Common Drug Review
Clinical Review Report

November 2016

Drug	Canakinumab (Ilaris)
Indication	Treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older
Reimbursement request	Treatment of active systemic juvenile idiopathic arthritis in patients 2 years and older who are contraindicated to, or have discontinued, any biologic therapy for lack of efficacy or intolerance
Dosage form(s)	150 mg subcutaneous injection
NOC date	December 12, 2013
Manufacturer	Novartis Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included two clinical experts in rheumatology and pediatric rheumatology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

The information in this report is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment with respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this document to ensure that its contents are accurate, complete, and up-to-date as of the date of publication, CADTH does not make any guarantee to that effect. CADTH is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in the source documentation. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the information in this document or in any of the source documentation.

This document is intended for use in the context of the Canadian health care system. Other health care systems are different; the issues and information related to the subject matter of this document may be different in other jurisdictions and, if used outside of Canada, it is at the user's risk. This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

CADTH takes sole responsibility for the final form and content of this document, subject to the limitations noted above. The statements and conclusions in this document are those of CADTH and not of its advisory committees and reviewers. The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada or any Canadian provincial or territorial government. Production of this document is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

ACR Pedi	American College of Rheumatology Pediatric
AE	adverse event
CHAQ	Child Health Assessment Questionnaire
CHQ	Child Health Questionnaire
CI	confidence interval
DB	double blind
DMARD	disease-modifying antirheumatic drug
HR	hazard ratio
ITC	indirect treatment comparison
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
sJIA	systemic juvenile idiopathic arthritis
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Juvenile idiopathic arthritis (JIA) is a relatively common, chronic childhood disorder,[1-4] with clinical manifestations mainly related to joint inflammation and including joint effusion, joint line tenderness and warmth, restricted range of movement, and limitation of movement secondary to pain.[3] Systemic onset JIA (sJIA) is a subtype of the disease accounting for approximately 4% to 15% of patients,[5,6] and is defined as arthritis in one or more joints for at least 6 weeks in a child younger than 16 years with or preceded by fever of at least 2 weeks that is documented to be daily for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis.[5,6] Patients with sJIA experience an intense inflammatory state leading to a particularly refractory course and persistent disease.[5,6] As a result, these patients are at high risk for serious complications such as joint damage and growth impairment, [5,6] as well as macrophage activation syndrome (MAS), a life-threatening complication developing in 10% to 15% of children with sJIA and associated with a mortality rate that may reach 20%.[5-8]

Canakinumab is a fully human monoclonal antibody that selectively binds and neutralizes interleukin-1 beta,[9,10] which plays a key role in the inflammatory process of sJIA.[5,6,9-11] Canakinumab has a Health Canada indication for the management of active sJIA in patients 2 years and older.[10] The manufacturer has requested that canakinumab be evaluated for reimbursement for the management of active sJIA in patients 2 years and older who are contraindicated to, or have discontinued, any biologic therapy for lack of efficacy or intolerance. The objective of this report was to perform a systematic review of the beneficial and harmful effects of canakinumab subcutaneous injection for the management of active sJIA in patients aged ≥ 2 years.

Results and Interpretation

Included Studies

Two published, manufacturer-sponsored, double-blind (DB), placebo-controlled randomized controlled trials (RCTs) were included in the systematic review. Study 2301 (n = 100)[12] evaluated the superiority of canakinumab compared with placebo based on the primary outcome of time to flare events, using a flare prevention design (randomized treatment withdrawal in responders). Study 2301 included an open-label (O/L) run-in design where all patients received canakinumab to induce and maintain, at a minimum, an adapted American College of Rheumatology Response Pediatric (ACR Pedi) 30 response. The adapted ACR Pedi 30 criteria consist of the ACR Pedi criteria for JIA, with the addition of a variable related to fever, which is a core sign of the systemic subtype of JIA. The O/L run-in had a maximum duration of 32 weeks, but patients spent a median of 16 weeks in this study phase. Patients were randomized in the DB phase to receive either canakinumab 4 mg/kg or placebo, administered subcutaneously (SC) every 4 weeks. The study was stopped when the required number of 37 flare events had occurred; resulting in a median DB phase duration of 32 weeks in the canakinumab group and 23 weeks in the placebo group.

Study 2305 (n = 84)[12] evaluated the superiority of canakinumab compared with placebo based on the proportions of patients who achieved at least an adapted ACR Pedi 30 response at day 15. Patients were randomized to receive a single SC injection of either canakinumab 4 mg/kg or placebo and were followed-up for a total of 4 weeks. All patients with active disease and meeting the International League Against Rheumatism (ILAR) definition for sJIA were allowed to participate in Study 2301 and Study 2305;

however, baseline characteristics indicate that both trial populations involved patients with a high level of disease activity. In addition, the majority of patients received prior treatment with various initial therapeutic options including oral steroids, methotrexate, anakinra and etanercept, which were discontinued mostly due to lack of efficacy or tolerability.

One limitation of the included studies was the fact that a high proportion of patients in the placebo group discontinued from both studies (52% in Study 2301 and 90% in Study 2305), mostly due to unsatisfactory therapeutic effect. Although this is not unexpected, the impact of these discontinuations on the interpretation of the findings is uncertain. Other limitations of the studies are related to generalizability. The use of an adapted ACR Pedi 30 level in order to show adequate response to treatment in Study 2301 and Study 2305 is considered to be an insufficient reflection of the desired response in clinical practice, as remission or inactive disease is the treatment goal; however, achievement of remission or inactive disease were secondary outcomes in the included studies. The withdrawal design of Study 2301 is frequently seen, but is considered less informative regarding therapeutic decisions in clinical practice. The results were obtained in a population of patients with an initial response to canakinumab, but identifying patients who are likely to benefit from the drug in the general population may prove difficult to achieve. Most importantly, real-life management of sJIA is indefinite and the natural course of the disease in patients from the placebo group is uncertain. Indeed, discontinuing treatment in patients once a response is obtained may not systematically result in a disease flare. This may bias the result against canakinumab, complicating interpretation of the findings.

Efficacy

Results from Study 2305 demonstrate the superiority of canakinumab compared with placebo in order to achieve an adapted ACR Pedi 30 response after 15 days of treatment in patients with sJIA, as shown by the OR = 62 (95% CI, 12 to 306; $P < 0.0001$). Patients receiving canakinumab were also statistically significantly more likely to achieve an adapted ACR Pedi 90 response (OR = 41; 95% CI, 5 to 315; $P < 0.0001$) or an adapted ACR Pedi 100 response (OR = 23; 95% CI, 3 to 183; $P < 0.0001$) after 30 days of treatment. These were considered particularly relevant and clinically meaningful according to the pediatric expert consulted, as they may be consistent with the treatment goal of remission. With its withdrawal design, Study 2301 demonstrated the sustained efficacy of canakinumab, which was associated with a statistically significant reduction in the risk of a disease flare compared with placebo, with a hazard ratio (HR) = 0.36 (95% CI, 0.17 to 0.75; $P = 0.0032$), in patients who previously achieved a minimum response with the drug. Canakinumab was also superior to placebo to reduce the risk of a worsening in adapted ACR Pedi response level throughout the study duration (HR = 0.49; 95% CI, 0.27 to 0.90; $P = 0.0131$).

Although often used in JIA trials, an ACR Pedi 30 response level does not represent a meaningful degree of improvement. According to the consulting clinical expert, the goal of therapy is remission or inactive disease, which was assessed as a secondary outcome. In Study 2301, the use of canakinumab was associated with a statistically significant higher likelihood of inactive disease compared with placebo (OR = 3.4; 95% CI, 1.5 to 8.0; $P = 0.0020$). No further relevant statistical analysis was reported; however, numerically higher proportions of patients receiving canakinumab compared with placebo achieved ≥ 24 weeks of inactive disease during Study 2301. These results were consistent with assessments from Study 2305, where numerically more patients in the canakinumab group achieved inactive disease and fewer patients experienced a disease flare compared with patients in the placebo group at four weeks.

Health-related quality of life (HRQoL), including pain, as well as functional outcomes, were identified as important outcomes for patients according to the patient input received by CADTH. These were

measured using reliable and validated tools in Study 2301 and Study 2305. Results of Study 2305 indicated that canakinumab was associated with a statistically significant and clinically meaningful benefit on HRQoL, pain and functionality compared with placebo, as measured by change from baseline in the Child Health Assessment Questionnaire (CHAQ) and Child Health Questionnaire (CHQ) scores, as well as pain intensity assessment, after 29 days of treatment. Results of Study 2301 showed a non-significant trend favouring canakinumab compared to placebo with regard to these outcomes; however, the withdrawal design complicates interpretation of the findings. Real-life management of sJIA is usually indefinite; however, discontinuing the medication once a treatment response is obtained may be considered under some rare circumstances according to the clinical expert, and experience suggests that stopping treatment does not systematically result in a disease flare. Therefore, the natural course of the disease in patients from the placebo group is uncertain, which may undermine the potential for canakinumab to show a statistically significant between-group difference in these circumstances.

Both Study 2301 and Study 2305 included a proportion of patients who had previous experience with oral steroids, a DMARD, and/or a biologic drug. In Study 2301, 62% of patients randomized to the DB phase were using oral steroids, and 54% were using methotrexate, at baseline. In Study 2305, 70% of patients were using oral steroids, and 63% were using methotrexate, at baseline. The concomitant use of oral steroid and methotrexate was allowed throughout both trials, under pre-specified dispositions. Prior experience with anakinra was reported in 45% of patients in Study 2301, and 37% of patients in Study 2305. Few patients had prior experience with tocilizumab (5% of patients randomized in Study 2301 and 4% of patients in Study 2305). In both trials, the most common reasons for discontinuation of anakinra or tocilizumab were lack of efficacy or tolerability. A total of 26% of patients in Study 2301, and 36% of patients in Study 2305, reported prior use of other biologic drugs, mainly etanercept, which was almost exclusively discontinued due to lack of efficacy. Only limited results pertaining to these particular patients were available and no statistical comparison between treatment groups was reported.

No controlled data are available to inform on the sustainability of beneficial treatment effects observed with canakinumab in patients with sJIA beyond the mean Study 2301 duration of approximately 50 weeks. Findings from the non-comparative O/L extension Study 2301E1 (n = 271) are consistent with those from Study 2301 and Study 2305 with regard to the efficacy of canakinumab to maintain an adapted ACR Pedi response and achievement of inactive disease throughout a median duration of canakinumab treatment ranging between 96 weeks and 166 weeks according to the cohort of patients analyzed. Additional details are provided in 0.

There is a lack of evidence with which to directly compare canakinumab with other drugs used in treating sJIA, especially the interleukin inhibitor tocilizumab. To inform this evidence gap, the CADTH Common Drug Review (CDR) reviewed and critically appraised available indirect evidence. A literature search was undertaken to identify relevant published indirect treatment comparisons (ITCs). One relevant publication was included, in addition to one manufacturer-provided, unpublished ITC. Otten et al. 2013[13] assessed the comparative efficacy of canakinumab, anakinra, and tocilizumab in the management of sJIA; the manufacturer's ITC focused on canakinumab and tocilizumab in a population of patients with sJIA including patients who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. [redacted] Safety outcomes were not assessed. The main limitation was the small number of studies included and the small sample sizes, which results in a high degree of uncertainty

surrounding the indirect findings. [redacted]

Harms

Canakinumab is approved for one other indication besides sJIA (ongoing management of cryopyrin-associated periodic syndromes) and the overall harms in Study 2301 and Study 2305 results suggest that the potential harms in sJIA patients are similar to those reported for patients with other conditions.

Mortality, as well as the overall incidence of SAEs during Study 2301 and Study 2305, did not differ between canakinumab and placebo. The most commonly reported SAEs for both treatments groups were relatively infrequent (≤ 2%) and included MAS and juvenile arthritis. More patients treated with canakinumab experienced AEs compared with placebo, and the most common AEs that occurred more frequently in canakinumab-treated patients included arthralgia, cough, pyrexia, abdominal pain, and pain in extremity. However, withdrawal due to adverse events (WDAEs) was infrequent in the O/L run-in phase of Study 2301, and no patients in the canakinumab treatment groups discontinued due to AEs.

Some AEs of particular interest were identified by CADTH based on the canakinumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of MAS (which is a life-threatening complication of sJIA), serious infections, malignancies, neutropenia, uveitis, and abnormalities of growth. There were fewer cases of adjudicated MAS in the canakinumab groups compared with placebo in both trials. MAS, also referred to as histiocytosis hematophagic, accounted for the two deaths that occurred in Study 2301 and was the most frequently reported SAE. Experience from specialists' clinical practice indicated that the incidence of MAS observed in the trials was not higher than would be expected in real-life patients with sJIA. Results for serious infections and malignancies were characterized by low and similar proportions of patients experiencing the event in both treatment groups in Study 2301 and Study 2305. A few cases of neutropenia were reported in patients receiving canakinumab, while few patients receiving placebo experienced AEs of uveitis. No data were reported for abnormalities of growth.

No data were available to directly or indirectly compare the potential harms of canakinumab versus other drugs used in sJIA.

Conclusions

The results of Study 2305 demonstrated that canakinumab is superior to placebo in achieving a treatment response in patients with sJIA, as reflected by the significantly greater proportion of canakinumab-treated patients who achieved adapted ACR Pedi 30, 50, 70, 90, and 100 responses at day 15. The results of the withdrawal Study 2301 demonstrated that canakinumab treatment is associated with sustained efficacy in patients with sJIA who had previously responded to canakinumab, as reflected by a significant reduction in the risk of a disease flare compared with placebo. In addition, the results of the Study 2301 demonstrated that canakinumab is associated with a reduced risk of disease worsening and a higher likelihood of inactive disease compared with placebo. Canakinumab was associated with a statistically and clinically significant improvement in HRQoL, reduced pain and improved functionality compared with placebo in Study 2305. While the effects of canakinumab on these outcomes did not reach statistical significance compared with placebo in Study 2301, this is likely attributable to the limitations associated with the withdrawal design of Study 2301, which might have reduced the likelihood of demonstrating differences between treatments. Overall, the harms reported for Study 2301 and Study 2305, as well as the results of a long-term O/L extension study, did not raise any new

concerns regarding the safety of canakinumab. The comparative efficacy of canakinumab versus other relevant treatments has not be studied directly, [redacted] While both Study 2305 and Study 2301 included patients who had prior treatment experience with oral steroids, a DMARD or a biologic drug that was discontinued due to lack of efficacy or tolerability, few patients had been treated previously with tocilizumab. Therefore, there is a dearth of evidence regarding the efficacy of canakinumab in patients who have discontinued tocilizumab treatment due to an insufficient response or intolerance.

