tumour necrosis factor (TNF-α) inhibitors.

Tocilizumab is a recombinant human interleukin-6 (IL-6) immunoglobulin monoclonal antibody that competes for both membrane-bound and soluble forms of IL-6 receptors. According to the Health Canada-approved product monograph, tocilizumab should be given in combination with methotrexate, but may be given as monotherapy in cases of intolerance to methotrexate or where treatment with methotrexate is not appropriate. Tocilizumab is available as a 20 mg/mL concentrate solution for infusion. The indication under review is listed below:

Indication under review
For the treatment of signs and symptoms of active polyarticular juvenile idiopathic arthritis in patients two years of age and older who have responded inadequately to previous therapy with disease-modifying antirheumatic drugs and systemic corticosteroids.
Listing criteria requested by sponsor
For the treatment of active polyarticular juvenile idiopathic arthritis in patients two years of age and older who are intolerant to, or have had an inadequate response to, one or more disease-modifying antirheumatic drugs.

The objective of this systematic review is to examine the beneficial and harmful effects of IV tocilizumab in the treatment of active pJIA.

Results and Interpretation

Included Studies

One manufacturer-sponsored, randomized, placebo-controlled, double-blind (DB) withdrawal study met the criteria for the systematic review. CHERISH (n = 166) evaluated the efficacy and safety of tocilizumab, in combination with methotrexate or as monotherapy, in patients with pJIA who had previously had an inadequate response or intolerance to methotrexate. Patients received 16 weeks of tocilizumab treatment in an open-label (O/L) lead-in phase, after which patients achieving a JIA ACR 30 response (a 30% improvement in 3 of the 6 JIA ACR core criteria) entered a 24-week double-blind (DB) withdrawal phase in which patients were randomized to either continued tocilizumab or placebo, stratified by concomitant methotrexate and oral corticosteroid use. The primary efficacy outcome of the CHERISH study was the proportion of patients who experienced a JIA ACR 30 flare (relative to week 16) during the 24-week DB withdrawal phase. Other outcomes included the proportion of patients achieving JIA ACR 30, JIA ACR 50, and JIA ACR 70 responses at week 40 (relative to week 0).

The limitations of the available evidence include the lack of trials directly comparing tocilizumab with other biologic treatments for pJIA. Limitations of the CHERISH study include the short duration of the DB phase, the potential for bias in a number of secondary efficacy end points due to the unequal proportion of patients escaping from the DB phase, the use of last observation carried forward (LOCF) to account for the missing data, and the selection of an "enriched" patient population through the use of a withdrawal design that limits the generalizability of efficacy and safety results (description to follow). In addition, given the characteristics of patients included in the CHERISH study, there is limited evidence for children younger than seven years of age and for children with low disease activity.

Efficacy

Among children who achieved a minimum JIA ACR 30 response after 16 weeks of tocilizumab treatment in the O/L phase of the CHERISH study, the proportion of children experiencing a JIA ACR 30 flare over the subsequent 24 weeks was statistically less in the tocilizumab group compared with the placebo group (25.6% versus 48.1%; adjusted risk difference (RD) = –0.21; 95% CI, –0.35 to –0.08). Results for the primary outcome (proportion experiencing a JIA ACR 30 flare) were supported by a statistically significantly greater proportion of children who achieved JIA ACR 50 and JIA ACR 70 responses in the tocilizumab group compared with the placebo group at the end of the DB phase (week 40) (73.2% versus 51.9%, and 64.6% versus 42.0%, respectively). Subgroup analyses suggest that the benefit of tocilizumab compared with placebo is achieved both with and without concomitant methotrexate.

JIA ACR responses are composite end points that include six core components. Only two of the core components (number of joints with active arthritis and physician global assessment of disease activity) were reported to be statistically significantly improved for tocilizumab-treated patients compared with placebo. The findings for these two outcomes are subject to potential bias due to differential escape from DB treatment and the potential violations of the assumptions of LOCF imputation, as data was not missing completely at random. In addition, the clinical importance of the between-treatment differences for these two core components is uncertain.

The CHERISH study is limited by its design, in which patients who entered the DB phase had to have achieved a JIA ACR 30 response in the O/L lead-in phase. This necessarily led to an enriched patient population in the DB phase of the trial; thus, the response rates were likely higher than what would have been expected in a non-enriched or tocilizumab-naive population. In addition, the short duration of its comparator phase and the resultant focus on short-term improvements in symptoms and function mean that evidence of comparative long-term efficacy is lacking. Finally, CHERISH did not examine outcomes of patient satisfaction or quality of life.

Harms

Comparisons of the proportion of patients reporting adverse events (AEs) in the DB phase are hampered by unequal escape to O/L tocilizumab, after which AEs were not attributed to the DB treatment. While the differential escape is expected to bias against tocilizumab given the longer duration of exposure to DB tocilizumab compared with placebo in the DB phase, it should be noted that patients entering the DB phase had already tolerated treatment with tocilizumab in the O/L lead-in phase.

There were no notable safety issues, including malignancy and neutropenia. Although no cases of neutropenia were reported, there were decreases in neutrophil counts throughout the study. The CHERISH study was not informative of the incidence of malignancy due to its relatively short duration and small sample size.

Pharmacoeconomic Summary

Tocilizumab is available for IV infusion in 80 mg ($179.20), 200 mg ($448.00), and 400 mg ($896.00) single-use vials. The recommended dosing of tocilizumab for pJIA is 10 mg/kg every four weeks for patients who weigh less than 30 kg, and 8 mg/kg every four weeks for those weighing 30 kg or more. The manufacturer submitted a cost-minimization analysis comparing tocilizumab to etanercept pre-filled syringes, adalimumab, abatacept, and two different regimens of infliximab (3 mg/kg and 6 mg/kg) in pJIA patients (although infliximab is not indicated for use in pJIA in Canada). The perspective of the cost-minimization analysis was that of a public drug plan, and it considered the annual costs per patient for the first and subsequent years of treatment and the average annual cost of treatment for the first three years. Only drug and administration costs were considered. Based on the manufacturer's analysis, the average annual cost of the first three years for treating an average-weight child with pJIA with tocilizumab was less than each of the selected comparators. According to Common Drug Review (CDR) calculations of costs that assume weight-based dosing, tocilizumab is the least expensive treatment for pJIA patients who weigh between 34 kg and 75 kg, but tocilizumab is more expensive than abatacept, adalimumab, and etanercept in pJIA patients who weigh more than 75 kg. Tocilizumab may also be more expensive than abatacept, etanercept multi-use vials, and 3 mg/kg infliximab in some pJIA patients who weigh less than 34 kg.

Conclusions

One randomized, placebo-controlled, DB, withdrawal study (CHERISH) evaluating the efficacy and safety of tocilizumab, in combination with methotrexate or as monotherapy, in patients with pJIA was included in the systematic review. The results of the CHERISH study suggest that, among children with pJIA who achieve a JIA ACR 30 response after 16 weeks of tocilizumab treatment, continuation of tocilizumab is superior to placebo in reducing the risk of JIA ACR 30 flare during the subsequent 24 weeks. This finding was supported by the statistically significantly greater proportion of patients achieving JIA ACR 30/50/70 responses in the tocilizumab group than in the placebo group at the end of the DB phase (week 40). The proportion of patients experiencing AEs was reported to be similar in the tocilizumab and placebo groups; however, this finding may be biased due to unequal escape from DB treatment. Serious infections were rare and there was no incidence of neutropenia or malignancy. The CHERISH study is limited by the lack of an active comparator, its short duration, and the selection of an "enriched" patient population through the use of a withdrawal design that limits the generalizability of efficacy and safety results. Finally, CHERISH did not examine outcomes of patient satisfaction or quality of life.

TABLE 1: SUMMARY OF RESULTS

	Tocilizumab (N = 82)	Placebo (N = 81)
Patients with JIA ACR 30 flare (relative to week 16)		
n (%)	21 (25.6)	39 (48.1)
Adjusted RD [95% CI][a]	–0.21 [–0.35 to –0.08]	
P value	0.0024	
JIA ACR 30 responders[b]		
n (%)	61 (74.4)	44 (54.3)
Adjusted RD [95% CI][a]	[redacted]	
P value	0.0084	
JIA ACR 50 responders[b]		
n (%)	60 (73.2)	42 (51.9)
Adjusted RD [95% CI]	[redacted]	
P value	0.0050	
JIA ACR 70 responders[b]		
n (%)	53 (64.6)	34 (42.0)
Adjusted RD [95% CI][a]	[redacted]	
P value	0.0032	
Key harms outcomes, n (%)		
Mortality	0	0
AEs	[redacted]	[redacted]
SAEs	[redacted]	[redacted]
WDAEs	[redacted]	[redacted]
Other notable harms, n (%)		
Infections	[redacted]	[redacted]
Serious infections	[redacted]	[redacted]
Neutropenia	0	0
Malignancies	0	0

ACR = American College of Rheumatology; AE = adverse event; CI = confidence interval; JIA = juvenile idiopathic arthritis; RD = risk difference; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report (CSR) p. 95, 107, 1345, 1365, and 1381.[1] [redacted].[2]
[a] Analysis was adjusted for randomization stratification factors (methotrexate and oral corticosteroid use).
[b] Response was determined relative to baseline (week 0).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disorder diagnosed in children 16 years of age or younger, with the majority of cases occurring between six and 12 years of age.[3-6] It is defined as arthritis of unknown etiology persisting for greater than or equal to six weeks with the exclusion of other known conditions.[3-6] JIA is, in fact, a heterogeneous group of diseases, all of them with broad differential diagnoses;[4] as a result, the exclusion of conditions that mimic the signs and symptoms of JIA is important to ensure appropriate identification.[3] JIA was previously known as "juvenile rheumatoid arthritis (JRA)," an older terminology that is no longer in use.[6,7]

JIA is a relatively common chronic childhood disease,[4,5] with a prevalence reaching approximately 1 per 1,000 children in Canada[6] and elsewhere.[5] Clinical manifestations of JIA are mainly related to joint inflammation and include joint effusion, joint-line tenderness and warmth, restricted range of movement, and limitation of movement secondary to pain.[3] In addition, inadequately controlled disease may lead to abnormalities of growth such as short stature, localized bone overgrowth or premature fusion, as well as alteration of limb length.[3] Non-rheumatologic complications include asymptomatic uveitis, which can lead to glaucoma, cataracts, and loss of vision. Due to the high number of joints involved, patients with JIA tend to have a low spontaneous remission rate and a high rate of functional impairment, according to the clinical expert consulted for this review.

Polyarticular JIA is a subtype of JIA recognized by the International League of Associations for Rheumatology (ILAR). It comprises up to 30% of patients with JIA;[6,8,9] however, any form of JIA may follow a polyarticular course, including oligoarthritis, enthesitis-related arthritis, psoriatic arthritis, and systemic arthritis. By definition, polyarticular JIA (pJIA) involves five or more joints.[3,6,8,9] A further division is possible depending on the presence or absence of rheumatoid factors (RF).[3] The RF-negative form is by far the most frequent[6,9] and features a variable disease onset and course.[3] Patients with RF-positive pJIA tend to have a more severe form of the disease,[9] which will usually share several clinical and immunogenetic characteristics with adult rheumatoid arthritis (RA).[3]

1.2 Standards of Therapy

Therapy for pJIA targets the underlying inflammation in order to prevent the complications associated with the condition.[8] Nonsteroidal anti-inflammatory drugs (NSAIDs) are traditionally used as a first-line treatment option.[5,6,8] NSAIDs usually relieve joint pain and stiffness;[6,8] however, they do not delay or prevent joint damage and are unlikely to provide sufficient symptomatic control in the presence of polyarticular disease.[6,8] In addition, considering AEs such as gastrointestinal complications and cardiovascular events known to occur in adult patients,[3,6,8] they are not recommended by the 2011 American College of Rheumatology (ACR) Guidelines as a long-term treatment option.[5] Therefore, the vast majority of patients with pJIA will receive a disease-modifying antirheumatic drug (DMARD).[5,8] Despite some toxicity concerns, the use of DMARDs early in the course of the disease may prevent irreversible damage and lessen the burden of disease.[3,8] Of the various DMARDs, methotrexate is the most widely used and is established as a standard and effective therapy, although it does not have Health Canada's approval for use in JIA.[3,5,6,8] Although relatively well-tolerated in children,[3] potential AEs of importance include liver and pulmonary toxicities, hematologic abnormalities, and malignancies;[3,8] however, according to the clinical expert, these appear to be rarely seen in clinical practice.

The 2011 ACR Guidelines[5] and most other treatment reviews identified[3,6] recommend therapy with a biologic agent in patients with active disease despite the use of a DMARD such as methotrexate. Biologic agents for the treatment of pJIA include the TNF-α inhibitors etanercept and adalimumab (and infliximab, although it does not have a Health Canada indication for JIA), as well as abatacept, a T-cell targeted therapy. While these treatments have been shown to reduce the incidence of disease flares and increase ACR response rates, their drawbacks include the limited availability of long-term safety data in children as well as concerns regarding potential serious toxicities such as an increased risk of serious infection, autoimmune disorders, and pediatric malignancies.[10] Certain biologics (adalimumab, tocilizumab) may be used in combination with methotrexate; this may prevent the development of antibodies against the biologic.[3,5,8]

1.3 Drug

Tocilizumab (Actemra) is a recombinant human interleukin-6 (IL-6) immunoglobulin monoclonal antibody that competes for both membrane-bound and soluble forms of IL-6 receptors, decreasing signal transduction through gp130. IL-6 plays a significant role in the pathogenesis of pJIA through its involvement in inflammatory processes. For pJIA, tocilizumab is administered every four weeks through intravenous (IV) infusion at a recommended dose of 10 mg/kg for patients < 30 kg in weight and 8 mg/kg for patients ≥ 30 kg in weight. Tocilizumab should be given in combination with methotrexate, but may be given as monotherapy in cases of intolerance to methotrexate or where treatment with methotrexate is not appropriate. Tocilizumab is available as a 20 mg/mL concentrate solution for infusion. Tocilizumab is also indicated for systemic JIA and in adult patients for the treatment of RA.

TABLE 2: KEY CHARACTERISTICS OF PHARMACOLOGICAL TREATMENTS FOR POLYARTICULAR JIA

	Methotrexate	Biologics		
		TNFα-inhibitors (Etanercept and Adalimumab)	Abatacept	Tocilizumab
Mechanism of action	Immunomodulator and inhibitor of purine synthesis	**Etanercept**: TNF-α inhibitor **Adalimumab:** TNF-α inhibitor	**Abatacept**: T-cell costimulatory pathway inhibitor	**Tocilizumab**: IL-6 receptor inhibitor
Relevant Health Canada indication	Use as a DMARD in severe disabling RA (adult population; safety / effectiveness in pediatric patients not established)	**Etanercept**: Moderately to severely active pJIA in patients 4 to 17 years old who have responded inadequately to ≥ 1 DMARDs **Adalimumab**: With MTX or as monotherapy if MTX is not tolerated, moderately to severely active pJIA in patients 4 to 17 years old who have responded inadequately to ≥ 1 DMARDs	Moderately or severely active pJIA in pediatric patients (≥ 6 years) who have responded inadequately to one or more DMARDs	Active pJIA in patients 2 years of age and older who have responded inadequately to previous therapy with DMARDs and systemic corticosteroids
Route of administration	Oral, SC	**Etanercept**: SC **Adalimumab**: SC	IV	IV
Recommended dose	15 mg/m^2 or 0.5 mg/kg once a week	**Etanercept**: 0.4 mg/kg twice weekly (maximum 25 mg/dose) **Adalimumab**: 24 mg/m^2 every other week (maximum 40 mg/dose)	**< 75 kg**: 10 mg/kg; **≥ 75 kg**: Adult dose (maximum 1,000 mg) on week 0, 2, 4, then every 4 weeks	**< 30 kg**: 10 mg/kg once every 4 weeks **≥ 30 kg**: 8 mg/kg once every 4 weeks, alone or in combination with MTX
Serious adverse events / main safety issues	• Liver / hematologic / gastrointestinal toxicity • Infections	• Serious infections (e.g., opportunistic infections, tuberculosis) • Autoimmune disorders (e.g., demyelinization, systemic lupus erythematosus, vasculitic rashes, uveitis)		

DMARD = disease-modifying antirheumatic drug; IV = intravenous; MTX = methotrexate; pJIA = polyarticular juvenile idiopathic arthritis; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumour necrosis factor.Source: Gowdie and Tse;[8] Chédeville;[6] Lehman;[3] Humira (adalimumab) product monograph (2012);[10] Methotrexate product monograph (2011);[11] Enbrel (etanercept) product monograph (2012);[12] Remicade (infliximab) product monograph (2013);[13] Orencia (abatacept) product monograph (2012).[14]

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2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of IV tocilizumab in the treatment of active pJIA.