TABLE 1: SUMMARY OF RESULTS

	Study 2301 (Double-Blind Phase)		Study 2305	
	Canakinumab N = 50	Placebo N = 50	Canakinumab N = 43	Placebo N = 41
A. Adapted ACR Pedi Response				
Proportions of Adapted ACR Pedi Responders at Study End				
ACR Pedi 30, n (%)	NR		36 (84) at Day 15	4 (10) at Day 15
OR (95% CI), *P* value			**62 (13 to 306), *P* < 0.0001**	
ACR Pedi 90, n (%)			20 (47)	1 (2)
OR (95% CI), *P* value			**41 (5 to 315), *P* < 0.0001**	
ACR Pedi 100, n (%)			14 (33)	1 (2)
OR (95% CI), *P* value			**23 (3 to 183), *P* < 0.0001**	
Time to a Worsening in ACR Pedi Level				
HR (95% CI), *P* value	**0.49 (0.27 to 0.90), *P* = 0.0131**		nr	
B. Disease Activity				
Time to Flare Events				
HR (95% CI), *P* value	**0.36 (0.17 to 0.75), *P* = 0.0032**		nr	
C. Health-Related Quality of Life and Functional Outcomes				
CHAQ Disability Score – Change from Baseline				
LS Mean ± SE	0.1184 ± 0.17592	0.1258 ± 0.18241	–0.9 ± 0.15	–0.2 ± 0.20
Difference to PL (95% CI), *P* value	-0.0073 (-0.1407 to 0.1260), *P* = 0.4571 (ns)		**–0.69 (–1.05 to –0.32), *P* = 0.0002**	
Patient's Pain Intensity	**Change from Baseline**		**Between-Group Difference at Week 4**	
LS Mean ± SE	–7.1 ± 5.85	–3.6 ± 6.06	20.6 ± 5.59	62.5 ± 9.70
Difference to PL (95% CI), *P* value	–3.54 (–7.84 to 0.77), *P* = 0.0536 (ns)		**–41.86 (–59.81 to –23.90), *P* < 0.0001**	
CHQ-PF50 Physical Health Score – Change from Baseline				
LS Mean ± SE	3.9 ± 2.54	–0.3 ± 2.53	16.9 ± 3.46	4.9 ± 3.97
Difference to PL (95% CI), *P* value	4.2 (–0.1 to 8.4), *P* = 0.0280 (ns)		**12.07 (4.65 to 19.48), *P* = 0.0012**	
CHQ-PF50 Psychosocial Health Score – Change from Baseline				
LS Mean ± SE	2.5 ± 1.88	–0.5 ± 1.86	6.2 ± 2.15	–1.1 ± 2.49
Difference to PL (95% CI), *P* value	3.0 (–0.2 to 6.1), *P* = 0.0328 (ns)		**7.28 (2.61 to 11.94), *P* = 0.0017**	
D. Key Harms Outcomes				
Mortality, n (%)	0	1 (2.0)	0	0
SAEs, n (%)	6 (12.0)	6 (12.0)	2 (4.7)	2 (4.9)
AEs, n (%)	40 (80)	35 (70)	24 (56)	16 (39)
WDAEs, n (%)	0	6 (12.0)	0	0

	Study 2301 (Double-Blind Phase)		Study 2305	
	Canakinumab N = 50	Placebo N = 50	Canakinumab N = 43	Placebo N = 41
Notable Harms, n (%)				
Infections: SAEs	2 (4.0)	2 (4.0)	2 (4.7)	1 (2.4)
Neutropenia: AEs	0	0	0	0
Neutropenia: SAEs	0	0	1 (2.3)	0
Malignancies: SAEs[a]	1 (2.0)	1 (2.0)	1 (2.3)	1 (2.4)
Adjudicated MAS	0	1 (2.0)	2 (4.7)	4 (9.8)
Uveitis: AEs	0	1 (2.0)	0	1 (2.4)

AE = adverse event; CI = confidence interval; HR = hazard ratio; LS = least square; MAS = macrophage activation syndrome; NR = not reported; ns = non-significant; OR = odds ratio; PL = placebo; SAE = serious adverse event; SE = standard error; WDAE = withdrawal due to adverse event.
Note: *P* values are statistically significant on a one-sided significance level of 0.025.
[a] All but one reported cases of malignancies fell under the preferred term of histiocytosis hematophagic (MAS).
Sources: Clinical Study Report 2301;[14] Clinical Study Report 2305[15]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disorder diagnosed in children 16 years or younger, primarily affecting joints.[1-4] It is defined as arthritis of unknown etiology persisting for ≥ 6 weeks with exclusion of other known conditions.[1-4] 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," an older terminology that is no longer in use.[2,16]

JIA is a relatively common chronic childhood disease,[1,4] with a prevalence reaching approximately 1 out of 1,000 children in Canada[2] and elsewhere.[1] 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, cataract, and loss of vision. According to various sources, uveitis may occur with an incidence of up to 20%.[2]

1.1.1 Systemic Juvenile Idiopathic Arthritis

Systemic onset JIA (sJIA) is a subtype of JIA recognized by the International League of Associations for Rheumatology (ILAR) accounting for approximately 4% to 15% of patients with JIA.[5,6] sJIA is defined as arthritis in one or more joints for at least 6 weeks in a child younger than 16 years with or preceded by fever of at least 2 weeks that is documented to be daily for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis.[5,6] The clinical experts consulted indicated that sJIA is characterized by an intense inflammatory state; several patients present with a particularly refractory course, associated with persistent disease.[5,6] As a result, these patients are at high risk for serious complications such as joint damage and growth impairment.[5,6]

Patients with sJIA are also at particularly high risk of developing macrophage activation syndrome (MAS), a life-threatening complication characterized by an overwhelming inflammatory reaction.[7] Between 10% and 15% of children with sJIA develop overt clinical features of MAS,[5-7] but an even higher prevalence of subclinical MAS is suspected.[7] The main symptoms of MAS include fever, organomegaly, cytopenias, liver dysfunction, coagulopathy resembling disseminated intravascular coagulation, hyperferritinemia, and other laboratory abnormalities.[5-7] MAS is associated with a mortality rate in children with sJIA that is estimated at 6% in hospitalized patients, but may be overall as high as 20% according to various references.[5-8]

1.2 Standards of Therapy

Therapy for sJIA targets the active inflammatory process in order to control the symptoms and prevent the complications associated with the condition.[5,6] The systemic subtype of JIA is distinct from other categories in that both interleukin-1 and interleukine-6 play a central role in the underlying inflammation process.[5-7] In clinical practice, the goal of therapy is remission or inactive disease, and treatment is indefinite. The choice of a therapeutic drug is based on the presence or absence of systemic features, the number of active joints, and the physician global assessment of the patient.

Initial therapeutic options recommended by the 2013 American College of Rheumatology (ACR) Recommendations for the Medical Therapy of Children with sJIA[5,6] include nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These medications usually relieve joint pain and inflammation; however, they do not prevent disease progression. In addition, they are associated with numerous safety issues[3,17,18] and their long-term use is not recommended.[5,6]

The 2013 ACR Guidelines also recommends the interleukin-1 inhibitor anakinra as an initial therapeutic option in patients with a higher degree of disease activity.[5,6] As interleukins play a key role in the inflammatory process of sJIA, interleukin inhibitors typically show good effectiveness in these hard-to-treat patients.[11] However, according to the pediatric clinical expert consulted and the patient input received by CADTH, anakinra does not come early in the treatment line in clinical practice due to its inconvenient mode of administration. The subcutaneous (SC) injections appear to be particularly painful, especially for a population consisting of children, and have to be repeated every day, resulting in a significant impact on quality of life. The interleukin-6 inhibitor tocilizumab and the interleukin-1 inhibitor canakinumab are recommended as a second-line treatment option in the presence of continued disease activity. Tocilizumab and canakinumab are the only treatment options having a Health Canada indication for the systemic subtype of JIA.[19] Tocilizumab is administered as an intravenous (IV) infusion every two weeks. Canakinumab will be reviewed in the present report.

Other recommended treatment options include the disease-modifying antirheumatic drug (DMARD) methotrexate or a biologic drug.[5,6] In clinical practice however, the role of these drugs is evolving, as some references even question their effectiveness for the systemic subtype of JIA.[8,11,20] Methotrexate is the most widely used DMARD in clinical practice.[3,21]Potential adverse events (AEs) of importance include liver and pulmonary toxicities, hematologic abnormalities, and malignancies.[3,21] Biologic drugs include tumour necrosis factor-alpha inhibitors (adalimumab, etanercept, and infliximab) and the T-cell inhibitor abatacept. These may be used in the absence of systemic features only. Drawbacks include the absence of a Health Canada indication for the systemic subtype of JIA, limited availability of long-term safety data in children, as well as concerns regarding potential serious toxicities including increased risk of infections, autoimmune disorders, and pediatric malignancies.[22-25]

Key characteristics for each comparator are provided in Table 2. Of note, flares are usually controlled using additional treatment that may be withdrawn once the symptoms are controlled. Individual response to each of the aforementioned treatment can vary significantly, as patients with the systemic form of JIA present with a disease that is typically harder to treat. However, therapeutic options are limited. According to the pediatric clinical expert consulted, convenience of administration is one of the main drivers of treatment choice. Convenience of administration was also noted as a significant concern in the patient input received by CADTH.

TABLE 2: KEY CHARACTERISTICS OF PHARMACOLOGICAL TREATMENTS FOR SYSTEMIC JIA

	NSAIDs[17]	Corticosteroids [18]	Methotrexate[21]	Biologics		Interleukin Inhibitors	
				TNF-alpha inhibitors[22-24]	Abatacept[25]	Anakinra[26]	Tocilizumab[19]
Mechanism of Action	Inhibition of cyclooxygenase.	Decrease of inflammation through multiple mechanisms.	Immunomodulator and inhibitor of purine synthesis.	**Adalimumab**: human anti-TNF-alpha immunoglobulin monoclonal antibody. **Etanercept**: humanized soluble TNF receptor. **Infliximab**: human and mouse derived chimeric anti-TNF-alpha antibody.	T-cell costimulatory pathway inhibitor.	Recombinant, non-glycosylated version of the human **interleukin-1** receptor antagonist.	Recombinant humanized anti-human **interleukin-6** receptor monoclonal antibody.
Relevant Health Canada Indication	Inflammatory disorders including RA / Mild-to-moderate pain associated with inflammation, including joint pain.	Rheumatic disorders: adjunctive therapy in various disorders such as RA (including JIA).	Use as a DMARD in severe disabling RA (adult population; safety / effectiveness in pediatric patients not established).	**Adalimumab**: Moderately to severely active pJIA in patients ≥ 2 years with inadequate response to ≥ 1 DMARD (with MTX, unless intolerance to MTX or if continued MTX not appropriate). **Etanercept**: Moderately to severely active pJIA in patients 4-17 years with inadequate response to ≥ 1 DMARD. **Infliximab**: With MTX, moderately to severely active RA; safety/efficacy in JIA children not established.	Moderately or severely active pJIA in children ≥ 6 years with inadequate response to ≥ 1 DMARDs.	Active RA in patients ≥ 18 years of age, for inhibiting the progression of structural damage despite treatment with MTX.	Active sJIA in patients ≥ 2 years of age, with inadequate response to previous therapy with one or more NSAIDs and systemic corticosteroids.
Route of Administration	PO	PO	PO, SC	**Adalimumab** and **Etanercept**: SC **Infliximab**: IV	IV	SC daily	IV
Recommended Dose	Dosage according to drug selected, administered every day in divided doses.	Dosage according to drug selected, administered daily.	15 mg/m^2 or 0.5 mg/kg once a week	**Adalimumab**: 24 mg/m^2 body surface area every other week (max 20 mg between 2 and 4 years and 40 mg if ≥ 4 years old). **Etanercept**: 0.4 mg/kg twice weekly (max 25 mg)	**< 75 kg**: 10mg/kg **≥ 75 kg**: Adult dose (max 1,000 mg) on week 0, 2, 4,	No pediatric dosage specified in Health Canada product monograph.	**< 30 kg**: 12 mg/kg **≥ 30 kg**: 8 mg/kg q two weeks as an IV infusion over 1 hour.

	NSAIDs[17]	Corticosteroids [18]	Methotrexate[21]	Biologics		Interleukin Inhibitors	
				TNF-alpha inhibitors[22-24]	Abatacept[25]	Anakinra[26]	Tocilizumab[19]
				Infliximab: 3 mg/kg to 5 mg/kg day 0, 2, 6, then q 8 weeks	then q 4 weeks		Alone or with MTX.
SAEs / Main Safety Issues[a]	– GI AEs – Increased risk of CV events	GI AEs; infections; mental or mood disturbances; growth suppression; fluid, endocrine, metabolic disturbances.	– Liver / hematologic toxicity – Infections	– Serious infections – Autoimmune disorders – Lymphoma and other pediatric malignancies		– Serious infections – Severe allergic reactions	– Serious infections – Malignancies
Other	Do not delay or prevent joint damage.	– Do not affect disease progression. – Abrupt discontinuation = adrenocortical insufficiency.	DMARDs leflunomide and sulfasalazine are not used in sJIA.	– Limited long-term safety data available in children. – Hold treatment in the event of active infection. – Administration of live vaccines contraindicated.		– Painful injections. – Daily regimen disadvantage.	– Only comparator with Health Canada indication for sJIA.

AE = adverse event; CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; GI = gastrointestinal; IV = intravenous; JIA = juvenile idiopathic arthritis; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; pJIA = polyarticular course juvenile idiopathic arthritis; PO = orally; q = every; RA = rheumatoid arthritis; sJIA = systemic juvenile idiopathic arthritis; SC = subcutaneous; SAE = serious adverse event; TNF = tumour necrosis factor.

[a] Note: Macrophage activation syndrome (MAS) is a notable harm associated with sJIA, regardless of treatment.

Additional references: [2,3]

1.3 Drug

Canakinumab is a fully human monoclonal antibody that selectively binds and neutralizes interleukin 1-beta.[9,10] Through its activity, it prevents gene activation and the production of downstream inflammatory mediators induced by interleukin-1 beta, which plays a key role in the inflammatory process of sJIA.[5,6,9-11] Canakinumab has a Health Canada indication for the management of active sJIA in patients 2 years and older.[10] The recommended dose of canakinumab is 4 mg/kg (up to a maximal dose of 300 mg) administered every 4 weeks through SC injection.[10]

Indication under review
Treatment of active systemic juvenile idiopathic arthritis in patients 2 years and older
Reimbursement criteria requested by sponsor
Treatment of active systemic juvenile idiopathic arthritis in patients 2 years and older who are contraindicated to, or have discontinued, any biologic therapy for lack of efficacy or intolerance

Canakinumab is also indicated for the ongoing management of cryopyrin-associated periodic syndromes (CAPS), in adults and children two years and older.[10]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of canakinumab subcutaneous injection for the management of active sJIA in patients ≥ 2 years.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Patients 2 years and older with active sJIA • Potential subgroup: patients contraindicated to, or who have discontinued any biologic therapy (including tocilizumab) for lack of efficacy or intolerance
Intervention	Canakinumab 4 mg/kg (up to a maximum of 300 mg) SC injection every 4 weeks
Comparators	**Key comparators:** Interleukin inhibitors: • Anakinra SC injection daily • Tocilizumab IV infusion every 2 weeks[a] **Other comparators, used alone or in combination:** Other biologic drugs (abatacept, adalimumab, etanercept, infliximab), DMARDs (methotrexate, leflunomide), corticosteroids, NSAIDs
Outcomes	**Key efficacy outcomes:** ACR Pedi response Disease activity including but not limited to: • absence of systemic features • number of joints affected • absence of disease flares • steroid tapering Health-related quality of life (e.g., CHQ) Functional and disability outcomes (e.g., CHAQ index) Pain reduction measured on a validated scale Patient's or parent's treatment satisfaction **Harms outcomes:** Mortality, SAEs, WDAEs AEs including but not limited to: • serious infections • neutropenia • pediatrics malignancies Notable complications including but not limited to: • abnormalities of growth • MAS • Uveitis
Study Design	Published and unpublished RCTs

ACR Pedi = American College of Rheumatology Pediatric; AE = adverse event; CHQ = Child Health Questionnaire; CHAQ = Child Health Assessment Questionnaire; DMARD = disease-modifying antirheumatic drug; IV = intravenous; MAS = macrophage activation syndrome; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; sJIA = systemic juvenile idiopathic arthritis; WDAE = withdrawal due to adverse event.

[a] Tocilizumab is the only comparator having a Health Canada indication for sJIA (administered as an intravenous infusion).

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 & 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 Ilaris (canakinumab).

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. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 28, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on May 18, 2016. 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 (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. 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 through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH 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; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

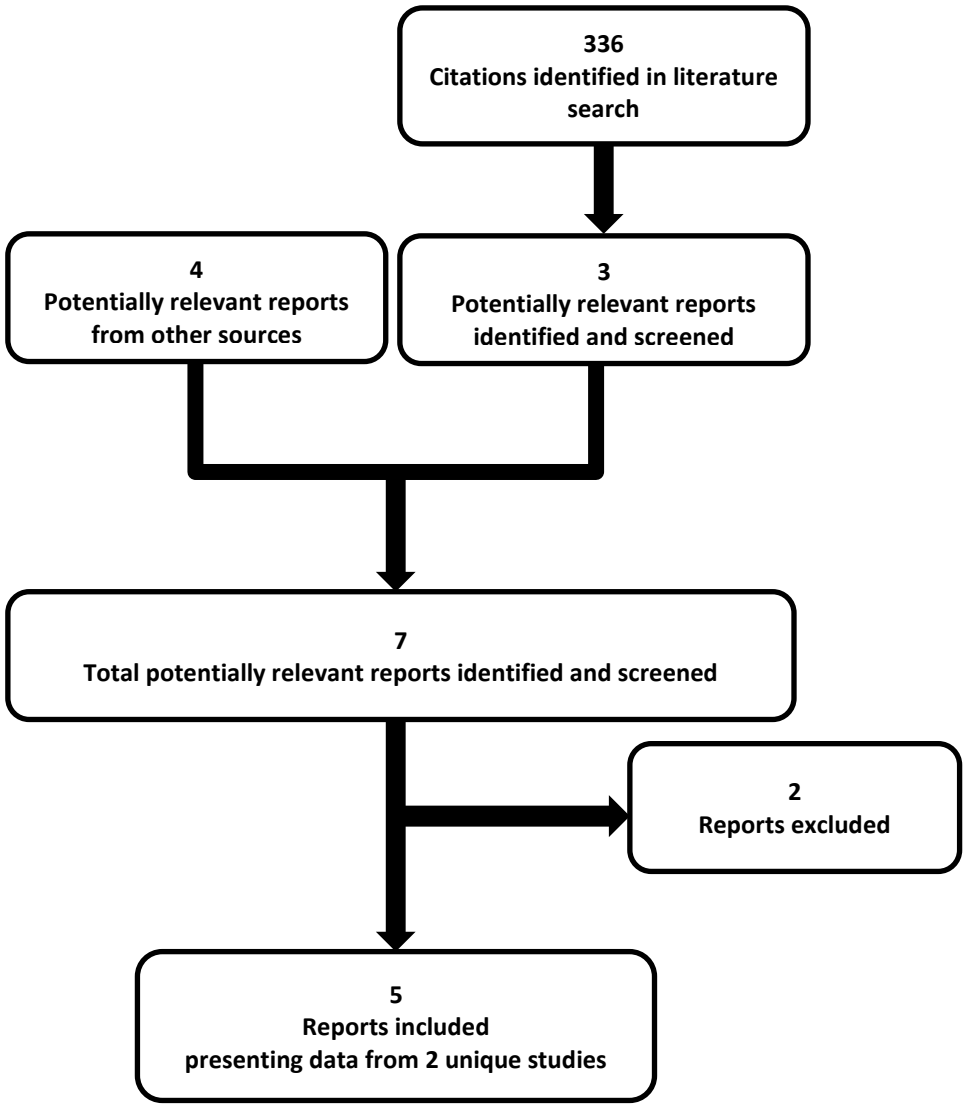


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 2301	Study 2305 Beta-SPECIFIC 1
DESIGNS AND POPULATIONS	**Study Design**	DB PL-controlled RCT (withdrawal study of flare prevention)	DB PL-controlled RCT (single-dose study)
	Locations	Multi-centre (21 countries): Europe, US, Canada, Latin America.	Multi-centre (18 countries): Europe, US, Latin America.
	Randomized (N)	N = 100	N = 84
	Inclusion Criteria	Patients ≥ 2 and < 20 years with diagnosis of sJIA: arthritis in ≥ 1 joints with or preceded by fever of ≥ 2 weeks duration that is daily/ quotidian for ≥ 3 days and accompanied by evanescent non-fixed erythematous rash, generalized lymph node enlargement, hepatomegaly / splenomegaly, and/or serositis. Active disease at enrolment was defined as ≥ 2 joints with active arthritis, spiking intermittent fever > 38°C, and elevated C-reactive protein.	
	Exclusion Criteria	MAS within 6 months; recent use of biologic therapies or prohibited medication; live vaccines within 3 months; underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions, including liver disease and impaired renal function; risk factors for tuberculosis; malignancy within five years; active or recurrent infection, including HIV or hepatitis B or C.	
DRUGS	**Intervention**	**O/L Run-in:**[a] Canakinumab 4 mg/kg SC every 4 weeks for all included patients **DB Phase:** Canakinumab 4 mg/kg SC every 4 weeks	Canakinumab 4 mg/kg SC injection on day 1
	Comparator(s)	**DB Phase:** Placebo SC every 4 weeks	Placebo SC injection on day 1
DURATION	**Phase**		
	O/L run-in	Maximum of 32 weeks Median exposure of 113 days (16.1 weeks)	None
	Double blind	Median exposure of 222 days (31.7 weeks) with canakinumab Median exposure of 164 days (23.4 weeks) with placebo	4 weeks
	O/L follow-up	Median exposure of 166 weeks (3.2 years) in O/L extension Study 2301E1	
OUTCOMES	**Primary End Point**	**O/L Run-in:** Proportion of patients on oral steroids at entry who were able to taper steroid. **DB Phase:** Time to a flare event.	Proportion of patients who responded to treatment at day 15 according to the adapted ACR Pedi 30 criteria.
	Other End Points	CHAQ CHQ Pain assessment	

NOTES		
	Publications	[12]

ACR Pedi = American College of Rheumatology Pediatric; CHQ = Child Health Questionnaire; CHAQ = Child Health Assessment Questionnaire; DB = double blind; HIV = human immunodeficiency virus; MAS = macrophage activation syndrome; O/L = open-label; PL = placebo; RCT = randomized control trial; SC = subcutaneous.
[a] The O/L run-in for Study 2301 aimed to identify canakinumab responders, and to allow steroid tapering prior to the DB phase.
Note: 4 additional reports were included.[9,14,15,27]
Sources: Clinical Study Report 2301;[14] Clinical Study Report 2305[15]

3.2 Included Studies

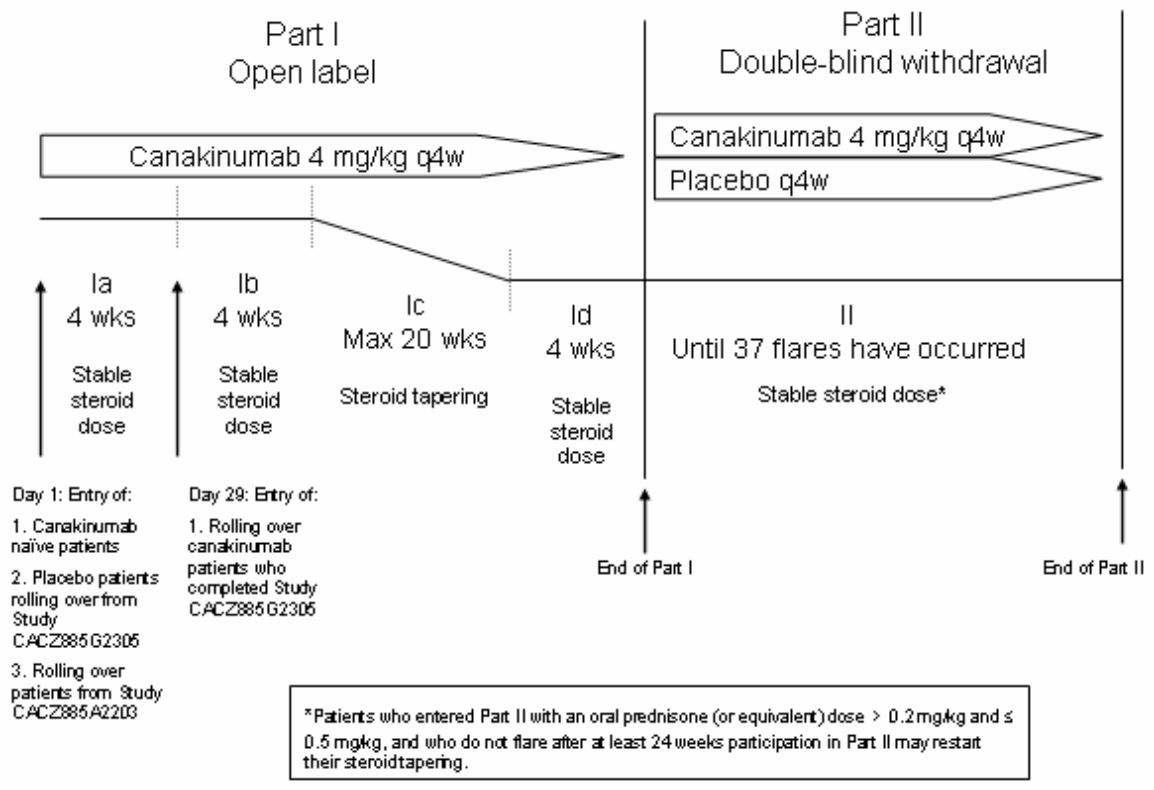
3.2.1 Description of Studies

Two published, manufacturer-sponsored, double-blind (DB) placebo-controlled RCTs were included in the systematic review.

Study 2301 (n = 100)[12] evaluated the superiority of canakinumab compared with placebo based on the primary outcome of time to flare events, using a flare prevention design (randomized treatment withdrawal of responder patients). The purpose of the study was to demonstrate the sustained efficacy of canakinumab, as well as the ability of the drug to allow steroid tapering. The study design is illustrated in Figure 2.

Study 2301 included an open-label (O/L) active treatment period where all included patients received canakinumab 4 mg/kg administered subcutaneously (SC) every 4 weeks, with the objective of inducing and maintaining at least an adapted ACR Pedi 30 response. Patients who did not meet the adapted ACR Pedi 30 criteria at day 15 or at any time afterward in the study were discontinued. After 8 weeks of canakinumab treatment, responders were allowed to reduce or eliminate concomitant oral steroid use before the beginning of the DB phase. Patients who maintained at least an ACR Pedi 30 response after a minimum of 12 weeks of treatment with canakinumab, in addition to receiving a stable dose of concomitant oral steroids (if any) for a minimum of 4 weeks, were randomized in the DB phase to receive either canakinumab 4 mg/kg or placebo administered SC every 4 weeks. Steroid tapering could be restarted in the absence of disease flare after a minimum of 24 weeks of treatment in the DB phase.

FIGURE 2: DESIGN OF INCLUDED STUDY 2301 — WITHDRAWAL STUDY OF FLARE PREVENTION



Source:[14]

Study 2305 (n = 84)[12] evaluated the superiority of canakinumab compared with placebo based on the proportions of patients who achieved at least an adapted ACR Pedi 30 response after 15 days of treatment. Patients were randomized to receive a single dose of either canakinumab 4 mg/kg or placebo administered SC on day 1 and were followed for a total of 4 weeks. Patients who did not show clinical improvement before day 15, or who did not achieve an adapted ACR Pedi 30 response at day 15, were discontinued from the study.

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients were eligible for Study 2301 and Study 2305 if they were at least 2 years but less than 20 years with a confirmed diagnosis of sJIA as per the International League Against Rheumatism (ILAR) definition, that is, arthritis in one or more joints with or preceded by fever of at least 2 weeks duration that is documented to be daily/quotidian for at least 3 days and accompanied by one or more of the following: evanescent non-fixed erythematous rash, generalized lymph node enlargement, hepatomegaly or splenomegaly, and serositis. Diagnosis of sJIA was to be confirmed at least 2 months before enrolment, with an onset of disease before 16 years of age.

Participation in the trial required active disease at the time of enrolment, defined as having at least two joints with active arthritis; spiking, intermittent fever > 38°C for at least 1 day during the screening period and within 1 week before first treatment dose; and elevated C-reactive protein (CRP) > 30 mg/L.