2.2 Methods

Studies were selected for inclusion in the systematic review based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients with active pJIA Subgroups of interest: • Concomitant MTX use (Yes/No) • Concomitant steroid use (Yes/No) • Prior biologics (Yes/No) • Baseline CRP level • RF status (+/–) • Baseline weight
Intervention	IV tocilizumab[a] alone or in combination with DMARDs
Comparators[b]	• Biologic DMARDs (adalimumab, etanercept, abatacept) • Non-biologic DMARD (methotrexate) • Placebo
Outcomes	**Key efficacy outcomes** • ACR Pedi 30, 50, 70, 90 and 100 responses • Flare rate • Time to flare • Other outcomes of disease activity (e.g., number of joints affected, physician global assessment, patient global assessment) • HRQoL using a validated scaled (e.g., SF-36) • Functional and disability outcomes using a validated scale (e.g., CHAQ-DI index) **Other efficacy outcomes** • Pain reduction measured on a validated scale • Patient satisfaction **Harms outcomes** • AEs, SAEs, WDAEs, mortality • Notable harms/harms of special interest: severe infections, neutropenia, liver function, pediatric malignancies
Study Design	Published and unpublished RCTs

ACR Pedi = American College of Rheumatology Pediatric response measures; AE = adverse event; CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; HRQoL = health-related quality of life; IV = intravenous; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; pJIA = juvenile idiopathic arthritis; SAE = serious adverse event; RCT = randomized controlled trial; RF = rheumatoid factor; SF-36 = short form (36) health survey; WDAE = withdrawal due to adverse event.
[a] Health Canada-approved doses.
[b] Dosing and formulation available in Canada; used with or without analgesics (NSAIDs, COX2 inhibitors) and corticosteroids.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Actemra (tocilizumab) and juvenile idiopathic arthritis.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on September 5, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on February 19, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and by contacting appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4.

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in Section 3.2. There were no excluded studies.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

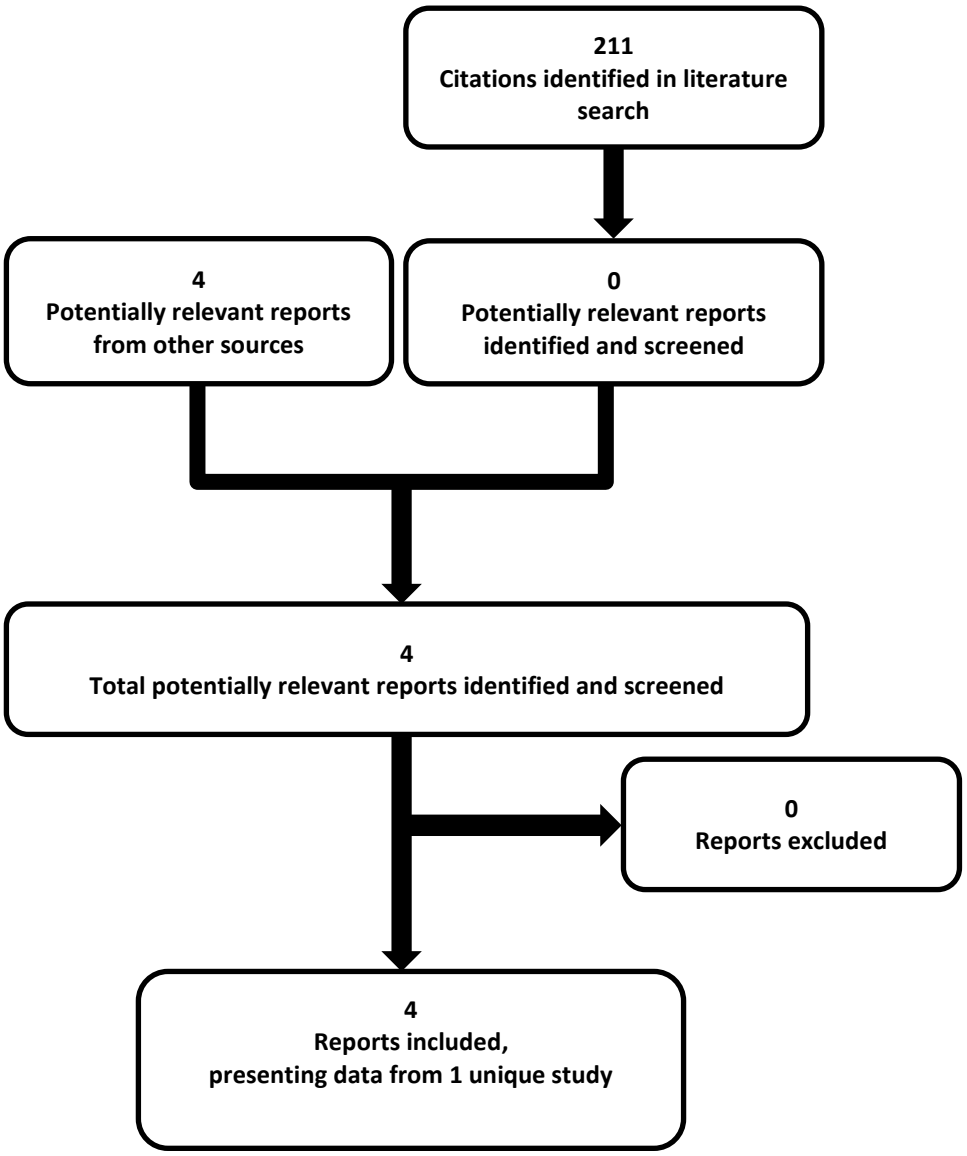


TABLE 4: DETAILS OF INCLUDED STUDY

		CHERISH
DESIGNS & POPULATIONS	**Study design**	DB PL-controlled RCT
	Locations	Multicentre: 15 countries, 58 study centres (including 7 centres in the US and 4 centres in Canada)
	Randomized (N)	166
	Inclusion criteria	Patients 2 to 17 years meeting ILAR criteria for pJIA (RF+ pJIA, RF– pJIA, or extended oligoarticular JIA) for at least 6 months who have had an inadequate response or intolerance to MTX: • ≥ 5 joints with active arthritis at screening and baseline • ≥ 3 joints with limitation of movement • had not received MTX for at least 4 weeks prior to and including the week of the baseline visit, or had taken at least 12 weeks of MTX on a stable dose between 10 and 20 mg/m^2 for at least 8 weeks prior to and including the week of the baseline visit • had not received oral corticosteroids at the baseline visit, or had taken oral corticosteroids at a stable dose of less than 10 mg/day for at least 4 weeks prior to and including the week of the baseline visit • had not received NSAIDs at the baseline visit, or had taken NSAIDs at a stable dose for at least 2 weeks prior to and including the week of the baseline visit • had not received prior biologics, or had discontinued previous biologics for a minimum of the following specified number of weeks prior to and including baseline: anakinra (1), etanercept (2), rilonacept (5), infliximab or adalimumab (8), abatacept (12), canakinumab (20)
	Exclusion criteria	[redacted] • [redacted] • Treatment with DMARDs (other than MTX), immunosuppressants (for example, azathioprine or cyclosporine), immunoglobulin, or parenteral/intra-articular corticosteroids within 4 weeks
DRUGS	**Intervention**	**O/L lead-in phase** Tocilizumab, at the following specified doses by IV every 4 weeks for 16 weeks (4 doses) • patients < 30 kg were randomized 1:1 to receive 8 mg/kg or 10 mg/kg • patients ≥ 30 kg received 8 mg/kg Patients who achieved a JIA ACR 30 response at week 16 entered the DB phase. **DB withdrawal phase** Patients with a JIA ACR 30 response in the O/L lead-in phase were randomized 1:1 to continue tocilizumab at the same dose regimen from the O/L lead-in phase or to receive placebo for 24 weeks. Patients who completed the DB phase or entered the escape phase (experienced a JIA ACR 30 flare during the DB phase) were eligible for the O/L extension phase.

		CHERISH
		O/L extension phase Tocilizumab, continued at the same dose regimen from the O/L lead-in phase for 64 weeks. [redacted] **Concomitant medication** Randomization in the DB phase was stratified by concomitant MTX and oral corticosteroid use.
	Comparator(s)	**DB withdrawal phase** DB PL administered by IV every 4 weeks for 24 weeks
DURATION	**Phase:**	
	Run-in	16 weeks, O/L lead-in phase
	DB	24 weeks, DB withdrawal phase
	Follow-up	64 weeks, O/L extension phase
OUTCOMES	**Primary end point**	Proportion of patients who developed a JIA ACR 30 flare relative to week 16 in the DB withdrawal phase (week 16 to week 40), defined as: • Worsening of ≥ 30% in ≥ 3 JIA ACR core criteria (list of core criteria follows) • Improvement of ≥ 30% in no more than one JIA ACR core criterion JIA ACR core criteria: Parent/patient global assessment of overall well-being; physician global assessment of disease activity; number of joints with active arthritis; number of joints with limitation of movement; physical function as measured by the CHAQ-DI; laboratory sign of inflammation as measured by the ESR

	Other end points	• Proportion of patients achieving JIA ACR 30, 50, 70, and 90 responses relative to baseline (week 0) at week 40
		• Proportion of patients with inactive disease at week 40
		• Time to JIA ACR 30 flare
		• Change from baseline at week 40 in
		  ○ number of joints with active arthritis
		  ○ number of joints with limitation of movement
		  ○ parent/patient's global assessment of overall well-being VAS
		  ○ physician's global assessment of disease activity VAS
		  ○ pain VAS
		  ○ CHAQ-DI score
		  ○ ESR
		  ○ JADAS-27

NOTES	**Publication**	[redacted]

ACR = American College of Rheumatology; CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; DB = double-blind; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; ILAR = International League of Associations for Rheumatology; IV = intravenous; JADAS-27 = juvenile arthritis disease activity score 27; JIA = juvenile idiopathic arthritis; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; O/L = open-label; pJIA = polyarticular juvenile idiopathic arthritis; PL = placebo; RCT = randomized controlled trial; RF = rheumatoid factor; TB = tuberculosis; VAS = visual analogue scale.
Source: CDR submission binder;[15] [redacted]; [2] Clinical Study Report (CSR); [1] European Public Assessment Report.[16]

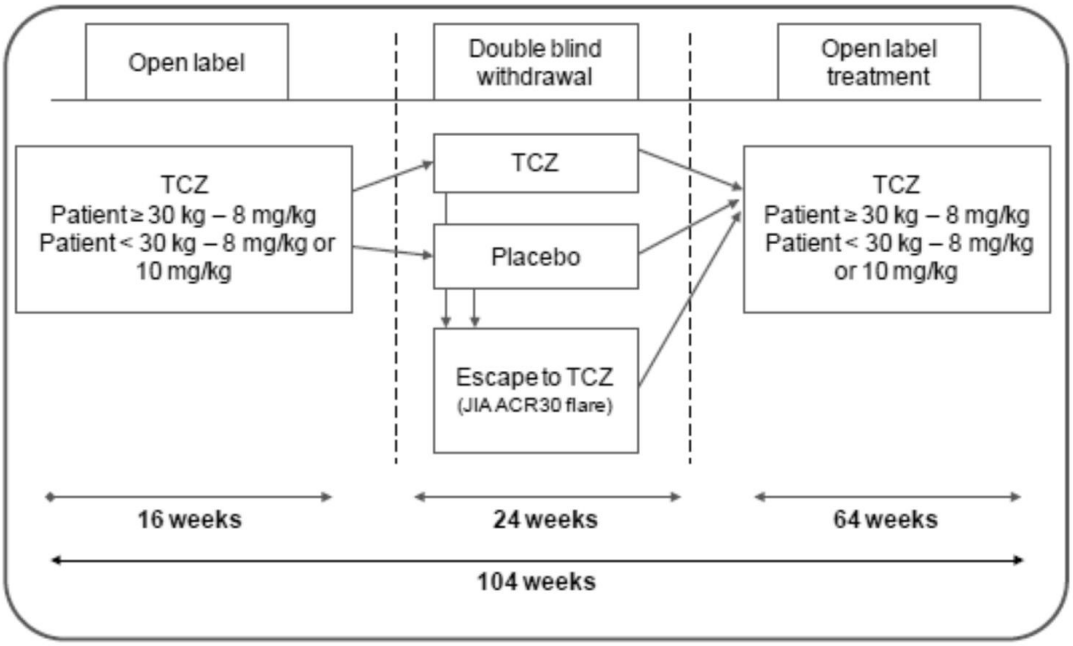
3.2 Included Studies

3.2.1 Description of Studies

One randomized, placebo-controlled, DB, withdrawal study met the inclusion criteria for this systematic review. CHERISH included patients with active pJIA who had previously had an inadequate response or intolerance to methotrexate. CHERISH (n = 166) evaluated the efficacy and safety of tocilizumab as monotherapy or in combination with methotrexate. Tocilizumab was administered by IV at a dosage of either 8 mg/kg or 10 mg/kg for patients < 30 kg in weight, and at 8 mg/kg for patients ≥ 30 kg in weight.

All patients received 16 weeks of tocilizumab treatment in an open-label (O/L) lead-in phase (Figure 2). Patients achieving a JIA ACR 30 response at 16 weeks entered the 24-week DB phase and were randomized in a 1:1 ratio with stratification by concomitant methotrexate and oral glucocorticoid use to tocilizumab or placebo. Patients who completed the DB phase, or who escaped due to a disease flare during the DB phase, were eligible to enter a 64-week O/L extension phase. This design was chosen to minimize the time that non-responders spent in the trial and to minimize the time spent by responders on placebo.

FIGURE 2: CHERISH STUDY DESIGN



ACR = American College of Rheumatology; JIA = juvenile idiopathic arthritis; TCZ = tocilizumab.
Source: CDR submission binder.[15]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients aged 2 to 17 years who had had an inadequate response or intolerance to methotrexate were eligible for inclusion in the CHERISH study. Patients had to be diagnosed with one of the following subtypes of active pJIA with a minimum disease duration of six months: RF-positive or RF-negative pJIA, or extended oligoarticular JIA. Active disease was defined as having a minimum of five joints with active arthritis (swollen, or if no swelling then limitation of movement plus pain on motion and/or tenderness with palpation), with at least three of the active joints having limitation of movement.

Patients were excluded if they had an ongoing or recent major infection including tuberculosis, positive hepatitis B or hepatitis C status, a history of malignancy or lymphoma, recent joint surgery or a history of infected joint prosthesis, and/or active uveitis. Patients with ongoing or recent treatment with DMARDs (other than methotrexate), immunosuppressants, immunoglobulin, or parenteral/intra-articular corticosteroids were also excluded.

b) Baseline Characteristics

Baseline characteristics are presented for the O/L lead-in phase (week 0) and for the DB phase (week 16) in Table 5 and Table 6. The patients enrolled in the CHERISH study had a mean age of 11 years, and 80% of the patients were older than seven years of age. This older age distribution coincided with a greater number of patients falling within the ≥ 30 kg weight category.