Key exclusion criteria included diagnosis of active MAS within 6 months. Patients were also excluded if they had recent use of biologic therapies (within days or week), prohibited medication, or live vaccines within 3 months. The presence of the following comorbidities also excluded patients from the trials: underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions, including liver disease or liver injury, as well as moderate to severe impaired renal function or evidence of urinary obstruction or difficulty in voiding; presence of any of the risk factors for tuberculosis; history of malignancy within 5 years; active or recurrent bacterial, fungal or viral infection, including HIV or hepatitis B or C.

b) Baseline characteristics

Details regarding baseline characteristics are provided in Table 5. There were a few imbalances in baseline characteristics between treatment groups in Study 2301 and Study 2305, none of which, however, were considered a significant source of concern according to the clinical experts consulted. Imbalances in characteristics that are likely reflective of disease severity did not systematically align to suggest that any particular treatment group may have a significantly higher level of disease severity. Patients randomized in Study 2301 and Study 2305 had a mean age of 9 years. Patients from all relevant age categories (2 to < 20 years) were included in the trials. The majority of patients were Caucasian.

Disease Characteristics — Study 2301

The median disease duration in Study 2301 was 2.7 years in the canakinumab group and 1.8 years in the placebo group. Most patients experienced between 1 and 5 disease flare in the previous year. The mean number of active joints, as well as the mean number of joints with limitation of motion, ranged between 11 and 12 among treatment groups; 10% of patients had more than 26 active joints at study entry.

A total of 62% of patients received concomitant oral steroid at baseline, at a mean dose of 0.3mg/kg/day to 0.4 mg/kg/day of prednisone equivalent. Approximately half of patients received concomitant methotrexate. As for prior use of a biologic drug, 50% of patients in the canakinumab group and 40% of patients in the placebo group had previous experience with anakinra, while n = 4 patients in the canakinumab group and n = 1 patient in the placebo group had previous experience with tocilizumab. Prior use of TNF-alpha inhibitors or other biologic drug was reported in 26% of patients.

Disease Characteristics – Study 2301

The median disease duration in Study 2305 was 2 years in both treatment groups. The mean number of flares in the previous year was 2.4 in the canakinumab group and 3.7 in the placebo group. Patients in the canakinumab group had a mean number of 16 active joints, and a mean number of 14 joints with limitation of motion. In the placebo group, the mean number of active joints, as well as the mean number of joints with limitation of motion, was 12. A total of 21% of patients in the canakinumab group and 12% of patients in the placebo group had more than 26 active joints at study entry.

A total of 70% of patients received concomitant oral steroid at baseline, at a mean dose of 0.4 mg/kg/day of prednisone equivalent in the canakinumab group and 0.9 mg/kg/day in the placebo group. More than half of patients received concomitant methotrexate. As for prior use of a biologic drug, 37% of patients had previous experience with anakinra, while n = 1 patient in the canakinumab group and n = 2 patients in the placebo group had previous experience with tocilizumab. Prior use of TNF-alpha inhibitors or other biologic drug was reported in 36% of patients.

Prior Experience with Other Treatment Options

Both Study 2301 and Study 2305 included a proportion of patients who had previous experience with oral steroids, a DMARD, and/or a biologic drug. In Study 2301, 62% of patients randomized to the DB

phase were using oral steroids, and 54% were using methotrexate, at baseline. In Study 2305, 70% of patients were using oral steroids, and 63% were using methotrexate, at baseline.

Prior experience with anakinra was reported in 45% of patients in Study 2301, and 37% of patients in Study 2305. Only a few patients previously used tocilizumab (5% of patients randomized in Study 2301 and 4% of patients in Study 2305). In both trials, the most common reasons for discontinuation of anakinra or tocilizumab were lack of efficacy or tolerability. A total of 26% of patients in Study 2301, and 36% of patients in Study 2305, reported prior use of other biologic drugs, mainly etanercept, which was almost exclusively discontinued due to lack of efficacy. Details are provided in Table 6.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Baseline Characteristics	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Age					
Mean ± SD, years	8.7 ± 4.5	9.1 ± 4.2	9.0 ± 4.8	8.3 ± 5.1	9.7 ± 4.3
Age Categories, n (%)					
2 to < 4 years	21 (12)	5 (10)	5 (10)	9 (21)	0
4 to < 6 years	32 (18)	5 (10)	11 (22)	8 (19)	7 (17)
6 to < 12 years	76 (43)	24 (48)	18 (36)	14 (33)	22 (54)
12 to < 20 years	48 (27)	16 (32)	16 (32)	12 (28)	12 (29)
Gender, n (%)					
Male	79 (45)	22 (44)	23 (46)	16 (37)	18 (44)
Female	98 (55)	28 (56)	27 (54)	27 (63)	23 (56)
Disease Duration — Years					
Median	2.1	2.7	1.8	2.3	2.0
Interquartile range	0.8 to 4.3	1.3 to 6.2	0.4 to 4.3	1.0 to 4.7	1.2 to 5.2
Presence of Systemic Signs After the First 6 Months of Disease					
n, (%)	148 (84)	45 (90)	36 (72)	33 (77)	34 (83)
Number of Flares in the Past 12 Months, n (%)					
Mean ± SD	NR	NR	NR	2.4 ± 1.9	3.7 ± 3.7
Number of Active Joints					
Mean ± SD	14.9 ± 13.7	10.5 ± 11.2	11.6 ± 10.7	15.8 ± 15.3	12.4 ± 12.2
> 26 joints, n (%)	34 (19)	5 (10)	5 (10)	9 (21)	5 (12)
Number of Joints with Limitation of Motion					
Mean ± SD	14.7 ± 14.4	10.8 ± 12.6	12.3 ± 12.2	14.3 ± 15.0	12.4 ± 12.9
Physician's Global Assessment of Disease Activity (100 mm VAS — 100 representing the worst score)					
Mean ± SD, mm	66.5 ± 18.9	60.0 ± 21.1	64.7 ± 17.8	65.3 ± 19.1	65.7 ± 19.6
Patient's/Parent's Global Assessment of Overall Well-Being (100 mm VAS — 100 representing the worst score)					
Mean ± SD, mm	60.7 ± 25.6	58.1 ± 24.3	60.5 ± 26.2	62.9 ± 24.6	55.6 ± 31.8

DB = double blind; NR = not reported; O/L = open label; PL = placebo; SD = standard deviation; VAS = visual analogue scale.
Sources: Clinical Study Report 2301: p .110-7, p. 351-60;[14] Clinical Study Report 2305: p.75-9, p. 148-51;[15] Ruperto et al. 2012: p.2,400.[12]

TABLE 6: PRIOR EXPERIENCE WITH OTHER TREATMENT OPTIONS

Baseline Characteristics	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Oral Prednisone Equivalent at Baseline					
n (%)	128 (72)	32 (64)	30 (60)	31 (72)	28 (68)
Mean dose ± SD, mg/kg/day	0.4 ± 0.3	0.3 ± 0.3	0.4 ± 0.3	0.4 ± 0.2	0.9 ± 2.8
Use of Methotrexate at Baseline					
n (%)	93 (53)	28 (56)	26 (52)	29 (67)	24 (59)
Prior Use of Interleukin Inhibitors, n (%)					
Anakinra	83 (47)	25 (50)	20 (40)	16 (37)	15 (37)
Reasons for discontinuation:					
Lack of efficacy	37 (21)	7 (14)	6 (12)	6 (14)	3 (7)
Lack of tolerability	20 (11)	10 (20)	4 (8)	3 (7)	4 (10)
Other	33 (19)	12 (24)	10 (20)	8 (19)	8 (20)
Tocilizumab	10 (6)	4 (8)	1 (2)	1 (2)	2 (5)
Reasons for discontinuation:					
Lack of efficacy	7 (4)	2 (4)	0	1 (2)	1 (2)
Lack of tolerability	4 (2)	3 (6)	1 (2)	0	2 (5)
Prior Use of Other Biologic Drugs (Anti-TNF or Other), n (%)					
Overall	62 (35)	14 (28)	12 (24)	14 (33)	16 (39)
Prior use of individual drugs:					
Etanercept	56 (32)	13 (26)	11 (22)	13 (30)	15 (37)
Reasons for discontinuation:					
Lack of efficacy	58 (33)	13 (26)	11 (22)	13 (30)	15 (37)
Other	4 (2)	0	0	0	0
Adalimumab	9 (5)	4 (8)	2 (4)	3 (7)	4 (10)
Reasons for discontinuation:					
Lack of efficacy	9 (5)	4 (8)	2 (4)	3 (7)	4 (10)
Abatacept	0	0	0	0	0

DB = double blind; O/L = open label; PL=placebo; SD = standard deviation; TNF = tumour necrosis factor.
Sources: Clinical Study Report 2301;[14] Clinical Study Report 2305[15]

3.2.3 Interventions

Study 2301 and Study 2305 both evaluated the superiority of canakinumab compared with placebo based on a DB trial design. Study 2301 included an O/L active treatment period where all included patients received canakinumab 4 mg/kg administered SC every 4 weeks. In the DB phase of Study 2301 and in Study 2305, patients were randomized to receive either canakinumab 4 mg/kg or placebo administered SC on day 1 in the single-dose Study 2305, and every 4 weeks thereafter in Study 2301.

In both studies, concomitant use of second-line drugs in the management of sJIA was not allowed, with a few exceptions, as follows:

- doses of methotrexate were allowed up to a maximum of 20 mg/m^2/week, as long as they were stable for at least 8 weeks before the screening visit
- doses of no more than one NSAID were also allowed, as long as they were stable for at least 2 weeks before the screening visit
- doses of steroid treatment equal or less than 1.0 mg/kg/day of oral prednisone or equivalent (maximum 60 mg/day for children over 60 kg) were allowed as long as they were stable for at least 3 days before baseline.

3.2.4 Outcomes

a) Primary Efficacy Outcomes

The primary efficacy outcome for Study 2301 was time to flare events. The occurrence of flare was an assessment during the course of Study 2305, but it was not an outcome of the study. In both Study 2301 and Study 2305, flare was defined as at least one of the following:

- Reappearance of fever (> 38°C, lasting for at least two consecutive days) not due to infections; or
- Flare according to the JIA pediatric criteria for flare:
  - ≥ 30% worsening in at least 3 of the first 6 response variables; and
  - ≥ 30% improvement in not more than 1 of the first 6 response variables.

  Note:
  - if the physician or parent global assessment questionnaire was 1 of the 3 response variables used to define flare, worsening of ≥ 20 mm must have been present
  - if the number of active joints or joints with limitation of motion was one of the 3 response variables used to define flare, worsening in ≥ 2 joints must have been present
  - if CRP was used to define flare, CRP must have been > 30 mg/L.

Study 2301 also aimed to demonstrate the ability of canakinumab to allow steroid tapering, based on the proportion of patients on oral steroids at study entry who were able to taper their steroid dose throughout the O/L run-in phase duration. In order to be considered a successful steroid taperer, patients must have minimally maintained an adapted ACR Pedi 30 response, and met one of the following criteria:

- Patients with a steroid dose > 0.8 mg/kg of oral prednisone or equivalent, who were able to reduce their steroid dose to ≤ 0.5 mg/kg.
- Patients with a steroid dose ≥ 0.5 mg/kg and ≤ 0.8 mg/kg of oral prednisone or equivalent who were able to reduce their steroid dose by at least 0.3 mg/kg/day from baseline.
- Patients who were able to achieve an oral prednisone or equivalent dose ≤ 0.2 mg/kg/day.

The primary efficacy outcome for Study 2305 was the proportion of patients who responded to treatment at day 15 according to the adapted ACR Pedi 30 criteria.

The adapted ACR Pedi 30 criteria that are used in Study 2301 and in Study 2305 are in line with the ACR Pedi criteria for JIA, with the addition of a variable related to fever, which is a core sign of the systemic subtype of JIA. The adapted ACR Pedi response variables were the following:

- Physician's global assessment of disease activity on a 0 to 100 mm visual analogue scale (VAS).
- Parent's or patient's (if appropriate in age) global assessment of patient's overall well-being based upon the 0 to 100 mm VAS in the Child Health Assessment Questionnaire (CHAQ).
- Functional ability based on the CHAQ measure.
- Number of joints with active arthritis.

- Number of joints with limitation of motion.
- Laboratory measure of inflammation=, that is, CRP (mg/L).
- Absence of intermittent fever due to sJIA during the preceding week.

An adapted ACR Pedi 30 response was defined as at least 30% improvement from baseline in at least 3 of the first 6 variables in the core set, with no intermittent fever (body temperature ≤ 38°C) in the preceding week, and no more than 1 of the remaining variables worsening by more than 30%.

b) Secondary Efficacy Outcomes

Relevant secondary efficacy outcomes for Study 2301 included the following:

- Time to inactive disease and percentage of patients who would meet the definition of inactive disease on medication.
- Change in disability by use of the cross-culturally adapted and validated version of the CHAQ.
- Change in health-related quality of life (HRQoL) by use of the cross-culturally adapted and validated version of the Child Health Questionnaire (CHQ).

Relevant secondary efficacy outcomes for Study 2305 included the following:

- Various levels of adapted ACR Pedi Responses.
- Overall pain over the last week assessed on a 0 to 100 mm VAS.
- Clinical signs of response, as shown by the absence of fever.
- Change in disability by use of the cross-culturally adapted and validated version of the CHAQ.
- Change in HRQoL by use of the cross-culturally adapted and validated version of the CHQ.

Inactive disease was a secondary outcome of Study 2301. In Study 2305, inactive disease was included in the assessments during the course of the study, but it was not an outcome of the study. Inactive disease was defined as meeting all of the following:

- no joints with active arthritis
- no fever (body temperature ≤ 38°C)
- no rheumatoid rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA
- normal erythrocyte sedimentation rate or CRP
- physician's global assessment of disease activity indicating no disease activity (best possible score ≤ 10 mm).

The CHAQ is a 30-item, self- or parent-administered, reliable and sensitive instrument for measuring functional status in children with JIA.[28] The CHAQ assesses the eight following functional areas:

- dressing and grooming
- arising
- eating
- walking
- hygiene
- reach
- grip
- activities.

Responses for the 30 items are recorded using 4-point ordinal scales (0 = no difficulty, 1 = some difficulty, 2 = much difficulty, 3 = unable to do). Within each of the 8 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 8 functional areas and 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 evaluation of overall well-being.

The CHQ is a self-administered, generic, quality of life measure that assesses the physical, emotional, and social aspects of health status in children five and older and has been used to assess HRQoL in patients with JIA.[29] The questionnaire includes 14 domains and provides a physical score (PhS) and the psychosocial score (PsS) as its two summary measures.[29,30] Scores range between 0 and 100, with higher scores indicating better HRQoL.[29,31] The domains covered in the CHQ include physical health, mental health, pain, school, social, and family, and include varying response categories with measuring descriptions of 0 = poor well-being and 100 = excellent well-being.[31]

c) Harms Outcomes

Safety outcomes in Study 2301 and Study 2305 included AEs and serious adverse events (SAEs), clinical laboratory results, and vital signs.

3.2.5 Statistical Analysis

a) Statistical Methods for Study 2301

The primary objective of the O/L run-in was to assess if canakinumab allowed steroid tapering in at least 25% of the patients who were taking oral steroids at study entry. The analysis was descriptive only. The frequency and percentage of patients who were able to taper oral steroids together with a two-sided 90% exact confidence interval were presented. The statistical hypothesis was tested by means of a binomial test at the 5% level of significance.

The primary objective of Study 2301 (DB phase) was to test the superiority of canakinumab over placebo regarding the time to flare events. The two treatment groups were compared using a one-sided stratified log-rank test at the 2.5% significance level, with the stratification factors (level of corticosteroid use and level of adapted ACR Pedi response reached) entered as explanatory variables. Kaplan-Meier estimates of the probability to experience a flare event were calculated from the beginning of the DB phase. In addition, differences between treatment groups in time to event variables were analyzed using Cox's proportional hazards regression model after adjustment for the same stratification variables and presented as hazard ratios (HRs) and 95% two-sided confidence intervals.

For the primary outcome, inclusion of 29 patients per group provided 90% power to detect a treatment difference, assuming that 25% of patients receiving canakinumab and 70% of patients receiving placebo would experience a flare in the first 24 weeks of the DB phase. These calculations were based on Fisher's exact test at the 0.025 one-sided level of significance. The number of events needed to achieve that 90% power was 37 (13 events in the canakinumab and 24 events in the placebo group).

Patients who discontinued due to inactive disease for at least 24 weeks while in the DB phase were censored at the time of study discontinuation. As the purpose of the study was to show sustained efficacy, patients who flared per definition, or who discontinued prematurely from the study while in the DB phase for any reason other than inactive disease for at least 24 weeks, were counted as having a flare event in the primary efficacy analysis.

b) Statistical Methods for Study 2305

The primary objective of Study 2305 was to test the superiority of canakinumab over placebo regarding the proportion of patients who responded to study treatment at the adapted ACR Pedi 30 level. The two treatment groups were compared using the Cochran-Mantel-Haenszel test, adjusting for the following stratification factors: number of active joints (≤ 26 or > 26), non-responder to anakinra (yes or no), and level of current corticosteroid use (≤ 0.4 mg/kg or > 0.4 mg/kg oral prednisone equivalent). Criteria were determined to protect the overall false-positive rate of the trial at 0.025 for the interim and final

analyses. In addition to the one-sided *P* value, the common odds ratio was estimated together with the associated 95% two-sided confidence interval.

For the primary outcome, inclusion of 122 patients randomized and treated provided 90% power to detect a treatment difference of 30%, assuming a responder rate of 60% in the canakinumab group and of 30% in the placebo group. These calculations were based on Fisher's exact test at the 0.025 one-sided level of significance.

Patients who did not respond, or who discontinued due to any reason before day 15, were considered as non-responders in the primary efficacy analysis.

c) Analysis populations

In Study 2301 and Study 2305, the primary analysis population was the full analysis set (FAS) population. It consisted of all randomized patients who received at least one dose of study drug. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization. There was no per-protocol (PP) analysis in any of the included studies.
The safety analysis population consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received. The statement that a patient had no AEs was considered as a safety assessment.

3.3 Patient Disposition

Details regarding baseline characteristics are provided in Table 7.

a) Study 2301

A total of 177 patients were enrolled in the O/L run-in; of these, 44% of patients discontinued the study before the beginning of the DB phase. The most frequent reason for discontinuation was unsatisfactory therapeutic effect (41%).

A total of 100 (57%) patients completed the O/L run-in and were randomized into the DB phase. There was imbalance in the discontinuation rates between treatment groups, with 22% of patients who discontinued the study in the canakinumab group compared with 52% of patients in the placebo group. The most frequent reason for discontinuation was once again unsatisfactory therapeutic effect (22% in the canakinumab group and 40% in the placebo group). In the placebo group, other reasons for discontinuation included AEs (8%), protocol deviation (2%), and withdrawal of consent (2%).

b) Study 2305

A total of 84 patients were randomized in Study 2305. There was imbalance in the discontinuation rates between treatment groups, with 14% of patients who discontinued the study in the canakinumab group compared with 90% of patients in the placebo group. All discontinuations in the study were attributable to unsatisfactory therapeutic effect.

TABLE 7: PATIENT DISPOSITION

	Study 2301			Study 2305	
	O/L Run-In	DB Phase			
	Canakinumab	Canakinumab	PL	Canakinumab	PL
Enrolled, N	177	—		—	
Completed O/L Phase, n (%)	100 (57)	—		—	
Discontinued, n (%)	77 (44)	—		—	
Most frequent reasons for discontinuation in O/L run-in phase, n (%)					
Unsatisfactory therapeutic effect	72 (41)	—	—	—	—
Adverse events	4 (2)	—	—	—	—
Death	1 (<1)	—	—	—	—
Randomized — Overall	—	100		84	
Randomized — Per group	—	50	50	43	41
Completed study, n (%)	—	39 (78)	24 (48)	37 (86)	4 (10)
Discontinued, n (%)	—	11 (22)	26 (52)	6 (14)	37 (90)
Most frequent reasons for discontinuation, n (%)					
Unsatisfactory therapeutic effect	—	11 (22)	20 (40)	6 (14)	37 (90)
Adverse events	—	0	4 (8)	0	0
Protocol deviation	—	0	1 (2)	0	0
Withdrawal of consent	—	0	1 (2)	0	0
Analysis sets					
FAS, N	177	50	50	43	41
PP, N	—	—	—	—	—
Safety, N	177	50	50	43	41

FAS = full analysis set; PL = placebo; PP = per-protocol.
Note: There was no per-protocol analysis in any of the two included trials.
Sources: Clinical Study Report 2301: p. 106, p 108;[14] Clinical Study Report 2305: p. 73-4.[15]

3.4 Exposure to Study Treatments

Details regarding exposure to study treatments are provided in Table 8. In Study 2301, patients spent a mean time of 17 weeks (± 10.4) in the O/L run-in, followed by a mean duration in the DB phase of 33 weeks (± 22.0) in the canakinumab group and 26 weeks (± 18.4) in the placebo group. In Study 2305, the mean overall duration in the study was 28 days (± 4.4) in the canakinumab group and 11 days (± 8.5) in the placebo group.

TABLE 8: EXPOSURE TO STUDY TREATMENTS

	Study 2301			Study 2305	
	O/L Run-In	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Overall Duration in the Study (or Study Phase)					
	Weeks			**Days**	
Mean ± SD	17.1 ± 10.4	33.2 ± 22.0	25.9 ± 18.4	27.6 ± 4.4	10.7 ± 8.5
Range	0.6 to 33.3	1.1 to 88.1	2.7 to 81.0	15 to 34	3 to 30

DB = double blind; O/L = open-label; PL = placebo; SD = standard deviation.
Sources: Clinical Study Report 2301: p.163-4;[14] Clinical Study Report 2305: p.106.[15]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Study Design, Intervention and Comparator

Two studies were included in the systematic review, with substantial differences in trial designs.

Study 2301 was a placebo-controlled, withdrawal RCT of flare prevention that was likely conducted with methodological rigour. The withdrawal design minimized patients' exposure to placebo. As a result of this particular design, patients entering the DB phase were already considered responders. Withdrawal trials are frequent in JIA; however, they are considered less informative for clinical practice. Real-life management of sJIA is usually indefinite; however, discontinuing the medication once a treatment response is obtained may be considered under some rare circumstances according to the clinical expert, and experience suggests that stopping treatment does not systematically result in a disease flare. Therefore, the natural course of the disease in patients from the placebo group is uncertain, which may undermine the potential for canakinumab to show a statistically significant between-group difference in these circumstances. In addition, Study 2301 provides no controlled data to assess the effects of canakinumab at the beginning of treatment, which may inform clinicians' choice of therapeutic drug.

Study 2305 was a placebo-controlled, single-dose, parallel-group RCT that was likely conducted with methodological rigour. The relatively short four-week duration minimized patients' exposure to placebo. As a classic parallel-group design, patients in the canakinumab group are expected to experience substantial disease improvement, while patients randomized to placebo are expected to maintain a similar degree of disease activity, or improve slightly mainly due to the use of concomitant medication.

b) Selection, Allocation and Disposition of Patients

Study 2301 and Study 2305 were performed using appropriate allocation strategies. Randomization was performed centrally, and was stratified by the following factors:

- Study 2301: level of corticosteroid use and level of adapted ACR Pedi response reached.
- Study 2305: number of active joints, previous response to anakinra and level of current corticosteroid use.

The trials were conducted in a DB fashion, and both used a matching placebo for the comparator group, which is appropriate. There was no indication of unplanned sources of unblinding.

There were a few imbalances in baseline characteristics between treatment groups in both Study 2301 and Study 2305, none of which, however, were considered a significant source of concern according to

the clinical experts consulted. Imbalances in characteristics that are likely reflective of disease severity did not systematically align to suggest that any particular treatment group may have a significantly higher level of disease severity. However, it is impossible to exclude that randomization may not have been successful in ensuring balance in known and unknown relevant characteristics due to the small sample sizes.

In both Study 2301 and Study 2305, higher proportions of patients discontinued from the study in the placebo treatment group compared with the canakinumab group, mostly due to unsatisfactory therapeutic effect, which is not unexpected when a placebo is administered. However, the impact of this limitation on the interpretation of the findings is uncertain.

c) Outcome Measures

The outcome measures and definitions used in Study 2301 and Study 2305, including flare events, steroid tapering and adapted ACR Pedi response, are considered appropriate to evaluate treatment response in sJIA clinical trials. Patient-reported outcome measures, that is., CHAQ and CHQ, are also frequently used in JIA and are considered valid and reliable.

d) Statistical Analysis

Study 2301 and Study 2305 had sufficient power to demonstrate statistical significance for testing of the primary outcome. As the purpose of Study 2301 was to show sustained efficacy, patients who flared per definition, or who discontinued prematurely from the study while in the DB phase for any reason other than inactive disease, were counted as having a flare event in the primary efficacy analysis.

3.5.2 External Validity

a) Patient Selection

Inclusion and exclusion criteria in Study 2301 and Study 2305 appeared relevant and reasonable. Baseline characteristics were consistent with a population of patients experiencing a high degree of disease activity and refractory to initial therapeutic options. Indeed, diagnosis of sJIA was not recent based on the median disease duration; patients presented with a high number of active joints, accompanied by significant joint damage; and most patients received concomitant oral steroid or had prior use of biologic drugs. In addition, with a mean age of nine years old, patients were somewhat older compared with real-life practice. According to the clinical expert consulted, it is likely that the effectiveness and safety of canakinumab observed in such a population would translate into at least similar benefits in a population of patients with a lower disease activity.

Various groups of patients with comorbid conditions were excluded, including diagnosis of active MAS within 6 months; underlying metabolic, renal, hepatic, infectious or gastrointestinal conditions; risk factors for tuberculosis; malignancy within five years; bacterial, fungal or viral infection, including HIV or hepatitis B or C. The findings from Study 2301 and Study 2305 are not generalizable to these patients.

b) Treatment Regimen and Length of Follow-up

Study 2301 and Study 2305 used appropriate and realistic canakinumab treatment regimen for patients with sJIA. The use of placebo as a comparator in both trials yields uncertainty regarding the effects of canakinumab compared with other drugs recommended as treatment for sJIA. In order to inform this gap, additional evidence was gathered in the form of indirect treatment comparisons (ITCs).

In Study 2301, the mean overall duration of approximately 50 weeks in the canakinumab group (including the time spent in the O/L run-in) was deemed appropriate. For Study 2305, the duration of

4 weeks was considered sufficient in order to see the effect of canakinumab on the various outcome measures. Experience from clinical practice suggests response to treatment within a few weeks, and patients may continue to improve for up to three months. Therefore, results from Study 2305 may be considered conservative. The sustainability of beneficial treatment effects and long-term safety beyond the trials' duration remain uncertain.

c) Outcome Measures

In clinical practice, the goal of therapy is remission or inactive disease. In Study 2301 and Study 2305, an ACR Pedi 30 level was selected to show adequate response to treatment, as is often the case in JIA trials. This may affect generalizability, as patients only achieving an ACR Pedi 30 response in clinical practice would likely discontinue treatment for another treatment option. However, this concern is mitigated by the fact that other ACR Pedi levels were reported, in addition to analyses of patients with inactive disease.

Experience from specialists' clinical practice suggests that the instruments selected for assessment of patient-reported outcomes, although considered valid and reliable, may not be routinely used in clinical practice. In addition, they can show high variability and may not be as sensitive as objective measures, such as inactive disease.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See *0 for detailed efficacy data.*

3.6.1 Adapted ACR Pedi Response

The adapted ACR Pedi response was assessed during the course of Study 2301, as all patients continuing the study had to maintain at least an adapted ACR Pedi 30 from day 15 and onward, but it was not an outcome of the study. After a mean canakinumab treatment duration of 17 weeks in the O/L run-in phase, 77% of patients achieved an adapted ACR Pedi 30 response. Figure 3 (0) presents uncontrolled data pertaining to the various adapted ACR Pedi response levels achieved in the O/L run-in phase. Analysis of adapted ACR response during the DB phase demonstrated that the use of canakinumab was associated with a statistically significant reduction in the risk of a worsening in adapted ACR Pedi level compared with placebo, as shown by the HR = 0.49 (95% CI, 0.27 to 0.90; $P = 0.0131$). No other analyses of adapted ACR Pedi response were reported.

The primary efficacy outcome for Study 2305 was the proportion of patients who responded to treatment at day 15 according to the adapted ACR Pedi 30 criteria. At day 15 and day 29, patients receiving canakinumab were statistically significantly more likely to achieve an adapted ACR Pedi 30 response compared with patients randomized to placebo (OR = 62; 95% CI, 12 to 306; $P < 0.0001$ for both time points). Other levels of adapted ACR Pedi responses (50, 70, 90, and 100 levels) were assessed throughout the study as secondary outcomes. The proportions of responders were statistically significantly higher in patients treated with canakinumab versus placebo for all levels of adapted ACR Pedi response. These results are in Table 9. A total of 47% of patients in the canakinumab group compared with only 2% of patients in the placebo group achieved an adapted ACR Pedi 90 response (OR = 41; 95% CI, 5 to 315; $P < 0.0001$); and 33% of patients receiving canakinumab compared with 2% of patients under placebo achieved an adapted ACR Pedi 100 response (OR = 23; 95% CI, 3 to 183; $P < 0.0001$). These were considered particularly relevant and clinically meaningful according to the pediatric expert consulted, as they may be consistent with the treatment goal of remission.