The majority of participants were female (77%) and the mean disease duration was approximately four years. Approximately 32% of patients had received a previous biologic treatment for pJIA (Table 5). Baseline characteristics for patients randomized in the DB phase were generally balanced between-treatment groups (Table 6 and Table 7). There were some differences between-treatment groups in the DB phase in the disease severity measures (i.e., patient/parent global assessment and C-reactive protein [CRP] levels), but the clinical expert consulted for this review did not consider these differences to be a concern (Table 6 and Table 7).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS — O/L LEAD-IN PHASE (ITT POPULATION)

Characteristics	CHERISH			
	TCZ 10 mg/kg (< 30 kg) (N = 35)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	All TCZ (N = 188)
Age, years (SD)	6.9 (3.0)	7.6 (2.7)	13.1 (2.8)	11.0 (4.0)
≤ 7 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
8–12 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 13 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Female sex, n (%)	30 (85.7)	24 (70.6)	90 (75.6)	144 (76.6)
Baseline weight, kg (SD)	20.7 (5.7)	22.4 (5.3)	50.0 (12.6)	39.6 (17.3)
Disease duration, years (SD)	3.4 (2.4)	3.5 (2.6)	4.7 (4.2)	4.2 (3.7)
Disease Severity				
Number of joints with active arthritis, mean (SD)	23.9 (18.3)	21.2 (13.6)	18.9 (13.0)	20.3 (14.3)
Number of joints with LOM, mean (SD)	23.1 (19.2)	17.3 (13.3)	16.0 (12.7)	17.6 (14.4)
Patient/Parent Global Assessment VAS, mean (SD)	51.5 (26.9)	59.1 (26.2)	51.6 (24.1)	52.9 (25.0)
Physician Global Assessment VAS, mean (SD)	64.7 (20.5)	64.7 (18.5)	59.4 (21.3)	61.4 (20.7)
CHAQ-DI score, mean (SD)	1.7 (0.71)	1.8 (0.68)	1.2 (0.69)	1.4 (0.74)

Characteristics	CHERISH			
	TCZ 10 mg/kg (< 30 kg) (N = 35)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	All TCZ (N = 188)
ESR, mm/hour (SD)	35.1 (24.1)	36.6 (23.0)	34.2 (26.7)	34.8 (25.5)
CRP, mg/L (SD)	[redacted]	[redacted]	[redacted]	[redacted]
RF Status, n (%)				
Positive	[redacted]	[redacted]	[redacted]	54 (28.7)
Negative	[redacted]	[redacted]	[redacted]	126 (67.0)
Missing	[redacted]	[redacted]	[redacted]	8 (4.3)
Therapy Prior to Enrolment				
No biologics, n (%)	27 (77.1)	28 (82.4)	72 (60.5)	127 (67.6)
Biologics, n (%)	8 (22.9)	6 (17.6)	47 (39.5)	61 (32.4)
1 biologic	[redacted]	[redacted]	[redacted]	[redacted]
2 biologics	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 biologics	[redacted]	[redacted]	[redacted]	[redacted]
Number of biologics, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of DMARDs, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]

CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; ITT = intention to treat; LOM = limitation of movement; MTX = methotrexate; O/L = open-label; RF = rheumatoid factor; SD = standard deviation; TCZ = tocilizumab; VAS = visual analogue scale (range 0 to 100).
Source: Clinical Study Report (CSR) p. 90;[1] [redacted].[2]

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS — DB PHASE (ITT POPULATION, INDIVIDUAL WEIGHT GROUPS)

Characteristics	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
Age, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≤ 7 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8–12 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 13 years, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female sex, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline weight, kg (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease duration, years (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Severity						
Number of joints with active arthritis, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Characteristics	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
Number of joints with LOM, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient/Parent Global Assessment VAS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician Global Assessment VAS, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHAQ-DI score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ESR, mm/hour (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP, mg/L (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF Status, n (%)						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Therapy Before Enrolment						
No biologics, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Biologics, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 biologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 biologics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 3 biologics	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of biologics, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of DMARDs, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CHQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CRP = C-reactive protein; DB = double-blind; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; ITT = intention to treat; LOM = limitation of movement; MTX = methotrexate; RF = rheumatoid factor; SD = standard deviation; TCZ = tocilizumab; VAS = visual analogue scale (range 0 to 100).Source: Clinical Study Report (CSR) p. 345 and 355.[1]

TABLE 7: SUMMARY OF BASELINE CHARACTERISTICS — DB PHASE (ITT POPULATION, COMBINED WEIGHT GROUPS)

Characteristics	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
Age, years (SD)	[redacted]			[redacted]		
≤ 7 years, n (%)	[redacted]			[redacted]		
8–12 years, n (%)	[redacted]			[redacted]		
≥ 13 years, n (%)	[redacted]			[redacted]		
Female sex, n (%)	[redacted]			[redacted]		
Baseline weight, kg (SD)	[redacted]			[redacted]		
Disease duration, years (SD)	[redacted]			[redacted]		
Disease Severity						
Number of joints with active arthritis, mean (SD)	[redacted]			[redacted]		
Number of joints with LOM, mean (SD)	[redacted]			[redacted]		
Patient/Parent Global Assessment VAS, mean (SD)	[redacted]			[redacted]		
Physician Global Assessment VAS, mean (SD)	[redacted]			[redacted]		
CHAQ-DI score, mean (SD)	[redacted]			[redacted]		
ESR, mm/hour (SD)	[redacted]			[redacted]		
CRP, mg/L (SD)	[redacted]			[redacted]		
RF Status, n (%)						
Positive	[redacted]			[redacted]		
Negative	[redacted]			[redacted]		
Missing	[redacted]			[redacted]		
Therapy Before Enrolment						
No biologics, n (%)	[redacted]			[redacted]		
Biologics, n (%)	[redacted]			[redacted]		
1 biologic	[redacted]			[redacted]		
2 biologics	[redacted]			[redacted]		
≥ 3 biologics	[redacted]			[redacted]		
Number of biologics, mean (SD)	[redacted]			[redacted]		

Characteristics	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
Number of DMARDs, mean (SD)		[redacted]			[redacted]	

CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CRP = C-reactive protein; DB = double-blind; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; ITT = intention to treat; LOM = limitation of movement; MTX = methotrexate; RF = rheumatoid factor; SD = standard deviation; TCZ = tocilizumab; VAS = visual analogue scale (range 0 to 100).
Source: Clinical Study Report (CSR) p. 345 and 355.[1]

3.2.3 Interventions

a) O/L lead-in Phase (Week 0 to Week 16)

Tocilizumab was administered at the following specified doses intravenously every four weeks for 16 weeks (4 doses):

- patients < 30 kg were randomized 1:1 to receive either 8 mg/kg or 10 mg/kg
- patients ≥ 30 kg received 8 mg/kg

Patients who achieved a JIA ACR 30 response moved to the DB withdrawal phase.

b) DB Withdrawal Phase (Week 16 to Week 40)

Patients were randomized 1:1 to receive either tocilizumab at the same dose regimen from the O/L lead-in phase or placebo, for 24 weeks. Patients in the tocilizumab and placebo groups who completed the DB phase or entered the escape phase (i.e., experienced a JIA ACR 30 flare during the DB phase) were eligible for the O/L extension phase at week 40. Patients who flared and entered the escape phase received O/L tocilizumab, but did not start the O/L extension phase until week 40.

c) O/L Extension Phase (Week 40 to Week 104)

Tocilizumab was continued or resumed at the same dose regimen from the O/L lead-in phase for 64 weeks. Because children could have grown during the course of the trial, dosing adjustments were made: [redacted]

d) Concomitant Medication

Stable doses of NSAIDs, low-dose glucocorticoids (≤ 10 mg/day), and methotrexate (10 to 20 mg/m^2 body surface area per week) were permitted during the study provided that the study patients had been taking these medications at stable doses starting weeks before and including the week of the baseline visit (Table 4). Normal-release paracetamol and other analgesics for pain were also permitted, but were not to be taken within six hours prior to a clinical efficacy assessment. Treatment with other biologic therapies was not permitted during the study.

3.2.4 Outcomes

The primary efficacy outcome in the CHERISH study was the proportion of patients who developed a JIA ACR 30 flare relative to week 16 in the DB phase (week 16 to week 40). (Note: the manufacturer referred to the proportion of patients who developed a JIA ACR flare as the *JIA ACR flare rate,* which will be used interchangeably throughout this review.) A JIA ACR 30 flare was defined as a worsening of ≥ 30% in at least three of the six JIA ACR core criteria in addition to a ≥ 30% improvement in no more than one JIA ACR core criterion. The six JIA ACR core criteria are as follows:

- physician's global assessment of disease activity on a 0 mm to 100 mm visual analogue scale (VAS; 0 — very good, 100 — very bad)
- patient or parent's global assessment of overall well-being on a 0–100 mm VAS (0 — very well, 100 — very poorly)
- number of joints with active arthritis (defined as swelling or, in the absence of swelling, limitation of movement accompanied by pain)
- number of joints with limitation of movement
- physical function, using the Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI; 0 — best, 3 — worst)
- laboratory assessment of inflammation (erythrocyte sedimentation rate).

[redacted]

Secondary outcomes of interest included the following:

- proportion of patients achieving JIA ACR 30/50/70/90 responses in comparison to baseline (week 0) at week 40 (i.e., improvement of 30%/50%/70%/90% in at least three of the six JIA ACR core criteria)
- time to JIA ACR 30 flare in the DB phase
- pain, change from baseline (week 0) at week 40, based on a 0 to 100 mm VAS (0 — no pain, 100 — pain as bad as it could be)
- proportion of patients with a minimally clinically important improvement (MCII) in CHAQ-DI score from baseline (week 0) at week 40. The MCII was defined by the manufacturer as 0.13.

Safety outcomes included AEs, SAEs, withdrawals due to AEs, assessments of physical examination results, vital signs, and laboratory data. Of note, comparisons of AEs during the DB phase did not include AEs experienced after patients had escaped.

3.2.5 Statistical Analysis

- A JIA ACR 30 response rate of 65% was anticipated for the O/L lead-in phase for the purpose of sample size calculations. Assuming JIA ACR 30 flare rates of 35% in the tocilizumab group and 65% in the placebo group, 60 patients needed to be randomized to each treatment group in the DB phase to achieve at least 80% power to detect a significant difference in the JIA ACR 30 flare rates between groups, using a two-sided significance test ($\alpha = 0.05$).
- All efficacy analyses were performed using the intention-to-treat (ITT) population relevant to the study part of reporting (O/L lead-in phase [ITT-1] or DB phase [ITT-2]).
- All statistical hypotheses for the primary and secondary end points were tested at the 5% significance level ($\alpha = 0.05$) using 2-sided tests.

- The primary efficacy end point used the Cochran-Mantel-Haenszel (CMH) test under consideration of the stratification factors (background use of methotrexate and oral glucocorticoids). Statistical tests for both the per-protocol population and ITT-2 populations were conducted for the primary efficacy end point.
- An analysis of variance (ANOVA), adjusted for baseline difference between groups and stratification variables (methotrexate and oral glucocorticoids), was used to analyze continuous, variable end points.

[redacted]

- In the DB phase, patients who experienced a JIA ACR 30 flare and escaped to O/L treatment were classified as JIA ACR non-responders. The efficacy data collected on these patients while on O/L treatment were not considered in the analysis.
- Missing data for binary end points (JIA ACR flare, JIA ACR 30/50/70/90) were considered as a worst-case scenario of a flared/non-responder. For continuous end points (JIA core components, pain VAS), a LOCF analysis was conducted in order to take into account the data of patients who escaped.
- The secondary end points were tested in a hierarchical, fixed-sequence approach, with each end point in the sequence needing to be significant ($P < 0.05$) in order for the subsequent end point in the chain to be considered significant (Table 8).

[redacted]

TABLE 8: HIERARCHICAL FIXED SEQUENCE OF EFFICACY END POINTS

Order Number	End Point
1	Proportion of patients who develop a JIA ACR 30 flare relative to week 16 in the DB phase
2	Proportion of patients achieving a JIA ACR 30 response relative to baseline at week 40
3	Proportion of patients achieving a JIA ACR 50 response relative to baseline at week 40
4	Proportion of patients achieving a JIA ACR 70 response relative to baseline at week 40
5	Change from baseline in the number of joints with active arthritis at week 40
6	Change from baseline in physician's global assessment of disease activity VAS at week 40
7	Change from baseline in pain VAS at week 40
8	Change from baseline in the number of joints with limitation of movement at week 40
9	Change from baseline in parent/patient's global assessment of overall well-being VAS at week 40
10	Change from baseline in ESR at week 40
11	Change from baseline in CHAQ-DI score at week 40
12	Proportion of patients achieving a JIA ACR 90 response relative to baseline at week 40
13	Proportion of patients with inactive disease at week 40

ACR = American College of Rheumatology; CHAQ-DI = Childhood Health Assessment Questionnaire; DB = double-blind; ESR = erythrocyte sedimentation rate; JIA = juvenile idiopathic arthritis; VAS = visual analogue scale.

a) Analysis Populations

In the CHERISH study, the following data sets were defined:

Intention-to-treat population for the O/L lead-in phase (ITT-1)
This included all patients who were in the O/L lead-in phase and who subsequently received at least one dose of tocilizumab. Analyses were performed with patients assigned to the tocilizumab dose group to which they were initially randomized at baseline (week 0).

Intention-to-treat population for the DB phase (ITT-2)
This included the subset of patients from the ITT O/L lead-in phase who were subsequently randomized 1:1 at week 16 to either placebo or tocilizumab and who received at least one infusion of study medication. Analyses were performed with patients assigned to the study treatment group to which they were initially randomized at week 16.

Per-protocol population
This included all patients in the ITT-2 population who were without major violation of the protocol inclusion/exclusion criteria or protocol procedures in the O/L lead-in phase and the DB phase.

Safety data set
This included all patients who were in the O/L lead-in phase and who received at least one dose of tocilizumab. Analyses were performed with patients assigned to the tocilizumab treatment dose group which they first received at baseline (week 0).

3.3 Patient Disposition

The disposition of patients in the CHERISH study is presented in Table 9. A total of 188 patients were enrolled in the O/L lead-in phase of the CHERISH study. Patients were randomized to receive tocilizumab at either 8 mg/kg or 10 mg/kg if they were < 30 kg in weight, or at 8 mg/kg if they were ≥ 30 kg in weight. A total of 166 (88%) patients who completed the O/L lead-in phase and who achieved a JIA ACR 30 response were randomized 1:1 to either continue on their assigned dose of tocilizumab or switch to placebo in the DB phase. For the 22 patients (12%) who discontinued treatment during the O/L lead-in phase, the most common reason was a lack of JIA ACR 30 response.

In describing patient disposition in the DB phase, the manufacturer did not report patients who escaped (to O/L tocilizumab) due to disease flare as having withdrawn from the DB phase. [redacted]

TABLE 9: PATIENT DISPOSITION

Criteria	CHERISH			
Screened, N	218			
Ineligible, n (%)	30 (13.8)			
O/L Lead-In Phase (n, %)	**TCZ 10 mg/kg (< 30 kg)**	**TCZ 8 mg/kg (< 30 kg)**	**TCZ 8 mg/kg (≥ 30 kg)**	**All TCZ**
Included in lead-in phase	35 (100)	34 (100)	119 (100)	188 (100)
Completed lead-in phase	31 (88.6)	24 (70.6)	111 (93.3)	166 (88.3)
Discontinued lead-in phase	4 (11.4)	10 (29.4)	8 (6.7)	22 (11.7)
• Lack of JIA ACR 30 response	4 (11.4)	6 (17.6)	5 (4.2)	15 (8.0)
• Adverse event	0	1 (2.9)	2 (1.7)	3 (1.6)
• Withdrew consent	0	2 (5.9)	1 (0.8)	3 (1.6)
• Failure to return	0	1 (2.9)	0	1 (0.5)
ITT	35 (100)	34 (100)	119 (100)	188 (100)
Safety	35 (100)	34 (100)	119 (100)	188 (100)

DB Phase	Tocilizumab			Placebo		
	TCZ 10 mg/kg (< 30 kg)	**TCZ 8 mg/kg (< 30 kg)**	**TCZ 8 mg/kg (≥ 30 kg)**	**TCZ 10 mg/kg (< 30 kg)**	**TCZ 8 mg/kg (< 30 kg)**	**TCZ 8 mg/kg (≥ 30 kg)**
Randomized						
N	82			84		
N (%)	16 (100)	11 (100)	55 (100)	15 (100)	13 (100)	56 (100)
Completed DB Phase						
n (%)	[redacted]			[redacted]		
	15 (93.8)	11 (100)	[redacted]	15 (100)	13 (100)	[redacted]
Discontinued DB Phase						
n (%)	[redacted]			[redacted]		
	1 (3.2)	0	[redacted]	0	0	[redacted]
• Adverse event, n (%)	1 (3.2)	0	0	0	0	[redacted]
• Insufficient therapeutic response, n (%)	0	0	1 (1.8)	0	0	1 (1.8)
• Withdrew consent, n (%)	0	0	1 (1.8)	0	0	0
ITT[a]						
n (%)	[redacted]			[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Criteria	CHERISH					
DB Phase	Tocilizumab			Placebo		
	TCZ 10 mg/kg (< 30 kg)	TCZ 8 mg/kg (< 30 kg)	TCZ 8 mg/kg (≥ 30 kg)	TCZ 10 mg/kg (< 30 kg)	TCZ 8 mg/kg (< 30 kg)	TCZ 8 mg/kg (≥ 30 kg)
PP						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Safety						
n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; DB = double-blind; ITT = intention-to-treat; JIA = juvenile idiopathic arthritis; O/L = open-label; PP = per-protocol; TCZ = tocilizumab.
Source: Clinical Study Report (CSR) p. 85–86;[1] [redacted].[2]
[a] Three patients did not receive IV infusion and were excluded from the ITT analysis.

3.4 Exposure to Study Treatments

The exposure to study treatment during the O/L lead-in phase and the DB phase is presented in Table 10. The majority of patients (94%) received all four tocilizumab infusions during the O/L lead-in phase. During the DB phase, a greater proportion of patients received all six tocilizumab infusions (70%) compared with the proportion of patients who received all six infusions of placebo (53%).

[redacted]

TABLE 10: EXTENT OF EXPOSURE IN THE CHERISH STUDY

Exposure to Tocilizumab in the O/L Lead-In Phase	CHERISH			
	TCZ 10 mg/kg (< 30 kg) (N = 35)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	All TCZ (N = 188)
Mean weeks of exposure (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Infusions, n (%)				
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	177 (94)
Concomitant Medications				
MTX, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean MTX weekly dose, mg/m^2 (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median MTX weekly dose, mg/m^2 (range)	[redacted]	[redacted]	[redacted]	[redacted]
Oral corticosteroids, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean corticosteroid dose, mg/kg/day (SD)	[redacted]	[redacted]	[redacted]	[redacted]
At least 1 pain medication treatment, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Exposure to Tocilizumab or Placebo in the DB Phase	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
Mean weeks of exposure (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Infusions, N (%)						
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Exposure to Tocilizumab or Placebo in the DB Phase	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
6	57 (70)			43 (53)		
	[redacted]					
Concomitant Medications						
MTX, N (%)	[redacted]					
Mean MTX weekly dose, mg/m^2 (SD)	[redacted]					
Median MTX weekly dose, mg/m^2 (range)	[redacted]					
Oral corticosteroids, N (%)	[redacted]					
Mean corticosteroid dose, mg/kg/day (SD)	[redacted]					
At least one pain medication treatment, N (%)	[redacted]					

MTX = methotrexate; O/L = open-label; SD = standard deviation; TCZ = tocilizumab.
Source: Clinical Study Report (CSR) p. 319, 339, 350, 360, 393, 407, 1264, 1267, 1268, and 1270.[1]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Randomization and Concealment of Treatment Allocation

Patients who completed the O/L lead-in phase were randomized to the DB phase by an interactive voice response system, to facilitate concealment of allocation.

Blinding

The trial was described as DB in relation to patients/parents and investigators. A separate, blinded joint assessor performed all joint examinations in the O/L lead-in and DB phases. In addition, laboratory results, which may have resulted in unblinding such as those for CRP, were blinded to all study participants, the investigator, the sponsor, and site personnel until week 52 of the study.

Comparability of treatment groups

Randomization with stratification by methotrexate and corticosteroid use resulted in treatment groups with similar baseline characteristics. Measures of baseline CRP levels and patient/parent global assessment suggest that the disease may have been slightly more severe in the placebo group, although the clinical expert consulted for this review did not consider the differences to be clinically important. Patients were permitted to take pain medication during the study as long as it was not within six hours

prior to a clinical efficacy assessment. Although the proportion of patients taking pain medication was slightly higher in the placebo group compared with the tocilizumab group, this difference was small.

Statistical analysis

The sample sizes in the DB phase appear to be adequate based upon sample size calculations (greater than 60 participants in each group) for the primary end point. Hierarchical testing of secondary end points was planned to control for multiple testing. However, results for exploratory outcomes (time to JIA ACR 30 flare, proportion of patients with MCII in CHAQ-DI score at week 40) should be interpreted with caution, as statistical testing of these outcomes was outside of the planned hierarchical testing, and findings of statistical significance may be spurious.

Missing values during the DB phase were treated as disease flares or imputed as non-responders for both the placebo and tocilizumab groups, which could have potentially biased the results in favour of tocilizumab. This did not appear to be an issue, however, as there was one patient in each treatment group with missing data. LOCF analysis, which does not consider further worsening of an end point beyond a flare, was conducted for continuous data (JIA ACR core components, pain VAS) for patients who flared and escaped. Since more patients in the placebo group than in the tocilizumab group experienced a flare, the assumption of LOCF imputation that data was missing completely at random was violated, and caution must be used in interpreting the results of these end points.

Outcomes

The CHAQ-DI is a widely used and validated, disease-specific instrument for measuring functional status in children with JIA. One publication obtained by the CDR reviewers proposed a reduction of 0.13 (or –4.3%) in the CHAQ-DI as an MCII (APPENDIX 4: VALIDITY OF OUTCOME MEASURES).[17] However, this instrument appears to demonstrate ceiling effects and may be insensitive to clinically relevant, short-term changes in children with JIA.[18]

3.5.2 External Validity

a) Patient Selection

The severity of disease of these patients was quite high (~4 years disease duration and > 10 affected joints), and results would be generalizable to this population. Whether patients with less severe disease would benefit more or less from tocilizumab treatment is unknown.

Few patients less than seven years of age were enrolled in the study, and the overall results should be interpreted with caution in this age group of patients.

Patients who were < 30 kg in weight were randomized into two groups that were administered different doses of tocilizumab (8 mg/kg or 10 mg/kg). The Health Canada-recommended dosage for patients < 30 kg is 10 mg/kg.

Patients who did not achieve a JIA ACR 30 response in the O/L lead-in phase did not continue the trial, meaning that patients in the DB phase all had a known response to tocilizumab. Therefore, the response rates in the CHERISH study are likely higher than would be expected in a non-enriched or tocilizumab-naive population.

b) Study Design

The DB withdrawal phase was limited to 24 weeks; thus, there is a lack of evidence regarding the comparative long-term benefits and harms of tocilizumab.

c) Treatment Regimen

No randomized controlled trial (RCT) directly comparing tocilizumab with an appropriate active treatment for pJIA was identified. Thus, the efficacy and harms of tocilizumab in comparison with other available biologic DMARDs for the treatment of pJIA is uncertain.

d) Outcome Measures

The JIA ACR 30 is a level of response separating placebo from active treatment; it is derived as a meaningful outcome measure in clinical trials. JIA ACR 50, ACR 70 and ACR 90 responses have been suggested as more desirable levels of response in clinical practice.[19]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See APPENDIX 3: DETAILED OUTCOME DATA for detailed efficacy data. No data were reported on the outcomes of health-related quality of life or patient satisfaction. In addition, there was no subgroup analysis based on baseline CRP levels.

3.6.1 Efficacy — O/L Lead-In Phase

The proportion of patients achieving JIA ACR responses (30, 50, 70, and 90) were assessed during the O/L lead-in phase. At the end of the O/L phase (week 16), 89.4% of patients achieved a JIA ACR 30 response (Table 13 and Figure 3). The proportion of patients achieving ACR 50, ACR 70, and ACR 90 responses at the end of the O/L lead-in phase was 83.0%, 62.2%, and 26.1%, respectively.

The JIA ACR 30 response rate was slightly lower in the TCZ 8 mg/kg (< 30 kg) group (26/34, 76.5%) compared with the TCZ 10 mg/kg (< 30 kg) group (31/35, 88.6%).

3.6.2 Efficacy — DB Withdrawal Phase

a) JIA ACR 30 Flare Rate and Time to Flare

The primary efficacy outcome in the CHERISH study was the proportion of patients who experienced a disease flare during the DB phase (week 16 to week 40).

The proportion of patients experiencing a JIA ACR 30 flare was less in the tocilizumab group compared with the placebo group (25.6% versus 48.1%; adjusted RD = –0.21; 95% CI, –0.35 to –0.08; *P* = 0.0024) (Table 10). [redacted]

[redacted]

b) JIA ACR Responses

At the end of the DB phase (week 40), there was a statistically significant greater proportion of patients who achieved ACR 30, ACR 50, or ACR 70 responses in the tocilizumab group compared with the placebo group (Table 11). Although a numerically higher proportion of patients achieved ACR 90 responses with tocilizumab versus placebo, statistical significance testing for this end point was not calculated, as previous hierarchical chain assessments were non-significant.

c) Other Outcomes of Disease Severity

Results from the six JIA ACR core criteria used to assess ACR responses were reported separately (Table 15).

The reduction in the number of active joints was statistically significantly greater for the tocilizumab group compared with the placebo group (adjusted mean difference [MD] = –2.9; 95% CI [redacted]; *P* = 0.0435) and for the physician's global assessment of disease severity (VAS adjusted MD = –9.9; 95% CI [redacted]; *P* = 0.0031).

The reduction in the number of joints with limitation of movement was not statistically significantly different between-treatment groups (adjusted MD = 1.8; 95% CI [redacted]; *P* = 0.1229), which caused a break in the hierarchical sequence of secondary end points at week 40. Consequently, statistical differences between the tocilizumab and placebo treatment groups were not assessed for the patient/parent global assessment of overall well-being, ESR, and functional ability based on the CHAQ-DI score.

d) Functional and Disability Outcomes

[redacted]

e) Pain

[redacted]The change from baseline (week 0) in the pain VAS score at week 40 was assessed as a secondary descriptive end point. Patients in the tocilizumab group had a statistically significantly greater decrease in the pain VAS score compared with the placebo group (adjusted MD = –10.2; 95% CI [redacted]; *P* = 0.0076).

f) Subgroup Analyses

Of the subgroups of interest identified in the CDR review protocol, pre-planned subgroup analyses for JIA ACR 30 flare rate and JIA ACR 30/50/70/90 responses at week 40 were performed based on previous biologic use, concomitant methotrexate use, concomitant oral corticosteroid use, and baseline RF status. (Table 16, Table 17, Table 18, Table 19, Table 20).

Previous biologic use

The proportion of patients in the CHERISH study that had received previous biologic therapy was 32%. At week 40, the JIA ACR 30 flare rate was higher and the proportion of JIA ACR 30/50/70/90 responders in the tocilizumab and placebo groups was lower in patients that had previously been exposed to a biologic versus patients who had not previously been exposed. Flare rates and JIA ACR 30/50/70/90 results were more favourable in the tocilizumab group compared with the placebo group, regardless of whether patients had received a prior biologic or not. A test for interaction was not provided.

Concomitant methotrexate use

Approximately 80% of patients were taking concomitant methotrexate in the CHERISH study (Table 10). At week 40, the JIA ACR 30 flare rate was lower and the proportion of JIA ACR 30/50/70/90 responders

was higher in patients who were taking concomitant methotrexate compared with those who were not, in both the tocilizumab and placebo groups. Flare rates and JIA ACR 30/50/70/90 results were more favourable in the tocilizumab group compared with the placebo group, regardless of whether patients received concomitant methotrexate or not. A test of the interaction between-treatment assignment and concomitant methotrexate use was not statistically significant (*P* = 0.5073).

Concomitant oral corticosteroid use

The proportion of patients receiving background oral corticosteroids in the CHERISH study was 46%. Concomitant oral corticosteroid use appeared to have no differential effect on relative treatment response. A test of the interaction between-treatment assignment and concomitant oral corticosteroid use was not statistically significant (*P* = 0.3267).

Baseline rheumatoid factor status

The proportion of patients who were RF-positive was 29% and the proportion of patients who were RF-negative was 67% (the status of 4% was missing). Both JIA ACR flare rates and JIA ACR response rates were similar in RF-positive and RF-negative patients in both the tocilizumab and placebo treatment groups. A test for interaction was not provided.

TABLE 11: KEY EFFICACY OUTCOMES AT WEEK 40

	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
Patients With JIA ACR 30 Flare (Relative to Week 16)						
n (%)	3 (18.8)	2 (18.2)	16 (29.1)	8 (53.3)	5 (38.5)	26 (49.1)
	21 (25.6)			39 (48.1)		
Adjusted RD [95% CI][a]	–0.21 [–0.35 to –0.08]					
P value	0.0024					
JIA ACR 30 Responders[b]						
n (%)	61 (74.4)			44 (54.3)		
Adjusted RD [95% CI][a]	[redacted]					
P value	0.0084					
JIA ACR 50 Responders[b]						
n (%)	60 (73.2)			42 (51.9)		
Adjusted RD [95% CI][a]	[redacted]					
P value	0.0050					
JIA ACR 70 Responders[b]						
n (%)	53 (64.6)			34 (42.0)		
Adjusted RD [95% CI][a]	[redacted]					
P value	0.0032					
JIA ACR 90 Responders[b]						
n (%)	37 (45.1)			19 (23.5)		
Adjusted RD [95% CI][a]	[redacted]					
P value[c]						

ACR = American College of Rheumatology; CI = confidence interval; JIA = juvenile idiopathic arthritis; RD = risk difference; TCZ = tocilizumab.

Source: Clinical Study Report (CSR) p. 95 and 107;[1] [redacted].[2]

[a] Analysis was adjusted for randomization stratification factors (methotrexate and oral corticosteroid use).

[b] Response was determined relative to baseline (week 0).

[c] *P* value not provided, as ACR 90 fell below a non-significant parameter in the multiplicity hierarchy structure.

3.7 Harms

Only those harms identified in the review protocol are reported below (Section 2.2.1, Protocol). See APPENDIX 3: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse Events

[redacted]

3.7.2 Serious Adverse Events

[redacted]

3.7.3 Withdrawals Due to Adverse Events

During the O/L lead-in phase, [redacted] withdrew due to an adverse event; AEs included serum sickness-like reaction, pneumonia, hypertransaminasemia, and benign intracranial hypertension. During the DB phase, one patient in each treatment group withdrew due to an AE: abnormal blood bilirubin (tocilizumab group) and gastroenteritis (placebo group).

3.7.4 Mortality

No deaths were reported either in the O/L lead-in phase or in the DB phase of the CHERISH study.

3.7.5 Notable Harms

[redacted]

There were no reports of malignancies or neutropenia during either the O/L lead-in phase or DB phase. However, neutrophil counts across the population decreased during study treatment.

TABLE 12: HARMS

	O/L Lead-In Phase	DB Phase	
	Tocilizumab (N = 188)	Tocilizumab (N = 82)	Placebo (N = 81)
AEs			
Patients with > 0 AEs, N (%)	[redacted]	[redacted]	[redacted]
Most Common AEs (> 5%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
SAEs			
Patients with > 0 SAEs, N (%)	[redacted]	[redacted]	[redacted]
Most Common SAEs			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
WDAEs			
WDAEs, N (%)	[redacted]	[redacted]	[redacted]
Reasons			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Deaths			
Number of deaths, N (%)	[redacted]	[redacted]	[redacted]
Notable Harms, N (%)			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; DB = double-blind; O/L = open-label; SAE = serious adverse event; TCZ = tocilizumab; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report (CSR) p. 1345, 1365, and 1381;[1] [redacted].[2]

4. DISCUSSION

4.1 Summary of Available Evidence

One randomized, placebo-controlled, DB, withdrawal study (CHERISH; n = 166), evaluating the efficacy and safety of tocilizumab in combination with methotrexate or as monotherapy, was included in the systematic review. All patients had active pJIA and had previously had an inadequate response to, or intolerance to, methotrexate. CHERISH was a three-part study that consisted of a 16-week O/L lead-in phase during which all patients received tocilizumab, a 24-week DB phase during which patients were randomized to receive tocilizumab or placebo, and a 64-week O/L extension phase during which all patients received tocilizumab. Patients who achieved a JIA ACR 30 response in the O/L lead-in phase were eligible to continue to the DB withdrawal phase. Patients who completed the DB withdrawal phase or who experienced a JIA ACR 30 flare during the DB withdrawal phase entered the O/L extension phase.

The limitations of the available evidence include the lack of trials directly comparing tocilizumab with other biologic treatments for pJIA. The limitations of the CHERISH study include the short duration of the DB phase, the potential for bias in a number of secondary efficacy end points due to the unequal proportion of patients escaping, the use of LOCF to account for the missing data, and the selection of an "enriched" patient population through use of a withdrawal design that limits the generalizability of efficacy and safety results as further described below. In addition, given the characteristics of patients included in the CHERISH study, there is limited evidence for children younger than seven years of age and for children with low disease activity.

4.2 Interpretation of Results

4.2.1 Efficacy

Enrolment in the DB phase of the CHERISH study was restricted to patients who achieved a JIA ACR 30 response after a 16-week treatment with tocilizumab during the O/L lead-in phase. The clinical expert consulted for this review indicated that while JIA ACR 30 response is a valid outcome for measuring response in trials against placebo, if tocilizumab were the first biologic used in clinical practice and the patient were to achieve only a JIA ACR 30 response, the patient would likely be switched to another biologic instead of continuing on tocilizumab. JIA ACR 50, ACR 70, and ACR 90 responses have been suggested as more desirable parameters with which to evaluate true improvement in clinical practice.[19] However, it was noted that the majority of patients entering into the DB phase had also achieved a JIA ACR 50 response during the O/L lead-in phase.