The systematic review protocol included a subgroup of patients contraindicated to, or who have discontinued, any biologic therapy for lack of efficacy or intolerance. No data regarding these patients were reported in Study 2301. However, in Study 2305, a total of n = 6 patients (14%) in the canakinumab group and n = 3 patients (7%) in the placebo group had previously used and discontinued anakinra due to lack of efficacy. Of the 6 subgroup patients in the canakinumab group, a total of 5 patients were responders at day 15 (n = 2 achieved an adapted ACR Pedi 50 response, n = 1 achieved an adapted ACR Pedi 70 response, and n = 2 achieved an adapted ACR Pedi 100 response). All subgroup patients randomized to placebo failed to achieve at least an adapted ACR Pedi 30 response at day 15 (no further data shown).

3.6.2 Disease Activity

Measures of disease activity in Study 2301 and Study 2305 included the following: disease flares, inactive disease, absence of fever, and steroid tapering. No data were reported for the number of active joints or joints with limitation of motion.

a) Disease Flares / Inactive Disease

The primary efficacy outcome for Study 2301 was time to flare events. Results of Study 2301 demonstrated that the use of canakinumab was associated with a statistically significant reduction in the risk of a flare event compared with placebo, as shown by the HR = 0.36 (95% CI, 0.17 to 0.75; *P* = 0.0032). Patients who flared per definition, or who discontinued prematurely for any reason other than inactive disease, were counted as having a flare event in the primary efficacy analysis. A total of 6 patients discontinued for reasons other than flare or lack of efficacy, all from the placebo group (n = 4 patients withdrew due to AEs, n = 1 due to protocol deviation, and n = 1 due to withdrawal of consent). In a sensitivity analysis where these patients were censored at the time of study discontinuation, the use of canakinumab was associated with a non-significant reduction in the risk of a flare event compared with placebo (HR = 0.51; 95% CI, 0.23 to 1.12; *P* = 0.0445). However, censoring patients resulted in a reduction in the number of included events below the pre-specified minimum needed; therefore, the study did not have adequate power to show a statistically significant difference between treatments for such analysis.

In Study 2301, a total of 53% of patients had already achieved inactive disease upon entry into the DB phase (n = 26 randomized to receive canakinumab and n = 27 to receive placebo). At the end of the study, 62% of patients (n = 31) in the canakinumab group achieved the treatment goal of inactive disease compared to 34% of patients (n = 17) in the placebo group; the use of canakinumab was associated with a statistically significantly higher likelihood of inactive disease compared with placebo (OR = 3.4; 95% CI, 1.5 to 8.0; *P* = 0.0020). In addition, 40% of patients (n = 20) in the canakinumab group achieved ≥ 24 weeks of inactive disease compared with only 4% of patients (n = 2) in the placebo group. Finally, the use of canakinumab was associated with a non-statistically significant benefit regarding time to inactive disease compared with placebo (HR = 1.26; 95% CI, 0.79 to 1.99; *P* = 0.1446), which was a secondary outcome of the trial; however, this measure is considered less relevant due to the withdrawal trial design. Details are provided in Appendix 4 Table 12.

The occurrence of flare and inactive disease were assessed during the course of Study 2305, but were not outcomes of the study; therefore, this report shows no additional data regarding these outcomes. A total of 7% of patients (n = 3) in the canakinumab group experienced a disease flare throughout the study duration compared with 76% of patients (n = 31) in the placebo group. With the exception of three patients, all patients were non-responders at the time of the flare. On the other hand, 33% of patients (n = 14) in the canakinumab group achieved the treatment goal of inactive disease at day 15,

and 30% of patients (n = 3) still had inactive disease at day 29. No patient in the placebo group achieved inactive disease.

b) Systemic Features

Systemic features were not assessed in Study 2301. Absence of systemic features was an outcome of Study 2305, expressed as the absence of fever at day 3. All patients in the canakinumab group and 87% of patients in the placebo group achieved normal body temperature; the difference between treatment groups was statistically significant ($P = 0.0098$). Details are provided in Appendix 4 Table 13.

c) Steroid Tapering

One of the primary objectives of Study 2301 was to assess if canakinumab allowed tapering of steroids in at least 25% of the patients who entered the study taking a steroid. Uncontrolled data from the O/L run-in phase indicate that 45% of patients who were taking steroids at study entry were able to achieve successful steroid tapering ($P < 0.0001$), and that 33% of patients were steroid free. Steroid tapering was not assessed in Study 2305. Details are provided in Appendix 4 Table 14.

3.6.3 Health-Related Quality of Life and Functional Outcomes

HRQoL and functional outcomes were assessed using the CHAQ disability score (range from 0 = no disability to 3 = maximum disability) and the CHQ physical and psychosocial scores (range between 0 and 100, with higher scores indicating better HRQoL). Pain assessment on a VAS as part of the CHAQ was also reported separately (range from 0 to 100, with with higher scores indicating more intense pain). Outcome measures including HRQoL instruments are reviewed in Appendix 5, and detailed outcome data are provided in Appendix 4 Table 15 to Table 17.

All HRQoL and functional outcome results were consistent within each included study, and results should be viewed according to the study design. Results from Study 2301 showed a non-significant trend favouring canakinumab compared with placebo with regard to change from baseline in CHAQ disability score, pain intensity, and CHQ physical and psychosocial scores. Results of Study 2305 indicated that canakinumab was associated with a statistically significant and clinically meaningful benefit on HRQoL, pain and functionality compared with placebo, as measured by change from baseline in CHAQ and CHQ scores, as well as a pain intensity assessment at the study end.

3.7 Harms

Only those harms identified in the review protocol are reported below (2.2.1, Protocol). 0 has detailed harms data.

3.7.1 Adverse Events

A total of 78% of patients experienced at least one AE in the O/L run-in phase of Study 2301. In the DB phase, 80% of patients in the canakinumab group experienced AEs compared with 70% in the placebo group. In Study 2305, these proportions were 56% of patients receiving canakinumab compared with 39% in patients receiving placebo. The most common AEs reported with canakinumab (> 10% but < 25%) included arthralgia, cough, nasopharyngitis, pyrexia, upper respiratory tract infection, abdominal pain, and pain in extremity.

TABLE 9: KEY EFFICACY OUTCOMES

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
A. Adapted ACR Pedi Response				
Proportions of Adapted ACR Pedi Responders at Study End				
ACR Pedi 30, n (%)	NR		36 (84) at Day 15	4 (10) at Day 15
OR (95% CI), *P* value			**62 (13 to 306), *P* <0.0001**	
ACR Pedi 50, n (%)	NR		34 (79)	2 (5)
OR (95% CI), *P* value			**107 (16 to 701), *P* <0.0001**	
ACR Pedi 70, n (%)	NR		29 (67)	1 (2)
OR (95% CI), *P* value			**105 (12 to 923), *P* <0.0001**	
ACR Pedi 90, n (%)	NR		20 (47)	1 (2)
OR (95% CI), *P* value			**41 (5 to 315), *P* <0.0001**	
ACR Pedi 100, n (%)	NR		14 (33)	1 (2)
OR (95% CI), *P* value			**23 (3 to 183), *P* <0.0001**	
Time to a Worsening in ACR Pedi Level				
Number of events	18	29	nr	
HR (95% CI), *P* value	**0.49 (0.27 to 0.90), *P* = 0.0131**			
B. Disease Activity				
Time to Flare Events				
Number of events	11	26	nr	
HR (95% CI), *P* value	**0.36 (0.17 to 0.75), *P* = 0.0032**			
C. Health-Related Quality of Life and Functional Outcomes				
CHAQ Disability Score – Change from Baseline				
LS Mean ± SE	0.1184 ± 0.17592	0.1258 ± 0.18241	–0.9 ± 0.15	–0.2 ± 0.20
Difference to PL (95% CI), *P* value	–0.0073 (-0.1407 to 0.1260), *P* = 0.4571 (ns)		**–0.69 (–1.05 to –0.32), *P* = 0.0002**	
% change, Mean ± SD	–9% ± 101%	101% ± 323%	–69% ± 37%	–5% ± 73%
Patient's Pain Intensity	**Change from Baseline**		**Between-Group Difference at Week 4**	
LS Mean ± SE	–7.1 ± 5.85	–3.6 ± 6.06	20.6 ± 5.59	62.5 ± 9.70
Difference to PL (95% CI), *P* value	–3.54 (–7.84 to 0.77), *P* = 0.0536 (ns)		**–41.86 (–59.81 to –23.90), *P* < 0.0001**	
CHQ-PF50 Physical Health Score – Change from Baseline				
LS Mean ± SE	3.9 ± 2.54	–0.3 ± 2.53	16.9 ± 3.46	4.9 ± 3.97
Difference to PL (95% CI), *P* value	4.2 (–0.1, 8.4), *P* = 0.0280 (ns)		**12.07 (4.65 to 19.48), *P* = 0.0012**	
% change, Mean ± SD	6% ± 39%	–3% ± 84%	–466% ± 1798%	–50% ± 282%

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
CHQ-PF50 Psychosocial Health Score – Change from Baseline				
LS Mean ± SE	2.5 ± 1.88	–0.5 ± 1.86	6.2 ± 2.15	–1.1 ± 2.49
Difference to PL (95% CI), *P* value	3.0 (–0.2 to 6.1), *P* = 0.0328 (ns)		**7.28 (2.61 to 11.94), *P* = 0.0017**	
% change, Mean ± SD	5% ± 29%	–4% ± 15.234	29% ± 31%	2% ± 34%

CI = confidence interval; DB = double blind; HR = hazard ratio; LS = least square; NR = not reported; ns = non-significant; OR = odds ratio; PL = placebo; SD = standard deviation; SE = standard error.
Note: *P* values are statistically significant on a one-sided significance level of 0.025.
Sources: Clinical Study Report 2301;[14] Clinical Study Report 2305[15]

3.7.2 Serious Adverse Events

A total of 8.5% of patients experienced at least one SAE in the O/L run-in phase of Study 2301. Similar proportions of patients experienced SAEs in both treatment groups in the DB phase of Study 2301, with a total of 12% of patients in both groups. In Study 2305, the proportions of patients experiencing SAEs were also similar between patients receiving canakinumab and placebo, with a total of 5% of patients in both groups. The most common SAEs reported (≤ 2% in each treatment group) included histiocytosis hematophagic (also referred to as MAS) and juvenile arthritis.

3.7.3 Withdrawal Due to Adverse Events

Discontinuations due to AEs were low. A total of 3% of patients withdrew due to AEs during the O/L run-in phase of Study 2301, and the most frequent reason for discontinuation was histiocytosis hematophagic (MAS). The proportion of patients discontinuing the DB phase due to AEs was 12% in the placebo group; no WDAEs were reported in the canakinumab group. The most frequent reasons for discontinuation due AEs reported (< 5%) were histiocytosis hematophagic (MAS) and pneumonia. No WDAEs were reported in Study 2305.

3.7.4 Mortality

One patient died during the O/L run-in phase of Study 2301 due to MAS. In the DB phase, no deaths were reported in the canakinumab group; however, one patient in placebo group died, also from MAS. No deaths were reported in Study 2305.

3.7.5 Notable Harms

Several harms outcomes of particular interest were identified by CADTH and by the manufacturer based on the canakinumab mechanism of action and Health Canada warnings. Overall, these were characterized by a low incidence in Study 2301 and Study 2305. Similar proportions of patients receiving canakinumab and placebo experienced SAEs of infections (< 5%) and malignancies (< 3%). There were numerically fewer cases of adjudicated MAS in the canakinumab groups compared with placebo in both trials (0 with canakinumab versus 2% with placebo in Study 2301; and 5% versus 10%, respectively, in Study 2305). A few cases of neutropenia were reported in patients receiving canakinumab, while two patients receiving placebo experienced AEs of uveitis. No data were reported for abnormalities of growth. Detailed outcome data are provided in 0 Table 19.

TABLE 10: HARMS

	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Mortality, n (%)	**1 (0.6)**	**0**	**1 (2.0)**	**0**	**0**
Reported reason, n (%):					
MAS	1 (0.6)	0	1 (2.0)	0	0
SAEs, n (%)	**15 (8.5)**	**6 (12.0)**	**6 (12.0)**	**2 (4.7)**	**2 (4.9)**
Most frequently reported SAEs, n (%):					
Histiocytosis hematophagic*	4 (2.3)	0	1 (2.0)	1 (2.3)	1 (2.4)
Juvenile arthritis	2 (1.1)	0	2 (4.0)	0	0
AEs, n (%)	**138 (78)**	**40 (80)**	**35 (70)**	**24 (56)**	**16 (39)**
Most frequently reported AEs, n (%):					
Arthralgia	10 (5.6)	12 (24.0)	5 (10.0)	0	0
Cough	20 (11.3)	8 (16.0)	6 (12.0)	1 (2.3)	0
Nasopharyngitis	27 (15.3)	7 (14.0)	7 (14.0)	3 (7.0)	1 (2.4)
Pyrexia	18 (10.2)	7 (14.0)	5 (10.0)	2 (4.7)	0
Upper respiratory tract infection	18 (10.2)	6 (12.0)	5 (10.0)	3 (7.0)	0
Abdominal pain	17 (9.6)	6 (12.0)	4 (8.0)	2 (4.7)	0
Pain in extremity	7 (4.0)	6 (12.0)	4 (8.0)	1 (2.3)	1 (2.4)
Rhinitis	17 (9.6)	5 (10.0)	7 (14.0)	1 (2.3)	0
Headache	23 (13.0)	3 (6.0)	3 (6.0)	2 (4.7)	1 (2.4)
Vomiting	18 (10.2)	1 (2.0)	4 (8.0)	1 (2.3)	1 (2.4)
Diarrhea	17 (9.6)	1 (2.0)	3 (6.0)	3 (7.0)	1 (2.4)
WDAEs, n (%)	**5 (2.8)**	**0**	**6 (12.0)**	**0**	**0**
Most frequently reported AEs, n (%):					
Histiocytosis hematophagic[a]	2 (1.1)	0	1 (2.0)	0	0
Pneumonia	0	0	2 (4.0)	0	0
Notable Harms					
Infections: SAEs, n (%)	7 (4.0)	2 (4.0)	2 (4.0)	2 (4.7)	1 (2.4)
Neutropenia: AEs, n (%)	3 (1.7)	0	0	0	0
Neutropenia: SAEs, n (%)	0	0	0	1 (2.3)	0
Malignancies: SAEs, n (%)[b]	4 (2.3)	1 (2.0)	1 (2.0)	1 (2.3)	1 (2.4)
Growth abnormalities, n (%)	None reported				
Adjudicated MAS, n (%)	4 (2.3)	0	1 (2.0)	2 (4.7)	4 (9.8)
Uveitis: AEs, n (%)	0	0	1 (2.0)	0	1 (2.4)

AE = adverse event; DB = double blind; MAS = macrophage activation syndrome; O/L = open-label; PL = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

[a] MAS is also referred to in the trials as histiocytosis hematophagic.