Results from the 24-week DB phase of the CHERISH study suggest that tocilizumab is superior to placebo in reducing the risk of JIA ACR 30 flare in children with pJIA who achieve a minimum JIA ACR 30 response after 16 weeks of tocilizumab treatment. Results for the primary outcome (JIA ACR 30 flare) were supported by a statistically significantly greater proportion of patients in the tocilizumab group than the placebo group who achieved ACR 30, ACR 50, and ACR 70 responses at the end of the DB phase (week 40). Subgroup analyses suggest that the benefit of tocilizumab compared with placebo is achieved both with and without concomitant methotrexate. However, given that approximately 80% of patients in the DB phase of CHERISH were receiving concomitant methotrexate, the evidence for the comparative benefit of tocilizumab monotherapy in children with pJIA is limited. The Health Canada-approved product monograph indicates that tocilizumab should be given in combination with methotrexate, but may be given as monotherapy in cases of intolerance to methotrexate or where treatment with methotrexate is not appropriate. Subgroup analyses by prior biologic use (Yes/No) suggest that tocilizumab is efficacious (based on JIA ACR criteria) in both prior and non-prior users; however, it was

not clear whether prior users of biologics had had an inadequate response or had been intolerant to their prior biologic.

JIA ACR criteria are a composite of six measures of disease activity, and improvement is not required in all criteria in order to be considered a "responder." Ideally, improvements in the individual core criteria should support findings based on the composite outcome. Statistically significantly greater improvements in the tocilizumab versus the placebo groups were reported for only two of the individual JIA ACR core criteria before the chain of statistical significance in the hierarchical testing of secondary end points was broken at the number of joints with limitation of movement; statistical analyses were not performed on the remaining core criteria. While two core criteria evidenced statistical superiority for tocilizumab versus placebo (number of joints with active arthritis and physician global assessment of disease activity), these findings are subject to bias due to between-treatment inequality in the proportion of patients entering the escape phase and the potential violations of the assumptions of LOCF imputation, as data was not missing completely at random. In addition, the clinical importance of the differences was uncertain. For example, the reduction in the average number of joints with active arthritis differed by only three joints between the tocilizumab and placebo groups at the end of the DB phase (week 40). This magnitude of difference was considered to be of uncertain clinical importance by the clinical expert consulted for this review. The between-treatment difference in the 0 to 100 VAS physician global assessment score was less than 10 points. This seems unlikely to be clinically meaningful, given that the JIA ACR 30 criteria require a minimum 20-point worsening on the physician global assessment VAS score to be considered as worsening.

The CDR reviewer identified a number of issues related to the design of the CHERISH study that limit the interpretation of the findings. As noted, patients who entered the DB phase had to have achieved an ACR 30 response in the O/L lead-in phase on tocilizumab treatment. This necessarily led to an enriched patient population in the DB phase of the trial. Thus, the comparative efficacy of tocilizumab versus placebo is likely overstated compared with what may be achieved in clinical practice among all children eligible for treatment. Additionally, patients who experienced a JIA ACR 30 flare in the DB phase transitioned to the O/L extension phase, meaning there was no controlled data regarding the efficacy of continued treatment with tocilizumab upon flaring. It is unclear if patients who flare would be better switching to an alternative treatment or if continued use of tocilizumab despite a flare would still be beneficial to the patient. In clinical practice, it is likely that some patients would continue to use tocilizumab despite occasional disease flares. Furthermore, the clinical expert consulted for this review indicated that there is no set definition of a "remission," although criteria for defining clinically inactive disease have been proposed.[20] Stopping or temporarily suspending treatment may lead to disease exacerbation due to overexpression of IL-6.[21] As such, the appropriate duration of treatment in the absence of flare, and when it would be appropriate to stop treatment, are not known.

Much of the efficacy assessments in the CHERISH study focused on short-term assessments of symptoms based on JIA ACR composite measures and their individual core criteria. The duration of the DB phase (24 weeks) may be insufficient to accurately quantify the effect of tocilizumab compared with placebo. This is further complicated by the existence of the O/L lead-in phase. Since all patients received tocilizumab during the O/L lead-in phase (week 0 to week 16), there may have been some residual effect of tocilizumab in the placebo group during the DB phase. If so, these carry-over effects within the placebo group may bias against tocilizumab. Alternatively, the short duration of the DB phase may have overestimated a treatment effect for tocilizumab compared with placebo that may not be maintained over a longer treatment duration. At the end of the 64-week O/L extension phase, the JIA ACR 30/50/70/90 response rates were high and similar between continuously-treated patients and

patients that were re-initiated on tocilizumab after having received placebo during the DB phase; however, there was no untreated comparator group (APPENDIX 5: LONG-TERM BENEFITS AND HARMS OF TOCILIZUMAB IN JIA). The CHERISH study did not examine measures of patient satisfaction, health-related quality of life, or long-term remission, function, or disability.

Two different dosing regimens, 8 mg/kg and 10 mg/kg, were administered to patients that were < 30 kg in weight. At the end of the O/L lead-in phase (week 16), a greater proportion of patients who were < 30 kg in weight and who received 10 mg/kg tocilizumab achieved JIA ACR responses than patients who were < 30 kg in weight and who received 8 mg/kg tocilizumab. Pharmacokinetic analysis in the CHERISH study found that the tocilizumab serum concentration was markedly higher in patients who were ≥ 30 kg in weight compared with patients who were < 30 kg in weight, even at the same dose of 8 mg/kg tocilizumab. A dose of 10 mg/kg tocilizumab in patients who were < 30 kg in weight increased systemic exposure compared with an 8 mg/kg dose. In the Health Canada-approved product monograph, the recommended dose for patients with pJIA is 10 mg/kg for patients < 30 kg.[22]

The patients enrolled in the CHERISH study had severe pJIA, as evidenced by the long duration of disease, the high number of active joints at baseline, the extensive use of prior DMARDs, the proportion of patients who were RF positive, and the use of prior biologic therapy in one-third of the patients. The clinical expert consulted on this review noted that these disease characteristics would be expected for patients who had had an inadequate response to, or were intolerant to, methotrexate. However, these study results may not be generalizable to pJIA patients with lower disease activity. [redacted]

No head-to-head trials comparing tocilizumab with other active treatments for pJIA were identified by the CDR review team. Rather, placebo-controlled trials utilizing a withdrawal design similar to the CHERISH study were identified for etanercept, adalimumab, and abatacept in pJIA (one trial each). In addition, CDR identified a recent systematic review that included an indirect comparison of these three treatments in pJIA. However, no definitive conclusions could be reached regarding their comparative efficacy due to the small sample sizes, trial heterogeneity related to treatment duration, and patient characteristics (APPENDIX 6: SUMMARY OF COMPARATORS). According to the manufacturer, an indirect comparison was not possible due to differences in the design of, and the populations studied in, the available studies evaluating the efficacy of biologics for pJIA. Instead, the manufacturer provided an indirect comparison of biologic agents in the treatment of adult patients with RA.[15] However, this analysis could not be used to inform the CDR review because the population and disease entity were different.

The clinical expert consulted for this review noted that tocilizumab could have an added advantage over other biologics for pJIA, as it provides an option for children as young as two years of age. Etanercept and adalimumab are approved for children four years and older, while abatacept is approved for children six years and older.[23-25] However, the clinical expert consulted for this review also noted that the administration of IV tocilizumab may not be easy for very young children because of the invasive nature of an IV and the need to sit still for a prolonged period while the drug is being infused. A subcutaneous formulation of tocilizumab has recently been developed, and two phase 3 trials comparing the efficacy and safety of subcutaneous and IV tocilizumab in patients with RA have been published.[26,27] Additional clinical trials of subcutaneous tocilizumab in JIA patients are currently in progress.[28,29] A subcutaneous formulation could provide added convenience and flexibility, as patients would not need to travel to clinics for infusions.

4.2.2 Harms

[redacted] but serious infections were rare in both treatment groups. The proportion of patients reporting SAEs or withdrawing due to an adverse event was low and was balanced between-treatment groups. No deaths were reported.

Comparisons of the proportion of patients reporting AEs in the DB phase is hampered by unequal escape to O/L tocilizumab, after which AEs were not attributed to the DB treatment. While the differential escape is expected to bias against tocilizumab given the longer duration of exposure to DB tocilizumab compared with placebo in the DB phase, it should be noted that the DB phase specifically included patients who had tolerated tocilizumab treatment in the O/L lead-in phase.

There was no incidence of malignancy or neutropenia reported in either the O/L lead-in phase or the DB phase. However, the CHERISH study was not informative of the incidence of malignancy due to its relatively short duration. Although no cases of neutropenia were reported, neutrophil levels were monitored throughout the study and there were decreases in neutrophil counts. The Health Canada-approved product monograph for tocilizumab (Actemra) highlights that infection and low neutrophil counts are possible side effects of taking the drug.[22]

The AEs observed in the CHERISH study are consistent with those observed in another tocilizumab study in children with systemic JIA.[30] The incidence of infections in the CHERISH study was lower than that of children with systemic JIA, which is perhaps explained by differences in disease characteristics. The adverse event profile of tocilizumab in pJIA patients is comparable to that of other biologics, according to their respective product monographs (Table 2).

5. CONCLUSIONS

One randomized, placebo-controlled, DB, withdrawal study (CHERISH) evaluating the efficacy and safety of tocilizumab, in combination with methotrexate or as monotherapy in patients with pJIA, was included in the systematic review. The results of the CHERISH study suggest that, among children with pJIA who achieve a JIA ACR 30 response after 16 weeks of tocilizumab treatment, continuation of tocilizumab is superior to placebo in reducing the risk of JIA ACR 30 flare over the subsequent 24 weeks. This finding was supported by the statistically significantly greater proportion of patients achieving JIA ACR 30/50/70 responses in the tocilizumab group compared with the placebo group at the end of the DB phase (week 40). The proportion of patients experiencing AEs was reported to be similar in the tocilizumab and placebo groups; however, this finding may be biased due to the unequal escape from DB treatment. Serious infections were rare, and there was no incidence of neutropenia or malignancy. The CHERISH study is limited by the lack of an active comparator, its short duration, and the selection of an "enriched" patient population through use of a withdrawal design that limits the generalizability of efficacy and safety results. Finally, CHERISH did not examine the outcomes of patient satisfaction or quality of life.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed.

1. Brief Description of Patient Groups Supplying Input

Three patient groups submitted input regarding Actemra for polyarticular juvenile idiopathic arthritis (pJIA).

Arthritis Consumer Experts (ACE) is a national arthritis patient organization led by people living with the disease that provides free education and information programs. ACE's membership and program subscribers include people with arthritis, their families, their caregivers, rheumatologists, and other health professionals. It receives unrestricted grants from public and private sector organizations (AbbVie Corporation, Amgen Canada, Arthritis Research Centre of Canada, Bristol-Myers Squibb Canada, Canadian Institutes of Health Research, Canadian Rheumatology Research Consortium, GlaxoSmithKline, Hoffman-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Takeda Canada, Inc., and UCB Canada), as well as individual donations from the public. ACE declared no conflict of interest in the preparation of the submission.

Canadian Arthritis Patient Alliance (CAPA) is a grassroots, patient-driven, independent, national education and advocacy organization with members and supporters across Canada. It creates links among Canadians with arthritis, assists them to become more effective advocates, and seeks to improve the quality of life of all people living with the disease. Funding is provided by various pharmaceutical companies (not specified by CAPA). CAPA declared no conflict of interest in the preparation of the submission.

The Arthritis Society provides information and programs to the millions of Canadians with arthritis. The Society provides funds toward innovative research projects that are searching for the causes of, and better treatments for, arthritis. It also provides funds to train rheumatologists. Hoffmann-La Roche provides funding to the Society for educational programs and services. The Arthritis Society also accepts unrestricted funding from many other unspecified pharmaceutical companies. The vast majority of The Arthritis Society's funding comes from individual donors. The Arthritis Society declared no conflict of interest in the preparation of the submission.

2. Condition- and Current Therapy-Related Information

One group obtained information related to the condition and current therapies through one-on-one conversations with patients; one group requested information through its website and emails to members or subscribers, and one caregiver gave information in a telephone conversation; one group conducted an online survey, had conversations with patients and caregivers through Facebook, had discussions with rheumatologists, and conducted a literature search on the topic.

Polyarticular juvenile idiopathic arthritis is a serious, disabling autoimmune disease and one of the most severe forms of JIA, affecting five or more joints. When diagnosed as a child, one can expect to live with the disease for the rest of one's life. Girls are more likely to have this disease than boys, and it can affect children of all ages.

About 30% of all children with arthritis have a disease that begins as pJIA. Often, the small joints of the hands, as well as other joints, are affected symmetrically. Inflammation in the joint destroys the lining of the joint and ultimately the surrounding bone, resulting in the need for a total joint replacement. In children and youth with JIA, a joint replacement occurs at an even earlier age than those with RA (e.g., one patient required both knees and hips replaced at 13 years of age). Low-grade fever, weight loss, and anemia may occur. Unique complications associated with JIA include uveitis, which can cause vision impairment and blindness and growth retardation, which can be caused by the disease itself or by the use of corticosteroids.

Patients endure severe inflammation, chronic pain, and fatigue, which affect every aspect of their day-to-day life (physical, social, and emotional), including concentration and cognitive abilities in class and a reduced ability to perform tasks such as tying shoe laces, pulling zippers, or completing basic household chores. Children are unable to participate in sports, affecting their ability to socialize with other children. Children may sometimes need to be absent from school, causing them to fall behind in school. Parents also need to pay greater attention to their child with pJIA, thereby having less time and energy to devote to siblings and to each other. Hence, there may be added stress on sibling relationships, as non-arthritic children often feel like the child with arthritis is getting special attention from his or her parents. The disease can become a serious physical and psychological burden for children. One child reports: "*When it was really bad, I felt sad, lonely and scared. My dad would have to carry me to the washroom and everywhere else*." Furthermore, parents report increased stress as a result of employment absences and reduced productivity due to medical appointments. Some have to make long drives to visit the pediatric rheumatologists, who are available only in a few centres across Canada.

It is important to control joint destruction, pain, fatigue, reduction in range of motion, and stiffness. Loss of mobility, difficulty in performing school tasks, fatigue, and pain are the most debilitating aspects of pJIA.

Several treatment options have become available to treat JIA over the years. Many children rely on, and respond well to, DMARD therapy such as methotrexate; however, some children may experience nausea, which can lead to discontinuation of the drug. Some patients are not adequately controlled by methotrexate, and a biologic is usually the next treatment option.

A number of biologics are available that work by different mechanisms, and parents are eager to have many available pharmaceutical options to treat their child's arthritis. Adverse effects include nausea and diarrhea, infusion reaction, headaches and dizziness, increased risk of infection, and skin rash at the injection site. But the risks of permanent joint damage and a lifetime of disability are much greater than the risk of side effects from the medications. When properly monitored, the vast majority of side effects are reversible by adjusting the dose or switching medications.

Finally, the cost of medications requires private insurance for coverage; some parents who do not have insurance take on additional work to pay for the medications. Many provincial drug plans require significant paperwork and constant checking in to see if the patient requires the medication. The requirements to be approved for medications are onerous on the patient and the parents. Adjustments to provincial and private drug formularies may help to alleviate this hardship for children.

3. Related Information About the Drug Being Reviewed

Children diagnosed with pJIA live with their disease for their entire lives, thus needing treatment for 80 years or more.

Actemra will provide another treatment option to manage pJIA in patients who may not adequately respond at all to the biologics currently available or who become treatment resistant over time. Actemra is seen as an alternative in children prone to the side effects of anti-TNF biologics or in children for whom other treatments have failed. Furthermore, there are concerns that anti-TNF biologics may contribute to the risk of cancer later in life for children. Actemra has a different mechanism of action compared with other biologics currently approved for formulary listing, and it is thought that Actemra may not increase the risk of future cancers.