[b] All reported cases of malignancies fell under the preferred term of histiocytosis hematophagic, with the exception of n = 1 patient in the canakinumab group of Study 2301 (DB phase).

Sources: Clinical Study Report 2301;[14] Clinical Study Report 2305[15]

4. DISCUSSION

4.1 Summary of Available Evidence

Two published, manufacturer-sponsored, DB placebo-controlled RCTs were included in the systematic review. Study 2301 (n = 100)[12] evaluated the superiority of canakinumab compared with placebo based on time to flare events, using a flare prevention design (randomized treatment withdrawal in responders). Study 2301 included an O/L run-in where all patients received canakinumab 4 mg/kg SC every 4 weeks, aiming to induce and maintain at least an adapted ACR Pedi 30 response, and to reduce or eliminate concomitant steroids. Patients were randomized in the DB phase to receive either canakinumab 4 mg/kg or placebo, administered SC every 4 weeks. Study 2305 (n = 84)[12] evaluated the superiority of canakinumab compared with placebo based on the proportions of patients who achieved at least an adapted ACR Pedi 30 response after 15 days of treatment. Patients were randomized to receive a single SC injection of either canakinumab 4 mg/kg or placebo. All patients with active disease and meeting the ILAR definition for sJIA were allowed to participate in Study 2301 and Study 2305; however, both trial populations involved patients with a high level of disease activity. In addition, the majority of patients received prior treatment with various initial therapeutic options including oral steroids, methotrexate, anakinra and etanercept, which were discontinued mostly due to lack of efficacy or tolerability.

One limitation of the included studies was the fact that a high proportion of patients discontinued from both studies in the placebo arm, mostly due to unsatisfactory therapeutic effect. Although this is not unexpected in this patient population when a placebo is administered, the impact of these discontinuations on the interpretation of the findings is uncertain. Other limitations pertain to the generalizability of the findings and include the withdrawal design of Study 2301. Although frequently seen in this indication, withdrawal trials are considered less informative for clinical practice. The results were obtained in a population of patients with an initial response to canakinumab, but identifying patients who are likely to benefit from the drug in the general population may prove difficult to achieve. Most importantly, the natural course of the disease in patients from the placebo group is uncertain. Discontinuing treatment in patients once a response is obtained may not systematically result in a disease flare, which may bias the result against canakinumab. The patient populations from Study 2301 and Study 2305 had a higher level of disease activity than what is commonly seen in clinical practice, in addition to being refractory to initial therapeutic options. Therefore, the real-world effectiveness of canakinumab may vary from what was observed in the trial. In addition, remission or inactive disease was assessed as secondary outcomes in both trials, despite being the treatment goal in clinical practice. The use of an adapted ACR Pedi 30 level in order to show adequate response to treatment is considered to be an insufficient reflection of the desired response in clinical practice, as remission or inactive disease is the treatment goal. Finally, the strength of evidence was reduced by the lack of trials comparing canakinumab with other active treatments used for sJIA, and the lack of long-term controlled data on efficacy and safety.

4.2 Interpretation of Results

4.2.1 Efficacy

Results from Study 2305 demonstrate the superiority of canakinumab over placebo in order to achieve an adapted ACR Pedi 30 response after 15 days of treatment in patients with sJIA. Patients receiving canakinumab were also statistically significantly more likely to achieve an adapted ACR Pedi 90 or ACR Pedi 100 response after 30 days of treatment compared with placebo. These adapted ACR Pedi response levels were considered particularly relevant and clinically meaningful according to the pediatric expert

consulted, as they may be consistent with the treatment goal of remission. With its withdrawal design, Study 2301 demonstrated the sustained efficacy of canakinumab, which was associated with a statistically significant reduction in the risk of a disease flare compared with placebo in patients who previously achieved a minimum response with the drug. Canakinumab was also superior to placebo to reduce the risk of a worsening in adapted ACR Pedi response level throughout the study duration.

Although often used in JIA trials, an ACR Pedi 30 response level does not represent a meaningful degree of improvement. According to the consulting clinical expert, the goal of therapy is remission or inactive disease, which was assessed as a secondary outcome. In Study 2301, the use of canakinumab was associated with a statistically significant higher likelihood of inactive disease compared with placebo. No further relevant statistical analysis was reported in the trials; however, numerically higher proportions of patients receiving canakinumab compared with placebo achieved ≥ 24 weeks of inactive disease during Study 2301. These results were consistent with assessments from Study 2305, where numerically more patients in the canakinumab group achieved inactive disease and fewer patients experienced a disease flare compared with patients in the placebo group.

HRQoL, including pain, as well as functional outcomes, were identified as important outcomes for patients according to the patient input received by CADTH. These were measured using reliable and validated tools in Study 2301 and Study 2305. Results of Study 2305 indicated that canakinumab was associated with a statistically significant and clinically meaningful benefit on HRQoL, pain and functionality compared with placebo, as measured by change from baseline in CHAQ and CHQ scores, as well as pain intensity assessment, after 29 days of treatment. Results of Study 2301 showed a non-significant trend favouring canakinumab compared with placebo with regard to these outcomes; however, the withdrawal design complicates interpretation of the findings. Real-life management of sJIA is usually indefinite; however, discontinuing the medication once a treatment response is obtained may be considered under some rare circumstances according to the clinical expert, and experience suggests that stopping treatment does not systematically result in a disease flare. Therefore, the natural course of the disease in patients from the placebo group is uncertain, which may undermine the potential for canakinumab to show a statistically significant between-group difference in these circumstances.

Both Study 2301 and Study 2305 included a proportion of patients who had previously been treated with oral steroids, a DMARD, and/or a biologic drug. In Study 2301, 62% of patients randomized to the DB phase were using oral steroids, and 54% were using methotrexate, at baseline. In Study 2305, 70% of patients were using oral steroids, and 63% were using methotrexate, at baseline. Prior experience with anakinra was reported in 45% of patients in Study 2301, and 37% of patients in Study 2305. Only a few patients had prior experience with tocilizumab (5% of patients randomized in Study 2301 and 4% of patients in Study 2305). In both trials, the most common reasons for discontinuation of anakinra or tocilizumab were lack of efficacy or tolerability. A total of 26% of patients in Study 2301, and 36% of patients in Study 2305, reported prior use of other biologic drugs, mainly etanercept, which was almost exclusively discontinued due to lack of efficacy. Only limited results pertaining to these particular patients were available and no statistical comparison between treatment groups was reported. A relevant subanalysis of the data from the non-comparative O/L extension Study 2301E1 were reported as an abstract by Brunner et al. in 2015.[32] These authors pooled efficacy data from Studies 2301, 2305, and 2301E1 for patients who had prior experience with anakinra (42% of patients; n = 51) or tocilizumab (25% of patients; n = 31). They found that patients who were switched to canakinumab due to lack of efficacy or tolerability after being exposed to anakinra or tocilizumab demonstrated a similar adapted ACR Pedi 50 response after 12 months of treatment compared with patients without any prior biologic treatment exposure. This suggests that patients who fail to respond to or cannot tolerate tocilizumab

might respond to canakinumab. However, this unpublished evidence is associated with several major limitations, including the uncontrolled nature of the main study, a lack of blinding, absence of randomization, the use of simple pooling, and a small sample size.

There is a lack of evidence with which to directly compare canakinumab with other drugs used in the management of sJIA, especially the interleukin inhibitor tocilizumab. In order to inform this evidence gap, CDR reviewed and critically appraised available indirect evidence. A literature search was undertaken to identify relevant published ITCs. One relevant publication was included, in addition to one manufacturer-provided, unpublished ITC. Otten et al. 2013[13] assessed the comparative efficacy of canakinumab, anakinra, and tocilizumab in the management of sJIA; the manufacturer's ITC focused on canakinumab and tocilizumab in a population of patients with sJIA including patients who have responded inadequately to NSAIDs and corticosteroids. [redacted] Safety outcomes were not assessed. The main limitation was the small number of studies included and the small sample sizes, which results in a high degree of uncertainty surrounding the indirect findings. [redacted] However, there is a lack of evidence with which to compare canakinumab to other drugs used in the management of sJIA for patients who are contraindicated to, or have discontinued, any biologic therapy (including tocilizumab) due to lack of efficacy or intolerance.

The absence of compelling evidence demonstrating that canakinumab is effective in patients who fail tocilizumab, together with the fact that there is no evidence of any differences in the efficacy or safety of these two drugs, suggests that in practice, canakinumab and tocilizumab will be viewed as clinically equivalent therapeutic options for patients with sJIA. Indeed, this was confirmed by the clinical experts, who further suggested that canakinumab might in fact be used in preference to tocilizumab due to its convenient and less painful route of administration (subcutaneous injection versus intravenous infusion), which is a particularly important consideration for pediatric patients.

No controlled data are available to inform on the sustainability of beneficial treatment effects observed with canakinumab in patients with sJIA beyond the mean Study 2301 duration of approximately 50 weeks. Findings from the non-comparative O/L extension Study 2301E1 (n = 271) are consistent with those from Study 2301 and Study 2305 with regard to the efficacy of canakinumab to maintain an adapted ACR Pedi response and achievement of inactive disease throughout a median duration of canakinumab treatment ranging between 96 weeks and 166 weeks according to the cohort of patients analyzed. Additional details are provided in 0.

4.2.2 Harms

Canakinumab is approved for one other indication besides sJIA (ongoing management of CAPS) and the overall harms in Study 2301 and Study 2305 results suggest that the potential harms in sJIA patients are similar to those reported for patients with other conditions.

Mortality as well as the overall incidence of SAEs during Study 2301 and Study 2305 did not differ between canakinumab and placebo, and were not higher than would be expected in this patient population according to experience from specialists' clinical practice. The most commonly reported SAEs

for both treatments were relatively infrequent (≤ 2%). More patients treated with canakinumab experienced AEs compared with placebo, and the most common AEs that occurred more frequently in canakinumab-treated patients included arthralgia, cough, pyrexia, abdominal pain, and pain in extremity. However, WDAEs were low in the O/L run-in phase of Study 2301, and no patients in the canakinumab treatment groups discontinued due to AEs, suggesting adequate tolerability.

Some AEs of particular interest were identified by CADTH based on the canakinumab mechanism of action and Health Canada warnings, which have been issued with regard to the risks of MAS (which is a life-threatening complication of sJIA), serious infections, malignancies, neutropenia, uveitis, and abnormalities of growth. There were fewer cases of adjudicated MAS in the canakinumab groups compared with placebo in both trials. MAS, also referred to as histiocytosis hematophagic, accounted for the two deaths that occurred in Study 2301 and was the most frequently reported SAE. Experience from specialists' clinical practice indicated that the incidence of MAS observed in the trials was not higher than would be expected in real-life patients with sJIA. Results for serious infections and malignancies were characterized by low and similar proportions of patients experiencing the event in both treatment groups in Study 2301 and Study 2305. A few cases of neutropenia were reported in patients receiving canakinumab, while few patients receiving placebo experienced AEs of uveitis. No data were reported for abnormalities of growth.

Experience from specialists' clinical practice and patient input submitted to CADTH suggests that convenience of administration is a major factor in selecting sJIA treatment, and that there is a need for pharmacological drugs with added convenience and tolerability for use in these children. Canakinumab is administered SC once per month, compared with tocilizumab that needs to be administered intravenously every two weeks, and anakinra that needs to be administered SC daily and is reported to be particularly painful. In children, the availability of an option with a SC route of medication delivery that is well tolerated is a communicated advantage in terms of quality of life, often eliminating the need for a visit to a facility for administration and reducing the burden on the health care system. However, as there were no head-to-head studies of the aforementioned drugs, there is no evidence available to determine whether differences in the route and/or frequency of administration of the different treatments may be associated with differences in outcomes due to differences in compliance.

No data were available to directly or indirectly compare the potential harms of canakinumab versus other drugs used in the management of sJIA.

4.3 Potential Place in Therapy[1]

The management of sJIA focuses on the control of inflammation and symptoms in order to achieve remission and prevent associated comorbidities such as MAS, joint damage, and growth disturbances. Interleukin-1 (IL-1) and Interleukin-6 (IL-6) play a central role in the pathogenesis of sJIA. Traditional drugs used in sJIA include NSAIDs, steroids, and DMARDs; however, the use of targeted drugs that effectively inhibit interleukins is highly rational.

The severity of disease in a patient can be approximated by the number of active joints and the physician global assessment, which also incorporates the severity of systemic features. The 2013 ACR recommendations for the Medical Therapy of Children with sJIA[5,6] include NSAIDs or corticosteroids as initial therapy in patients with a lower level of disease activity, while anakinra (IL-1 inhibitor) is

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH CDR reviewers for the purpose of this review.

recommended in patients with a higher level of disease activity. Response to treatment is usually observed within a few weeks, but patients may continue to improve for up to 3 months. If the treatment goal of remission or inactive disease is not achieved, the ACR recommendations include tocilizumab (IL-6 inhibitor), canakinumab (IL-1 inhibitor), a TNF-inhibitor or DMARDs as second-line treatment options. NSAIDs and corticosteroids do not prevent disease progression and are associated with safety issues,[3,17,18] while the effectiveness of DMARDs and TNF-inhibitors may be limited in sJIA;[8,11,20] therefore, there is a need for targeted, effective drugs such as interleukin inhibitors in the management of this particularly refractory disease.

In clinical practice, treating physicians are aided by treatment guidelines such as those mentioned above, but other considerations influence the choice of treatment, such as the mode of administration. For example, despite the guidelines, anakinra is not necessarily administered early in the treatment sequence in clinical practice because this drug must be administered daily by subcutaneous injection, which is both inconvenient and particularly painful, especially for children. In Canada, treatment decisions are also influenced by additional factors, such as the fact that only tocilizumab and canakinumab have a Health Canada indication for sJIA; whereas, anakinra and TNF-inhibitors are not indicated for use in this population. Due to its relative convenience in terms of mode of administration, in clinical practice, canakinumab is likely to be used in preference to anakinra and tocilizumab, or in patients who have failed these treatments due to intolerance.