One patient group reported that one patient had a positive response to Actemra, as it relieved joint pain and morning stiffness effectively. Administration on a monthly basis is seen as effective; however, a disadvantage is that it must be administered by infusion in a clinic. Another patient group reported that a manufacturer's compassionate supply was difficult to obtain, as it was typically only supplied to children who were seriously ill, or for whom three to four prior therapies had failed.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 5, 2013
Alerts:	Weekly search updates until February 19, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Actemra* or RoActemra* or tocilizumab or atlizumab or R-1569 or R1569).ti,ot,ab,sh,rn,hw,nm.
2	("monoclonal antibody" adj2 MRA).ti,ab.
3	(Chugai adj2 MRA).ti,ab.
4	375823-41-9.rn,nm.
5	or/1-4
6	Arthritis, Juvenile Rheumatoid/
7	((juvenile* or pediatric* or paediatric* or child* or youth* or adolescent* or adolescence* or infant*) adj4 (arthrit* or arthropath* or rheumatoid* or rheumatolog* or pauciarticular* or pauciarthritis or oligoarthritis or oligoarticular* or polyarthritis or polyarticular* or spondyloarthropath*)).ti,ab.
8	((systemic* or pauciarticular* or oligoarticular* or polyarticular*) adj4 (arthrit* or arthropath*)).ti,ab.
9	(JRA or JA or JIA or JCA or sJIA or pJIA or soJIA).ti,ab.
10	((Chauffard or Still or Stills or Still's or Stiel) adj2 (disease* or syndrome*)).ti,ab.
11	(adolescent/ or exp child/ or exp infant/) and exp arthritis/
12	or/6-11
13	5 and 12
14	13 use pmez
15	*tocilizumab/
16	(Actemra* or RoActemra* or tocilizumab or atlizumab or R-1569 or R1569).ti,ab.
17	("monoclonal antibody" adj MRA).ti,ab.
18	(Chugai adj2 MRA).ti,ab.
19	or/15-18
20	Juvenile Rheumatoid Arthritis/
21	((juvenile* or pediatric* or paediatric* or child* or youth* or adolescent* or adolescence* or infant*) adj4 (arthrit* or arthropath* or rheumatoid* or rheumatolog* or pauciarticular* or pauciarthritis or oligoarthritis or oligoarticular* or polyarthritis or polyarticular* or spondyloarthropath*)).ti,ab.
22	((systemic* or pauciarticular* or oligoarticular* or polyarticular*) adj4 (arthrit* or arthropath*)).ti,ab.
23	(JRA or JA or JIA or JCA or sJIA or pJIA or soJIA).ti,ab.
24	((Chauffard or Still or Stills or Still's or Stiel) adj2 (disease* or syndrome*)).ti,ab.
25	(exp adolescent/ or exp adolescence/ or exp child/ or exp childhood/ or exp childhood diseases/) and exp *arthritis/
26	or/20-25
27	19 and 26
28	27 use oemezd
29	14 or 28
30	29 not conference abstract.pt.
31	remove duplicates from 30

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	August 2013
Keywords:	Actemra and synonyms; juvenile idiopathic arthritis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: DETAILED OUTCOME DATA

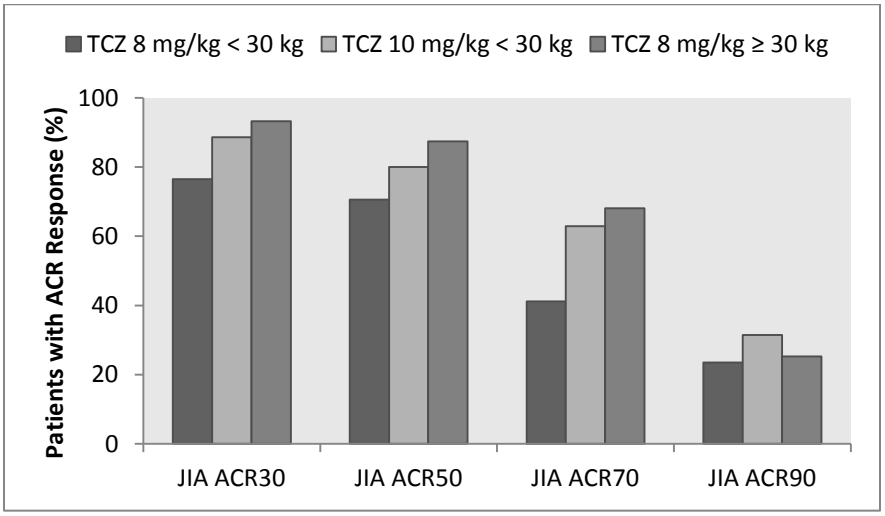
Efficacy — ACR Responses at End of O/L Lead-In Phase

TABLE 13: PROPORTION OF PATIENTS WITH JIA ACR RESPONSES AT THE END OF O/L LEAD-IN PHASE (WEEK 16)

	CHERISH			
	TCZ 10 mg/kg (< 30 kg) (N = 35)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	All TCZ (N = 188)
JIA ACR 30 Response, n (%)	31 (88.6)	26 (76.5)	111 (93.3)	168 (89.4)
JIA ACR 50 Response, n (%)	28 (80.0)	24 (70.6)	104 (87.4)	156 (83.0)
JIA ACR 70 Response, n (%)	22 (62.9)	14 (41.2)	81 (68.1)	117 (62.2)
JIA ACR 90 Response, n (%)	11 (31.4)	8 (23.5)	30 (25.2)	49 (26.1)

ACR = American College of Rheumatologists; JIA = juvenile idiopathic arthritis; O/L = open-label; TCZ = tocilizumab.
Source: Clinical Study Report (CSR) p. 96.[1]

FIGURE 3: ACR RESPONSE AT WEEK 16 — END OF O/L LEAD-IN PHASE



ACR = American College of Rheumatologists; JIA = juvenile idiopathic arthritis; O/L = open-label; TCZ = tocilizumab.
Source: Clinical Study Report (CSR) p. 96.[1]

Time to JIA ACR 30 Flare in the DB Phase

TABLE 14: TIME TO JIA ACR 30 FLARE IN THE DB PHASE

	Tocilizumab (N = 82)	Placebo (N = 81)
Median (days)	[redacted]	[redacted]
Range (days)	[redacted]	[redacted]
Hazard Ratio [95% CI]	[redacted]	
P value	[redacted]	
[redacted]		

ACR = American College of Rheumatology; CI = confidence interval; DB = double-blind; JIA = juvenile idiopathic arthritis.
Source: Clinical Study Report (CSR) p. 455.[1]

FIGURE 4: KAPLAN-MEIER CURVE OF TIME TO DISEASE FLARE — DB PHASE

[Confidential data regarding the Kaplan-Meier Curve of Time to Disease Flare were removed at the manufacturer's request.]

DB = double-blind.

Source: Clinical Study Report (CSR) p. 105.[1]

Efficacy — Individual JIA Core Criteria

TABLE 15: INDIVIDUAL JIA CORE CRITERIA — CHANGE FROM BASELINE

Mean Value for Individual JIA Core Criteria (SD)	Tocilizumab (N = 82)	Placebo (N = 81)
Number of Joints with Active Arthritis		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Change from baseline to week 40	–14.5 (11.1)	–11.5 (12.8)
Adjusted mean change from baseline to week 40	[redacted]	[redacted]
Adjusted MD [95% CI]	[redacted]	
P value	[redacted]	
Number of Joints with Limitation of Movement		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Change from baseline to week 40	–10.2 (9.0)	–8.1 (9.9)
Adjusted mean change from baseline to week 40	[redacted]	[redacted]
Adjusted MD [95% CI]	[redacted]	
P value	[redacted]	
Patient/Parent Global Assessment of Overall Well-Being VAS		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Change from baseline to week 40	–31.1 (28.5)	–32.4 (28.6)
Adjusted mean change from baseline to week 40	[redacted]	[redacted]
Adjusted MD [95% CI][a]	[redacted]	
P value[a]	[redacted]	
Physician Global Assessment of Disease Activity VAS		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Change from baseline to week 40	–45.6 (21.5)	–38.2 (24.8)
Adjusted mean change from baseline to week 40	[redacted]	[redacted]
Adjusted MD [95% CI]	[redacted]	
P value	[redacted]	
Physical Function (CHAQ-DI Score)		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Change from baseline to week 40	–0.80 (0.65)	–0.72 (0.69)

Mean Value for Individual JIA Core Criteria (SD)	Tocilizumab (N = 82)	Placebo (N = 81)
Adjusted mean change from baseline to week 40	[redacted]	[redacted]
Adjusted MD [95% CI][a]	[redacted]	
P value[a]	[redacted]	
Laboratory Assessment of Inflammation (ESR, mm/hr)		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Change from baseline to week 40	–25.2 (22.0)	–14.0 (28.5)
Adjusted mean change from baseline to week 40	[redacted]	[redacted]
Adjusted MD [95% CI][a]	[redacted]	
P value[a]	[redacted]	

CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CI = confidence interval; DB = double-blind; ESR = erythrocyte sedimentation rate; MD = mean difference; NS = not significant; O/L = open-label; CI = confidence interval; JIA = juvenile idiopathic arthritis; RD = risk difference; SD = standard deviation; VAS = visual analogue scale (0 = no symptoms; 100 = maximum disease activity).
Source: Clinical Study Report (CSR) p. 113 and 426.[1]
[a] *P* values not provided as they fall below a non-significant parameter in the hierarchical chain to address multiplicity.

Efficacy — Subgroup Analyses

TABLE 16: SUMMARY OF JIA ACR FLARE RATES FOR SUBGROUPS OF INTEREST IN THE DB PHASES (WEEK 16 TO WEEK 40)

	JIA ACR 30 Flare, n/N (%)	
	Tocilizumab (N = 82)	Placebo (N = 81)
Previous Biologic Use		
Yes	12/27 (44.4)	18/23 (78.3)
No	9/55 (16.4)	21/58 (36.2)
Concomitant MTX Use		
Yes	13/67 (19.4)	25/64 (39.1)
No	8/15 (53.3)	14/17 (82.4)
Concomitant Oral Corticosteroid Use		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Baseline RF Status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; MTX = methotrexate; RF = rheumatoid factor.
Source: Clinical Study Report (CSR) p. 673, 684, 691, and 695.[1]

TABLE 17: SUMMARY OF ACR 30 RESPONSES FOR SUBGROUPS OF INTEREST AT WEEK 40

	ACR 30 Responders, n/N (%)	
	Tocilizumab (N = 82)	Placebo (N = 81)
Previous Biologic Use		
Yes	15/27 (55.6)	6/23 (26.1)
No	46/55 (83.6)	38/58 (65.5)
Concomitant MTX Use		
Yes	53/67 (79.1)	39/64 (60.9)
No	8/15 (53.3)	5/17 (29.4)
Concomitant Oral Corticosteroid Use		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Baseline RF Status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]

ACR = American College of Rheumatology; MTX = methotrexate; RF = rheumatoid factor.
Source: Clinical Study Report CSR p. 673, 684, 691, and 695.[1]
Note: Values are compared with baseline (week 0).

TABLE 18: SUMMARY OF ACR 50 RESPONSES FOR SUBGROUPS OF INTEREST AT WEEK 40

	ACR 50 Responders, n/N (%)	
	Tocilizumab (N = 82)	Placebo (N = 81)
Previous Biologic Use		
Yes	14/27 (51.9)	5/23 (21.7)
No	46/55 (83.6)	37/58 (63.8)
Concomitant MTX Use		
Yes	52/67 (77.6)	38/64 (59.4)
No	8/15 (53.3)	4/17 (23.5)
Concomitant Oral Corticosteroid Use		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Baseline RF Status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]

ACR = American College of Rheumatology; MTX = methotrexate; RF = rheumatoid factor.
Source: Clinical Study Report CSR p. 673, 684, 691, and 695.[1]
Note: Values are compared with baseline (week 0).

TABLE 19: SUMMARY OF ACR 70 RESPONSES FOR SUBGROUPS OF INTEREST AT WEEK 40

	ACR 70 Responders, n/N (%)	
	Tocilizumab (N = 82)	Placebo (N = 81)
Previous Biologic Use		
Yes	13/27 (48.1)	2/23 (8.7)
No	40/55 (72.7)	32/58 (55.2)
Concomitant MTX Use		
Yes	45/67 (67.2)	30/64 (46.9)
No	8/15 (53.3)	4/17 (23.5)
Concomitant Oral Corticosteroid Use		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Baseline RF Status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]

ACR = American College of Rheumatology; MTX = methotrexate; RF = rheumatoid factor.
Source: Clinical Study Report CSR p. 673, 684, 691, and 695.[1]

TABLE 20: SUMMARY OF ACR 90 RESPONSES FOR SUBGROUPS OF INTEREST AT WEEK 40

	ACR 90 Responders, n/N (%)	
	Tocilizumab (N = 82)	Placebo (N = 81)
Previous Biologic Use		
Yes	5/27 (18.5)	2/23 (8.7)
No	32/55 (58.2)	17/58 (29.3)
Concomitant MTX Use		
Yes	32/67 (47.8)	18/64 (28.1)
No	5/15 (33.3)	1/17 (5.9)
Concomitant Oral Corticosteroid Use		
Yes	[redacted]	[redacted]
No	[redacted]	[redacted]
Baseline RF Status		
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
ACR = American College of Rheumatology; MTX = methotrexate; RF = rheumatoid factor.		

Source: Clinical Study Report CSR p. 673, 684, 691, and 695.[1]
Note: Values are compared with baseline (week 0).

Efficacy – CHAQ-DI

TABLE 21: PROPORTION OF PATIENTS WITH A MINIMALLY CLINICALLY IMPORTANT IMPROVEMENT IN CHAQ-DI SCORE AT WEEK 40

	Tocilizumab (N = 82)			Placebo (N = 81)		
	TCZ 10 mg/kg (< 30 kg) (N = 16)	TCZ 8 mg/kg (< 30 kg) (N = 11)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	TCZ 10 mg/kg (< 30 kg) (N = 15)	TCZ 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (≥ 30 kg) (N = 53)
CHAQ-DI responders, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weighted difference [95% CI]	[redacted]					
P value	[redacted]					

CHAQ-DI = Childhood Health Assessment Questionnaire-Disability Index; CI = confidence interval; TCZ = tocilizumab.
Source: Clinical Study Report (CSR) p. 613.[1]
Note: Values are compared with baseline (week 0).

Efficacy – Pain VAS

TABLE 22: MEAN PAIN VAS

	Tocilizumab (N = 82)	Placebo (N = 81)
Mean Pain VAS Score (SD)		
O/L baseline	[redacted]	[redacted]
DB baseline (week 16)	[redacted]	[redacted]
Week 40	[redacted]	[redacted]
Mean Change from Baseline in Pain VAS Score (SD)		
Week 16	[redacted]	[redacted]
Week 40	–31.5 (31.8)	–30.2 (27.1)
Adjusted Mean Change from Baseline in Pain VAS at Week 40[a]		
Mean change	[redacted]	[redacted]
Adjusted MD (95% CI)	[redacted]	
P value	[redacted]	

MD = mean difference; SD = standard deviation; VAS = visual analogue scale.
[a] Adjusted for randomization stratification factors (background use of methotrexate and oral corticosteroids).
Source: Clinical Study Report (CSR) p. 123, 657, and 663.[1]

FIGURE 5: PAIN VAS SCORE LINE PLOT

[Confidential data regarding the Pain VAS Score Line Plot were removed at the manufacturer's request.]

VAS = visual analogue scale.
Source: Clinical Study Report (CSR) p. 124.[1]

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the evidence regarding the validity and minimally clinically important difference (MCID) of measures of disease activity and functional status used in the trials included in the systematic review, specifically, the ACR Pediatric Criteria and the Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI).

Findings

American College of Rheumatology Response Criteria

The American College of Rheumatology (ACR) criteria for assessing joint status were initially developed for rheumatoid arthritis (RA) patients.[31,32] The ACR response is a dichotomous outcome (i.e., response or non-response) based on relative changes from baseline; it does not indicate the absolute level of disease severity.[33]

ACR Pediatric Criteria (ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi 90)

Following ACR criteria for adult RA, a set of preliminary core criteria was defined for pediatric arthritis,[34] referred to as ACR Pediatric criteria for juvenile idiopathic arthritis (JIA).[35,36] Although there is considerable overlap in the *core set of outcome variables* established for RA and JIA (i.e., number of active joints, patient/physician global assessment of disease activity and well-being, and erythrocyte sedimentation rate [ESR]), the definition of *improvement* in adult RA is not considered appropriate for use in JIA. There are several reasons for this: (a) JIA is considered a different disease entity; (b) some core variables are less often abnormal or have lower scores in children than in adults; and (c) their measurement is compromised due to age-related cognitive problems (e.g., self-reported pain). Therefore, Giannini et al.[37] developed a definition of improvement specific to JIA, which was termed ACR Pediatric 30 criteria (or ACR Pedi 30). ACR Pedi 30 is defined as at least 30% improvement from baseline in three of any six variables in the core set, while no more than one of the remaining variables can worsen by > 30%. The core criteria are: 1) physician global assessment of disease activity (scored on a 10 cm visual analogue score [VAS]); 2) parent/patient global assessment of overall well-being (scored on a 10 cm VAS); 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) ESR. (Due to the lack of valid, widely available biomarkers of inflammation in children, only ESR could be included as a biochemical marker of response.) This definition of improvement showed high sensitivity (100%) and specificity (85%), and low false-positive (11%) and false-negative (0%) rates.[37]

There are two important characteristics of the ACR Pedi 30 criteria. First, they include as a parameter the number of joints with limited motion. This is relevant since, in patients with short disease duration, this count can improve significantly through physical therapy. In contrast, patients with long-standing disease may have a number of joints with limited motion that cannot improve due to mechanical deformities not related to the presence of inflammation. Moreover, a patient can be designated as a responder on ACR Pedi 30 even if one (but not more than one) variable has worsened by > 30%.

ACR Pedi 50, 70, 90, and 100 criteria were subsequently developed to define improvement from baseline of at least 50%, 70%, 90%, or 100%, respectively, in at least three of the six core criteria, with no more than one of the remaining criteria worsening by > 30%. Importantly, Lurati et al. indicated that *prospective* validation of the improvement criteria is necessary, but results of such a validation have not been reported.[33] Further, while achievement of 30% improvement was initially considered clinically

important, more recently it has been suggested that this level of improvement may not represent a clinically meaningful degree of improvement.[19]

Childhood Health Assessment Questionnaire and Disability Index[38]

The Health Assessment Questionnaire (HAQ) was originally developed in 1978 at Stanford University for use in adults.[39] It was one of the first self-reported functional status (disability) measures, and has become the dominant instrument for use in many disease areas, including RA.[40,41]

The Childhood Health Assessment Questionnaire (CHAQ) is a 30-item, self- or parent-administered, reliable, and sensitive instrument for measuring functional status in children with juvenile rheumatoid arthritis (JRA, presently referred to as JIA). It takes fewer than 10 minutes to complete, and scoring is easily obtained in fewer than two minutes. The CHAQ was developed by Singh et al. as an adaptation of the Stanford HAQ for use in children aged 1–19 years.[38] It has several new questions compared with the HAQ, with at least one for each functional area, based on relevance to children of all ages. The eight functional areas measured by CHAQ are: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities. Responses for the 30 items are recorded using four-point ordinal scales (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to do). Activities that the child is unable to do because he/she is too young are marked as "not applicable for age," while the use of any aids or devices or help from another person (as applicable) is assigned a minimum score of 2 for that domain. Within each of the eight domains, the item with the highest disability score determines the score for that domain. The global **Disability Index** is obtained by calculating the mean of the eight functional areas; it can range from 0 (no disability) to 3 (maximum disability). The CHAQ also provides an assessment of discomfort using a 10 cm VAS for the evaluation of pain, and a 10 cm VAS for the evaluation of overall well-being.

The face validity of the instrument was first evaluated by a group of 20 health professionals and parents of 22 healthy children, and then administered to parents of 72 JRA patients. The instrument showed excellent internal consistency, strong correlations of the Disability Index (average of scores on all functional areas) with Steinbrocker functional class, number of involved joints, and morning stiffness, as well as a high test-retest reliability for the Disability Index itself. In addition, there was a high correlation between Disability Index scores from questionnaires administered to parents and those from questionnaires administered to older children, showing that parents can accurately report for their children.[38]

Further validity testing of the CHAQ was completed by Pouchot et al. in 306 patients with JIA. The objective was to determine whether the CHAQ is valid for the comparison of different age subgroups (≥ 10 years and < 10 years of age) and for longitudinal studies in JIA. The study found that the difficulty of eight out of 30 items of the CHAQ depends on the respondent's age. However, the impact of this age-related variation in item difficulty on the CHAQ Disability Index remained low (about 0.25 on a scale of 0–3). The authors therefore concluded that the design and scoring system of CHAQ adequately remove most of the expected physical development bias.[42]

CHAQ is thought to have advantages over other measures of physical function related to its multidimensionality (it assesses eight domains of physical function).[43] The CHAQ is in use internationally; cross-cultural adaptations were recently validated in 32 countries.[44] One of its drawbacks is that with 0 as the best possible score (representing no functional limitations), the CHAQ may suffer from a ceiling effect, whereby scores are clustered at the normal end of the scale (near 0).[45] The ceiling effect makes the scale intrinsically less sensitive to milder levels of disability.[46]

Minimally Clinically Important Difference in CHAQ Scores

Few studies are available to evaluate MCID in functional ability of children with JIA.[47] Based on a study involving 131 parents of JIA patients, Dempster et al. found that the median CHAQ scores corresponding to mild, mild-to-moderate, and moderate disability were 0.13, 0.63, and 1.75, respectively.[17] The MCII was a reduction in score of 0.13 (or –4.3%), whereas the MCID worsening was a median change in score of 0.75 (or 25%). This discrepancy between MCID improvement versus worsening was thought to be due to the ceiling effect seen with the CHAQ.[17]

Summary

- ACR Pedi 30 is defined as at least 30% improvement from baseline in three of any six core criteria, while no more than one of the remaining criteria can worsen by > 30%. It has been widely used in clinical trials, however, it has been suggested that a 30% improvement does not represent a meaningful difference.[19] Further, there has been no report indicating that it has been prospectively validated.
- The CHAQ is a widely used and validated disease-specific instrument for measuring functional status in children with JIA. Scores range from 0 to 3 (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to do). A reduction of 0.13 (or –4.3%) in the Childhood Health Assessment Questionnaire and Disability Index (CHAQ-DI) was proposed as minimal clinically significant improvement whereas the minimal clinically significant worsening was a median change in score of 0.75. This instrument appears to demonstrate ceiling effects, and may be insensitive to clinically relevant short-term changes in children with JIA.

APPENDIX 5: LONG-TERM BENEFITS AND HARMS OF TOCILIZUMAB IN JIA

Aim

To summarize the efficacy and harms data reported in the open-label (O/L) extension (Part 3) of the CHERISH trial and long-term safety data for tocilizumab from other sources.

Findings

1. Efficacy Data Reported in Open-Label Extension of the CHERISH Trial

The O/L extension of the CHERISH study was a 64-week O/L extension period initiated at the end of week 40 to evaluate the long-term benefits and harms of tocilizumab in polyarticular juvenile idiopathic arthritis (pJIA).[48] Patients who completed the double-blind (DB) phase of the CHERISH study, or who escaped due to a JIA American College of Rheumatology (ACR) 30 flare during the DB phase, received tocilizumab in the O/L extension.

In the O/L extension, patients received tocilizumab at the same dose as the O/L lead-in phase of CHERISH. [redacted]

TABLE 23: PROPORTION OF PATIENTS WITH JIA ACR RESPONSES AT THE END OF O/L EXTENSION PHASE OF CHERISH STUDY (WEEK 104)

	Patients Who Received Tocilizumab Continuously n (%)				Patients Previously on Placebo in DB Phase n (%)
	TCZ 10 mg/kg (< 30 kg) (N = 9)	TCZ 8 mg/kg (< 30 kg) (N = 18)	TCZ 8 mg/kg (≥ 30 kg) (N = 55)	All TCZ doses (N = 82)	All TCZ doses (N = 81)
JIA ACR 30 response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
JIA ACR 50 response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
JIA ACR 70 response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
JIA ACR 90 response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; O/L = open-label; TCZ = tocilizumab.

[redacted]

TABLE 24: PROPORTION OF PATIENTS WITH JIA ACR RESPONSE AFTER O/L TOCILIZUMAB — SUBGROUP OF PATIENTS ON PLACEBO WHO FLARED DURING THE DB PHASE OF THE CHERISH STUDY

	Patients Previously on Placebo Who Experienced Flare in DB Phase n (%)	
	[redacted]	[redacted]
JIA ACR 30 response	[redacted]	[redacted]
JIA ACR 50 response	[redacted]	[redacted]
JIA ACR 70 response	[redacted]	[redacted]
JIA ACR 90 response	[redacted]	[redacted]

[redacted]

ACR = American College of Rheumatology; DB = double-blind; JIA = juvenile idiopathic arthritis; O/L = open-label; TCZ = tocilizumab.

2. Long-Term Safety Data of Tocilizumab

a) CHERISH Study

[redacted]

[redacted]

TABLE 25: HARMS IN THE CHERISH STUDY (WEEKS 0 TO 104) BY DOSE

	Subgroup				All TCZ (N = 188)
	TCZ 10 mg/kg (< 30 kg) (N = 22)	TCZ 10 mg/kg to 8 mg/kg (< 30 kg) (N = 13)	TCZ 8 mg/kg (< 30 kg) (N = 34)	TCZ 8 mg/kg (≥ 30 kg) (N = 119)	
AEs					
[redacted]					
Most Common AEs by System Organ Class					
[redacted]					
[redacted]					
[redacted]					
SAEs					
[redacted]					
Most Common SAEs by System Organ Class					
[redacted]					

AE = adverse event; CI = confidence interval; SAE = serious adverse event; TCZ = tocilizumab.

[redacted]

TABLE 26: HARMS IN CHERISH STUDY, PATIENT-YEAR

	[redacted]	
Rate per 100 PY (95% CI)	**Week 40**	**Week 104**
Overall AEs	[redacted]	[redacted]
Infection and infestation AEs	[redacted]	[redacted]
Infusion-related AEs	[redacted]	[redacted]
Overall SAEs	[redacted]	[redacted]
Infection and infestation SAEs	[redacted]	[redacted]
WDAEs	[redacted]	[redacted]

AE = adverse event; CI = confidence interval; NR = not reported; PY = patient-year; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[redacted]

b) Literature

CDR identified no published studies examining long-term safety of tocilizumab in JIA. CDR One publication was identified that reported on the long-term safety of tocilizumab in adult patients with moderate to severe RA (age and sex not reported).[49] Data came from five RCTs (n = 4,211), their O/L extension phases (n = 3,512), and a drug interaction study (n = 23). All randomly assigned patients, regardless of previous treatment, were analyzed. Patients who received at least one dose of tocilizumab (4 mg/kg, 8 mg/kg, or 10 mg/kg) were included in the all-exposed population. The total duration of observation was 12,293 patient-years (PY) and the mean tocilizumab treatment duration was 3.1 years (maximum 4.6 years).[49]

AEs, SAEs, and WDAEs were highest in the first 12 months of therapy (Table 27). The most common adverse event and serious adverse event was infection, with a rate of 4.5 serious infections per 100 PY.[50] The most commonly reported serious infections were pneumonia and cellulitis. A total of 55 deaths were reported in the all-exposed population (0.45/100 PY); the most frequent causes of death were infection (n = 18), cardiac events (n = 12), malignancy (n = 6), and respiratory events (n = 5).[50]

The authors concluded that the long-term safety profile of tocilizumab was similar to data from earlier observations (2.4 years of treatment) from the same five RCTs, and that no new safety signals were observed based on up to 4.6 years of treatment data from controlled and uncontrolled studies in patients with moderate to severe RA.[49] Of note, this study was not based on a systematic review of the literature; therefore, it may not represent the entirety of available safety data.

TABLE 27: HARMS IN ADULT RHEUMATOID ARTHRITIS STUDIES

	All-Exposed Safety Population[a] Rate per 100 PY				
	Overall	**0–12 months**	**13–24 months**	**25–36 months**	**> 36 months**
Total duration, PY	**12,293**	**3,471**	**3,026**	**2,733**	**3,064**
Overall AEs	257.2	379.4	275.8	252.4	224.5
Infection and infestation AEs	68.7	96.7	83.8	80.8	73.7
Gastrointestinal	32.7	55.0	32.8	29.3	23.9
Musculoskeletal and connective tissue disorders	27.5	34.7	31.1	27.8	25.2
Overall SAEs	14.1	15.5	13.4	14.8	13.6
Infection and infestation SAEs	4.5	4.4	3.8	5.0	4.7
Gastrointestinal	1.2	1.5	1.0	1.1	1.2
Injury, poisoning, or procedural complications	1.2	1.4	1.5	1.0	1.0
Neoplasms (benign, malignant or unspecified)	1.2	1.0	1.0	1.4	1.3
WDAEs	5.2	9.2	4.4	3.8	2.9
Death	0.45	0.55	0.33	0.44	0.29

AE = adverse event; CI = confidence interval; PY = patient-year; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] The all-exposure population consisted of all patients who received at least one dose of tocilizumab (4,009 patients).

Source: Genovese et al. (2013).[49]

c) Post-Marketing Surveillance Databases

Both the European Database of Suspected Adverse Drug Reaction Reports[51] and the US Adverse Events database[52] were searched by CADTH. The European database did not contain any report on tocilizumab, whereas the US database reported AEs to tocilizumab for RA, juvenile arthritis, and Castleman disease. From 1997 to 2012, there were 3,839 reports of a SAE where tocilizumab was identified as the primary suspect drug causing that event. The top three AEs reported were death (185 reports), pneumonia (164 reports), and arthralgia (156 reports). These were followed by diarrhea (112 reports), pyrexia (108 reports), and sepsis (108 reports). Treatment duration with tocilizumab was 212 days on average, and the average patient age was 56 years. Data was not available exclusively for JIA; hence, the interpretation of findings in the pediatric population is limited.

[redacted]

TABLE 28: HARMS IN THE ROCHE POST-MARKETING SURVEILLANCE DATABASE

Event	[redacted]	[redacted]
Number of patients with SAE	[redacted]	[redacted]
Number of SAE	[redacted]	[redacted]
Number of SAE by System Organ Class (% events)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SAE = serious adverse event.
Source: Hoffman-La Roche Ltd Actemra Safety Update.[53]

Summary

[redacted]

Long-term safety data for tocilizumab is limited in the pediatric population. In general, infections were the most frequently reported AE and SAE among pediatric patients in the CHERISH study, among adults and children in post-marketing surveillance databases, and in controlled and uncontrolled studies in adults with RA. There is currently insufficient data to quantify the risk of uncommon AEs or SAEs, such as neoplasm, with tocilizumab given the small size and limited duration of clinical trials, the limited post-marketing data in children, and the potential for rheumatic diseases and immunosuppressant therapies to confer risk independently of tocilizumab therapy.

APPENDIX 6: SUMMARY OF COMPARATORS

Aim

To provide a summary of efficacy and safety evidence for comparator biologic agents in the treatment of polyarticular juvenile idiopathic arthritis (pJIA).

Findings

No head-to-head randomized controlled trials (RCTs) have compared biologic agents in the treatment of pJIA. However, three randomized, placebo-controlled withdrawal trials looked at the efficacy and safety of the comparators of interest (adalimumab, abatacept, and etanercept) in pJIA patients.[54-56] In addition, one indirect comparison of biologics which did not include tocilizumab was found in the literature.[57]

Placebo-Controlled Trials

Study Characteristics

The three RCTs that compared abatacept, adalimumab, or etanercept with placebo in patients with polyarticular JIA used a similar withdrawal design which consisted of an open-label (O/L) lead-in phase (whereby all patients received the drug), followed by a double-blind (DB) randomized phase (with patients either remaining on the drug or receiving placebo) (Table 29).[54-56] Polyarticular JIA was defined in all trials as having five or more active joints at any time during disease course. In two studies (etanercept and abatacept), patients with systemic arthritis and polyarticular JIA were also included in the trials. It is unclear if patients with systemic disease were included in the adalimumab trial. Samples sizes in the DB phase of the withdrawal trials ranged from 51 to 144. The primary outcome was disease flare.

The doses examined in the DB phase of the trials were: abatacept (10 mg/kg [maximum 1,000 mg] every 28 days), adalimumab (24 mg/m^2 [maximum 40 mg] every other week), and etanercept (0.4 mg/kg [maximum 25 mg] twice weekly), each of which was compared with placebo. Some concomitant medications (nonsteroidal anti-inflammatory drug [NSAIDs], low-dose steroids) were permitted in the included trials, but not within the 12-hour period prior to joint assessment. No concurrent use of methotrexate or disease-modifying antirheumatic drugs (DMARDs) was allowed in the etanercept study, and those on methotrexate or hydroxychloroquine stopped therapy before entering the study.[54] Concurrent use of methotrexate, but no other DMARDs or biologics, were allowed in the abatacept trial.[56] In the adalimumab study, patients were stratified based on history of methotrexate use: those currently treated with methotrexate and those who had either never received methotrexate or had discontinued methotrexate.[55]

Patient characteristics for JIA (particularly number of joints affected, physician's assessment of disease activity, and Childhood Health Assessment Questionnaire [CHAQ] scores) across the DB phase were similar with some noted exceptions. Baseline disease duration (which varied between 3.8 years and 5.8 years across trials) and age (mean age between 10.6 years and 12.3 years) were somewhat different between trials. Trial duration also differed, with the etanercept trial having a shorter DB phase duration (4 months compared with 6 and 8 months for the abatacept and adalimumab trials, respectively). The percentage of patients with systemic JIA and polyarticular JIA were reported as being unclear in the adalimumab trial, and varied between 19% and 33% in the abatacept and etanercept trials, respectively. In addition, no patients were included in either the etanercept or adalimumab trials that were previous non-responders to a TNF-α antagonist, whereas 17% of patients included in the abatacept trial fell into this category. In addition, there were some differences in co-medications used during the trials; in both

the abatacept and adalimumab studies, patients who were taking methotrexate at baseline maintained their methotrexate during the study.

In all three RCTs, patients who responded to treatment during Part 1 (O/L run-in phase) were eligible to enter the randomized DB Part 2. Response was defined using the ACR Pedi 30 criteria in two trials,[55,56] and was undefined in a third.[54] A total of 47 patients (25%) in the abatacept study enrolled in Part 1 did not proceed to Part 2 of the study due to a lack of response, and one additional patient left the study.[56] For adalimumab, a total of 38 patients (22%) of patients from Part 1 did not proceed to Part 2 of the trial due to various reasons (adverse events [AEs], lack of efficacy, protocol violation, withdrawal of consent, and lost to follow-up).[55] In the etanercept study, a total of 18 patients (26%) of patients from Part 1 did not proceed to Part 2 of the trial, mostly because of lack of efficacy.[54]

TABLE 29: CHARACTERISTICS OF STUDIES OF BIOLOGICS FOR POLYARTICULAR JIA

Study	Design, Duration, N	Intervention and Comparator	Patients Characteristics
Ruperto et al. (2008)[56]	O/L lead-in phase: 4 months (190 patients enrolled and treated; 170 patients completed O/L lead-in phase) Patients with ACR Pedi 30 response entered DB phase: 6 months (122 patients) O/L extension: 5 years (153 patients)	O/L lead-in phase: Abatacept IV 10 mg/kg (maximum 1,000 mg) on days 1, 15, 29, 57, and 85 DB phase: Abatacept IV 10 mg/kg (maximum 1,000 mg) every 28 days Placebo	Patients 6 to 17 years old with active pJIA (≥ 5 active joints and ≥ 2 joints with LOM), extended oligoarticular arthritis, or systemic arthritis who were intolerant to at least one DMARD including biologics pJIA: 66%, systemic JIA: 20% Median disease duration: 4 years RF positive: 22% Prior anti-TNF therapy: 17% (DB phase) Prior MTX use: NR Concurrent MTX use: 77%
Lovell et al. (2008)[55]	O/L lead-in phase: 16 weeks (171 patients) Patients with ACR Pedi 30 response entered DB phase:[a] 32 weeks (133 patients) O/L extension: duration NR (128 patients)	O/L lead-in phase and DB phase:[a] Adalimumab 24 mg/m^2 (maximum 40 mg) every other week Placebo	Patients 4 to 17 years old with active pJIA (with any type of onset) who had not responded adequately to treatment with NSAIDs pJIA: % unclear Median disease duration: 4 years RF positive: 22% Prior MTX use: 65% (DB phase) Concurrent MTX use: 56%
Lovell et al. (2000)[54]	O/L lead-in phase: 3 months (69 patients) Patients who improved were randomized in the DB phase: 4 months	O/L lead-in phase and DB phase: Etanercept SC 0.4 mg/kg (maximum 25 mg) twice weekly Placebo	Patients 4 to 17 years old with active pJIA (presence of ≥ 5 swollen joints and ≥ 3 joints with LOM), pauciarticular arthritis (≤ 4 swollen joints) or

Study	Design, Duration, N	Intervention and Comparator	Patients Characteristics
	(51 patients) O/L extension: duration NR (59 patients); some patients were followed for up to 8 years		systemic arthritis who were intolerant to, or had an inadequate response to, NSAIDs and MTX pJIA: 58%, systemic JIA: 33% Median disease duration: 6 years RF positive: 22% Prior MTX use: 100% (DB phase) Concurrent MTX use: 0%

ACR = American College of Rheumatology; DB = double-blind; DMARD = disease-modifying antirheumatic drug; IV = intravenous; LOM = limitation of motion; MTX = methotrexate; NR = not reported; NSAID = nonsteroidal anti-inflammatory drugs; O/L = open-label; Pedi = pediatric; pJIA = polyarticular juvenile idiopathic arthritis; RF = rheumatoid factor; SC = subcutaneous; TNF = tumour necrosis factor.
[a] Stratification according to concurrent methotrexate use.

Efficacy

The primary outcome was disease flare, which was defined according to the ACR Pedi 30 criteria in two studies,[55,56] and a modified ACR Pedi 30 criteria in the third study.[54] In general, patients with a flare showed a ≥ 30% worsening in at least three of six criteria (global assessment by physician, or parent/child, number of active joints, number of joints with limitation of motion, functional ability, and ESR) and had ≥ 30% improvement in no more than one of six criteria.

In the DB phase of the trials, statistically significantly fewer treated patients experienced a disease flare compared with placebo patients (Table 30). The risk difference between groups showed that 28% to 53% fewer patients who received an active agent experienced a disease flare versus placebo.

Secondary outcomes measured in the DB phase of studies included the ACR Pedi 30 response. An ACR Pedi 30 response was obtained in 82% of abatacept patients compared with 69% of placebo patients ($P = 0.17$),[56] and in 80% of etanercept patients compared with 35% of placebo patients ($P = < 0.01$). In the adalimumab study, 57% of adalimumab patients achieved an ACR Pedi 30 response compared with 32% of placebo patients in the subgroup not receiving concurrent methotrexate therapy ($P = 0.06$). In the subgroup receiving methotrexate, ACR Pedi 30 responses were obtained in 63% of adalimumab patients compared with 38% of placebo patients ($P = 0.03$). However, the study was not powered to detect differences between patients receiving methotrexate and those not receiving methotrexate.[55]

TABLE 30: DISEASE FLARE OUTCOME FROM THE DB PHASE OF STUDIES OF BIOLOGICS FOR POLYARTICULAR JIA

Study	Comparison	Patients Included (n)	Patients With Flare in Active Drug Arm, n/N (%)	Patients With Flare in Placebo Arm, n/N (%)	RR (95% CI)[a]	RD (95% CI)[a]
Ruperto et al. (2008)[56]	ABA versus placebo	122	12/60 (20)	33/62 (53)	0.38 (0.22 to 0.66)	–33% (–49% to –17%)
Lovell et al. (2008)[55]	Overall population[b] ADA versus placebo	133	27/68 (40)	44/65 (68)	0.59 (0.42 to 0.82)	–28% (–44% to –12%)
	No MTX subgroup ADA versus placebo	58	13/30 (43)	20/28 (71)	0.61 (0.38 to 0.97)	–28% (–52% to –4%)
	MTX subgroup ADA versus placebo	75	14/38 (37)	24/37 (65)	0.57 (0.35 to 0.92)	–28% (–50% to –6%)
Lovell et al. (2000)[54]	ETA versus placebo	51	7/25 (28)	21/26 (81)	0.35 (0.18 to 0.67)	–53% (–76% to –30%)

ABA = abatacept; ADA = adalimumab; CDR = Common Drug Review; CI = confidence interval; DB = double blinded; ETA = etanercept; JIA = juvenile idiopathic arthritis; MTX = methotrexate; PL = placebo; RD = risk difference; RR = relative risk.
[a] Calculated by CDR.
[b] The stratified methotrexate arms combined.

Harm

No deaths were reported in any of the trials. None of the patients withdrew from the DB phase due to AEs to adalimumab and abatacept. There were more AEs reported with adalimumab and abatacept compared with placebo (Table 31). There were more adalimumab-treated patients experiencing serious adverse events (SAEs) and infections compared with the placebo group.[55] No SAEs were reported in abatacept patients.[56] The proportion of patients with an infection was the same in the abatacept-treated group and the placebo group.[56]

Harms data were not clearly presented in the etanercept study although it is reported that two etanercept patients were hospitalized for SAEs (depression/personality disorder and gastroenteritis) during the study period. The authors reported that there was no difference in frequencies of AEs between treated and placebo patients during the DB phase.[54]

TABLE 31: SAFETY RESULTS FROM THE DOUBLE-BLIND PHASE OF STUDIES OF BIOLOGICS FOR POLYARTICULAR JIA

Study and Biologic	Adverse Events, n/N (%)		Serious Adverse Events, n/N (%)		Infections and Infestations, n/N (%)		Withdrawals Due to Adverse Events, n/N (%)	
	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo
Ruperto et al. (2008)[56] ABA	37/60 (62)	34/62 (55)	0	2/62 (3)	27/60 (45)	37/62 (44)	0	0
Lovell et al. (2008)[55] ADA (no MTX)	28/30 (93)	21/28 (75)	1/30 (3)	0	19/30 (63)	11/28 (40)	0	0
Lovell et al. (2008)[55] ADA (MTX)	32/38 (84)	27/37 (73)	3/38 (8)	2/37 (5)	22/38 (58)	19/37 (51)	0	0
Lovell et al. (2000)[54] ETA	NR	NR	NR	NR	NR	NR	NR	NR

ABA = abatacept; ADA = adalimumab; ETA = etanercept; JIA = juvenile idiopathic arthritis; MTX = methotrexate; NR = not reported.

Critical Appraisal

Allocation was adequately concealed in the abatacept study,[56] and was unclear for the other two trials.[55,58] Centralized computer-generated randomization[56] and block randomization schemes[54] were used in two trials. The randomization method was not reported in the adalimumab study.[55] All studies were DB; however, the degree to which patients or the medical team could discover treatment allocation due to differential AEs or changes in response is unknown. In the adalimumab study,[55] missing values were treated as disease flares, which may be more appropriate than the LOCF method used in the other two studies. The sample sizes of the studies were small, ranging from 51 to 144 patients. Of the two trials that reported power calculations,[55,56] only one appears to be adequately powered.[55]

All three trials used an enrichment design, whereby all patients received O/L active therapy; those showing an adequate response to treatment were then eligible to enter the randomized DB, placebo-controlled phase of the study. This design, while minimizing patients' exposure to placebo, may suggest higher efficacy results than may be achieved in clinical practice. In addition, the incidence of harms may be lower as those most likely to experience AEs withdraw from the study during the run-in phase. These factors could affect the generalizability of findings.

Indirect Comparison

Otten et al.[57] performed an indirect treatment comparison (ITC), which included abatacept, adalimumab, and etanercept in pediatric patients with JIA.

Methods

Eligibility Criteria:

The ITC was based on a systematic review of the available literature. The inclusion criteria for the systematic review included the following: RCTs (all designs) in the pediatric population (aged 4 to 17 years) with JIA (or the previously used criteria for JRA, any onset category) that compared a biologic treatment (with or without methotrexate) with placebo, a DMARD, or another biologic agent.

Description of Indirect Comparison:

The Bucher method for conducting adjusted ITC was used to determine the comparative efficacy of the biologics included. The results were presented as relative risks (RR) with 95% confidence intervals (CI) and two-sided *P* values.

Results

Study and Patient Characteristics:

The ITC included the three RCTs summarized in Table 29, in which abatacept (10 mg/kg [maximum 1,000 mg] every 28 days), adalimumab (24 mg/m^2 [maximum 40 mg] every other week), and etanercept (0.4 mg/kg maximum 25 mg] twice weekly), were compared with placebo.[54-56]

Results of the Indirect Comparison:

Relative risks (RR) for disease flare from the individual trials are reported in Table 32. All pairwise ITCs between etanercept, adalimumab, and abatacept were statistically non-significant, indicating that there is no evidence of a difference between these biologic agents in terms of the risk of disease flare (Table 32). Other outcomes such as the percentage of patients achieving ACR Pedi 30 were not reported.

TABLE 32: RELATIVE RISKS OF DISEASE FLARE FOR ABATACEPT, ADALIMUMAB, AND ETANERCEPT REPORTED IN OTTEN IDC

Indirect comparison	RR (95% CI)	*P* Value
ETA versus ADA (combined)[a]	0.59 (0.28 to 1.24)	0.16
ETA versus ADA (non-MTX)	0.57 (0.25 to 1.28)	0.17
ETA versus ADA (MTX)	0.61 (0.27 to 1.38)	0.23
ETA versus ABA	0.92 (0.39 to 2.18)	0.85
ADA (combined)[a] versus ABA	1.56 (0.81 to 2.99)	0.18
ADA (non-MTX) versus ABA	1.61 (0.78 to 3.33)	0.20
ADA (MTX) versus ABA	1.51 (0.72 to 3.13)	0.27
ADA (non-MTX) versus ADA (MTX)	1.07 (0.55 to 2.09)	0.85

ABA = abatacept; ADA = adalimumab; ETA = etanercept; MTX = methotrexate; RR = relative risk.
Source: Adapted from Otten et al.[57]
[a] The stratified methotrexate arms combined.

Critical Appraisal of Indirect Comparison

Strengths:

The overall conduct of the ITC was robust and met the majority of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) criteria (Table 33). The ITC was based on a systematic review of all available RCTs involving abatacept, adalimumab, and etanercept in pediatric patients with polyarticular JIA. The majority of patient characteristics were similar across trials, and the Bucher method was appropriate to conduct the adjusted indirect comparison.

Limitations:
Differences in population characteristics or trial methodology can affect the validity of indirect comparisons. Some discrepancies were noted upon examination of the detailed patient characteristics by the indirect comparison authors. In particular, patients enrolled in the etanercept trial had a longer mean disease duration of 5.8 years compared with 3.8 years and 3.9 years in the adalimumab and abatacept trials, respectively. In addition, 33% of patients in the etanercept trial had systemic JIA compared with 19% in the abatacept trial: it was unclear if the adalimumab study included those with systemic JIA. Another notable finding was that 17% of patients in the abatacept trial were previous non-responders to a TNF-α antagonist, suggesting that this cohort was more therapy-resistant than patients in the other trials. Further, 77% and 56% of patients in the abatacept and adalimumab trials, respectively, received concurrent methotrexate therapy, whereas in the etanercept study all patients using methotrexate were required to stop therapy prior to enrolment.

In terms of trial design, the duration of the DB withdrawal phase was shorter in the etanercept trial than in the abatacept and adalimumab trials (four versus six and eight months, respectively). With the shorter treatment duration, there is a smaller chance of reaching a time-dependent outcome like disease flare due to carry-over effects from the O/L lead-in period, potentially resulting in better outcomes and biasing results in favour of etanercept.

Sample sizes in all three trials were small, reducing the statistical power of the indirect comparison to detect differences between treatments. The lack of precision is evidenced by the relatively wide 95% CI's of the indirect estimates.

TABLE 33: APPRAISAL OF THE INDIRECT COMPARISON ANALYSES USING ISPOR CRITERIA

ISPOR Checklist Item	Details and Comments
1. Are the rationale for the study and the objectives stated clearly?	• The rationale for conducting an indirect comparison analysis and the study objectives were stated.
2. Does the Methods section include the following? • eligibility criteria • information sources • search strategy • study selection process • data extraction • validity of individual studies	• The eligibility criteria for RCTs were clearly stated. • A detailed search strategy was presented. • Study selection and data extraction were completed independently by two researchers. • Similarity of trials was assessed. Differences between trials that may modify treatment-effect measures were discussed; trials were deemed similar except for concurrent MTX use, duration of follow-up, and prior history of ant-TNF agents. • Validity of individual studies was assessed using the Jadad scale.
3. Are the outcome measures described?	• Outcomes assessed in the indirect comparison analysis (disease flare, ACR Pedi 30, and inactive disease) were stated and defined for comparison purposes.
4. Is there a description of methods for analysis/synthesis of evidence? • description of analyses methods/models • handling of potential bias/inconsistency • analysis framework	• Relative effectiveness was estimated by the Bucher method. • Network diagrams were presented; two networks were analyzed based on trial design (withdrawal trial, parallel design). • There were insufficient studies available to explore potential effect modifiers through meta-regression.

ISPOR Checklist Item	Details and Comments
5. Are sensitivity analyses presented?	• NA
6. Do the results include a summary of the studies included in the network of evidence? • individual study data? • network of studies?	• Summaries of patient and trial characteristics were presented. • Individual study results were presented.
7. Does the study describe an assessment of model fit? Are competing models being compared?	• NA
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported, including point estimates and 95% confidence intervals.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; MTX = methotrexate; NA = not applicable; RCTs = randomized controlled trial; TNF = tumour necrosis factor.

Summary

To date, no head-to-head RCTs have compared biologic agents in the treatment of pJIA. Three randomized, placebo-controlled withdrawal trials with etanercept, adalimumab, and abatacept showed that statistically significantly more placebo patients experienced a disease flare compared with treated patients. No deaths were reported in the trials, and no patients withdrew due to an AE in the DB phase.

In the absence of head-to-head trial data, one published indirect comparison (which did not include tocilizumab) was identified that assessed the comparative efficacy of biologics indicated for pediatric patients with JIA. No efficacy differences in terms of disease flare were apparent between abatacept, adalimumab, and etanercept. However, these results were not considered to definitively reflect equivalent efficacy between the three agents. Reasons for the lack of definitive conclusions included the small sample sizes of the included trials, and differences between trials in treatment duration, mean disease duration and other disease characteristics, co-medication use, and pre-trial biologic use. No indirect comparisons were performed for other outcomes such as ACR Pedi response, function/disability, or safety. Hence, considerable uncertainty remains regarding the comparative efficacy and safety of adalimumab, abatacept, and etanercept in pJIA.

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