5. CONCLUSIONS

The results of Study 2305 demonstrated that canakinumab is superior to placebo in achieving a treatment response in patients with sJIA, as reflected by the significantly greater proportion of canakinumab-treated patients who achieved adapted ACR Pedi 30, 50, 70, 90, and 100 responses at day 15. The results of the withdrawal Study 2301 demonstrated that canakinumab treatment is associated with sustained efficacy in patients with sJIA who had previously responded to canakinumab, as reflected by a significant reduction in the risk of a disease flare compared with placebo. In addition, the results of the Study 2301 demonstrated that canakinumab is associated with a reduced risk of disease worsening and a higher likelihood of inactive disease compared with placebo. Canakinumab was associated with a statistically and clinically significant improvement in HRQoL, reduced pain and improved functionality compared with placebo in Study 2305. While the effects of canakinumab on these outcomes did not reach statistical significance compared with placebo in Study 2301, this is likely attributable to the limitations associated with the withdrawal design of Study 2301, which might have reduced the likelihood of demonstrating differences between treatments. Overall, the harms reported for Study 2301 and Study 2305, as well as the results of a long-term O/L extension study, did not raise any new concerns regarding the safety of canakinumab. The comparative efficacy of canakinumab versus other relevant treatments has not be studied directly, [redacted] While both Study 2305 and Study 2301 included patients who had prior treatment experience with oral steroids, a DMARD, or a biologic drug that was discontinued due to lack of efficacy or tolerability, very few patients had been treated previously with tocilizumab. Therefore, there is a dearth of evidence regarding the efficacy of canakinumab in patients who have discontinued tocilizumab treatment due to an insufficient response or intolerance.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input
Two patient groups supplied input for this submission.

The 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 between 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 for grants and support has been received by the following organizational, professional, and pharmaceutical groups in the last year: AbbVie, Amgen Canada, Arthritis Alliance of Canada, The Arthritis Society, Canadian Rheumatology Association, Hoffmann-La Roche, Janssen, Novartis, Ontario Rheumatology Association, Pfizer Canada, Rx&D, and UCB Pharma. CAPA has also received financial support in the past from the Canadian Institutes for Health Research, Schering Canada, the Scleroderma Society, and STA Communications.

The Arthritis Society is Canada's principal health charity that provides education, programs, and support to 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. The vast majority of The Arthritis Society's funding comes from individual donors. During the 12 months preceding their submission, The Arthritis Society has received unrestricted funding from various pharmaceutical groups, including Abbvie, Amgen, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, Hospira, Janssen, Merck, Novartis, Pfizer, Purdue, Roche, and UCB.

The Arthritis Society declared no conflicts of interest with regard to their submission. CAPA declared that the author of their submission had received honorariums from Sanofi in 2015.

2. Condition Related Information
Information for this submission was obtained by personal communications with patients or the parents of patients with systemic juvenile idiopathic arthritis (sJIA), from personal experiences, one-on-one e-conversations through social media and websites, and an online survey.

sJIA is a serious, disabling, and chronic autoimmune disease that continually attacks the joint lining, leading to both the destruction of the joint and the surrounding bone. This inflammation can lead to abnormal shape and function of the joint due to the constant inflammation during a period of continual growth. Damage to the joint is irreversible and is associated with significant pain and disability. In addition to the joint inflammation, whole body rashes, recurrent fevers, and damage to other internal organs (such as the heart, liver, spleen, and lymph nodes) are also associated with sJIA. Should the disease be uncontrolled, patients may have to undergo major joint surgeries (sometimes during their youth), including joint replacements or fusions. In addition, many patients often require the use of technical or mobility aids such as bath lifts, wheelchairs, Para transport, and house modifications. One unique complication associated with sJIA that some patients experience is growth retardation (caused by either the disease or the use of corticosteroids).

Patients experiencing sJIA endure intense inflammation that is associated with pain and fatigue. This can lead the child to feel isolated, depressed, and angry. As one parent said, *"She is not able to play with her*

friends in the playground and she is too young to let her friends know why she can't keep up to them, so she is excluded. She doesn't have the words to say that she is hurt and gets disruptive and angry. Mommy knows why she is behaving that way but the teachers and students don't." Many children learn to deal with the pain and unpredictability of the disease at a very young age. sJIA affects every aspect of the patient's life, including day-to-day activities such as sleeping; caring for oneself; walking; participating in school, social, and recreational activities; and their ability to pursue hobbies and interests. The limitations associated with the inability to perform daily routine activities can cause severe psychological burden to the child and to their families and caregivers. As one parent stated, *"The biggest challenge is pain and the anxiety that goes with the pain. The inability to be a normal kid, instead forced to grow up too fast and deal with adult issues like pain."* Another parent described the psychological burden as the most significant aspect of sJIA, stating, *"[The] Psychological [aspect] has the biggest impact. She knows she has something different that none of her friends do and couple that with some of the physical limitations in sports, it makes her sad sometimes."* In the children that get recurrent fevers, these can spike numerous times a day, can occur over a prolonged period of time, and are often associated with a severe rash. One parent recollected, *"Then the fevers kicked in. The fevers lasted 22 days until he began treatment. During the fevers, for a period of a few days, a rash took over his entire torso which was painful to even look at*." The fevers are associated with intense fatigue and feelings of being unwell. In addition, since sJIA is a chronic disease, flare-ups often occur and are in turn associated with distress.

Caregivers are affected both psychologically and financially. As parents are usually the primary caregivers to children with sJIA, they often experience feelings of guilt regarding their child's illness, additional stress regarding the treatment and time off work, and in dealing with everyday responsibilities associated with family life. In addition, the main concerns highlighted by caregivers were the costs, time associated with medical appointments (as rheumatologists were not always close by) and treatment. One parent stated, *"Living so far from the paediatric rheumatology department, it is a challenge to work and juggle medical appointments,"* while the hardships associated with cost were stated by another parent, *"Having a very low income (social assistance) having to purchase all the extras not covered, like needles, syringes, Pediasure, and pills is very stressful!"* Siblings often experience feelings of resentment toward the child with sJIA as they do not understand why their sibling receives more attention. This can cause additional stress to the parents, as one parent stated, *"At home trying to explain special needs/attention to siblings. Trying to make certain that siblings understand that it (JIA) isn't a fun thing."* In addition, marital relationships often suffer due to the stress and depression associated with caring for a sick child, dealing with the unpredictability of the disease, and dealing with everyday family responsibilities.

3. Current Therapy Related Information

sJIA in children is treated aggressively, as research has identified that the best outcomes for children and youth with sJIA are associated with early aggressive treatment. The approaches used to treat sJIA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, anakinra, and tocilizumab. It is important to note that responses to the aforementioned treatments can vary significantly. Some patients may respond well to treatment, others may not respond at all, while others still will have their disease managed for only a short period of time before becoming non-responsive. Patients often have to switch medications to find the one that they will respond to. Side effects associated with the aforementioned treatments include nausea, vomiting, extreme fatigue, decreased immune function, and injection reactions. The pain associated with injections may have a significant impact on quality of life, as highlighted by one family, *"My wife and I routinely were in tears when giving his injection to the point where my wife refused to give it to*

him. Anakinra is a very painful drug and burns for 1 - 2 min after administering. Tough to give to your five year old child every day." Others reported psychological side effects from corticosteroids: *"Family life has been impacted because our daughter gets moody and anxious from prednisone […] so there is a lot of added stress on our family."*

4. Expectations About the Drug Being Reviewed

It is important to note that drugs that target interleukin-1 (e.g., canakinumab) and interleukin-6 (e.g., tocilizumab) are most effective for patients with sJIA. In addition, both of these have been studied in the pediatric population; hence, canakinumab offers another option for these patients.

Positive experiences for both patients and parents were noted with canakinumab (as part of a clinical trial). Parents, caregivers, and patients believe that canakinumab will offer another treatment option for patients suffering from sJIA. Although the potential for serious infections and allergic reactions remains with canakinumab, parents highlighted the importance of relieving the disabling symptoms of sJIA. The efficacy of canakinumab was noted by another parent, who stated, *"With the medication, he is completely symptom free."* One parent stated, *"I believe any adverse effects do outweigh the symptoms of SJIA."*

The most frequently mentioned positive change was an improved quality of life, not only from improving symptoms of the disease, but also with regard to the significantly reduced frequency of injections; going from daily to monthly (or every six weeks). As one father stated, *"Injections are clearly not as painful as anakinra. And only being one injection per month instead of daily, it appears to be just as effective, if not better. He does not appear to be getting sick as often," and, "Over the last 1.5 years my son has taken more needles than most people do in 10 lifetimes. At this point, the fewer needles my son has to take and still have a normal childhood is what is important to me."* One mother stated, *"It gave her the opportunity to not receive a daily injection and live with a 'normal' quality of life."*

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:	January 28, 2016
Alerts:	Monthly search updates until May 18, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.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

MUTLI-DATABASE STRATEGY	
#	**Searches**
1	(914613-48-2 or 37CQ2C7X93).rn,nm.
2	(ilaris* or canakinumab* or ACZ 885 or ACZ885).ti,ab,ot,hw,rn,nm,kf.
3	or/1-2
4	3 use pmez
5	*canakinumab/
6	(ilaris* or canakinumab* or ACZ 885 or ACZ885).ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	4 or 8
10	conference abstract.pt.
11	9 not 10
12	exp animals/
13	exp animal experimentation/ or exp animal experiment/
14	exp models animal/
15	nonhuman/
16	exp vertebrate/ or exp vertebrates/
17	animal.po.
18	or/12-17
19	exp humans/
20	exp human experimentation/ or exp human experiment/
21	human.po.
22	or/19-21
23	18 not 22
24	11 not 23
25	remove duplicates from 24

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	January 2016
Keywords:	Ilaris (canakinumab), Systemic 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 searching health-related grey literature" (https://www.cadth.ca/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.

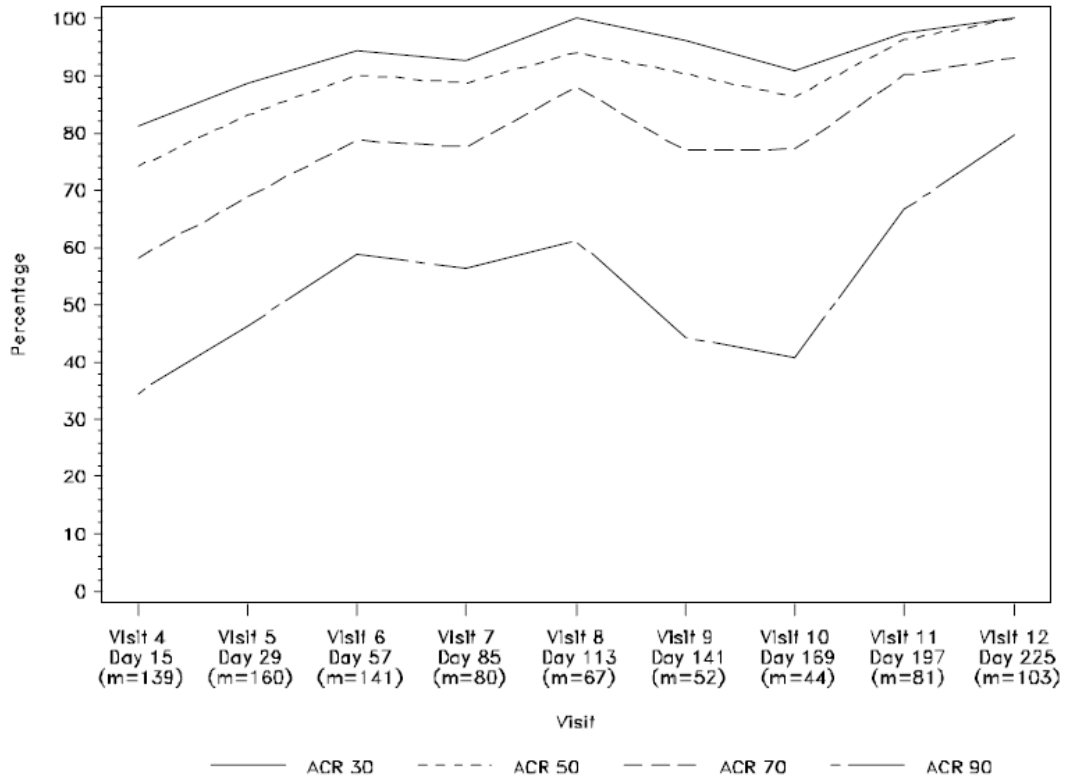
APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
[33]	Inappropriate Design
[34]	Inappropriate Design

APPENDIX 4: DETAILED OUTCOME DATA

1. Efficacy — Adapted ACR Pedi Response

FIGURE 3: MINIMUM ADAPTED ACR PEDI RESPONSE LEVEL ACHIEVED — STUDY 2301 OPEN-LABEL RUN-IN



Source: Clinical Study Report 2301[14]

TABLE 11: ADAPTED ACR PEDI RESPONSE

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
A. Adapted ACR Pedi 30 Responders				
Day 15 (*Primary Outcome of Study 2305*)				
n (%)	NR		36 (84)	4 (10)
OR (95% CI)			62.3 (12.7 to 306.1)	
P value			*P* < 0.0001	
DAY 29 (End of Study)				
n (%)	NR		35 (81)	4 (10)
OR (95% CI)			62.3 (12.7 to 306.1)	
P value			*P* < 0.0001	
B. Adapted ACR Pedi 50 Responders at End of Study				
n (%)	NR		34 (79)	2 (5)
OR (95% CI)			106.8 (16.3 to 701.1)	
P value			*P* < 0.0001	
C. Adapted ACR Pedi 70 Responders at End of Study				
n (%)	NR		29 (67)	1 (2)
OR (95% CI)			105.3 (12.0 to 922.8)	
P value			*P* < 0.0001	
D. Adapted ACR Pedi 90 Responders at End of Study				
n (%)	NR		20 (47)	1 (2)
OR (95% CI)			40.6 (5.2 to 315.2)	
P value			*P* < 0.0001	
E. Adapted ACR Pedi 100 Responders at End of Study				
n (%)	NR		14 (33)	1 (2)
OR (95% CI)			22.7 (2.8 to 183.2)	
P value			*P* < 0.0001	
F. Time to a Worsening in Adapted ACR Pedi Level				
Number of events	18	29	NR	
Median time in days (95% CI)[a]	Not estimable	141.0 (85.0 to 281.0)		
HR (95% CI)[b]	0.49 (0.27 to 0.90)			
P value[c]	*P* = 0.0131			

CI = confidence interval; DB = double blind; NR = not reported; OR = odds ratio; PL = placebo.
[a] Kaplan-Meier estimate. The median time to flare and median time to worsening in ACR Pedi levels were not observed for the canakinumab group, as less than 50% of patients experienced a worsening in ACR Pedi levels in the DB phase.
[b] Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and ACR Pedi 70 response reached at the end of O/L run-in.
[c] Statistically significant on one-sided significance level 0.025.
Sources: Clinical Study Report 2301: p. 147;[14] Clinical Study Report 2305: p. 81, p 84.[15]

2. Efficacy — Disease Activity

TABLE 12: SURVIVAL ANALYSIS OF DISEASE ACTIVITY

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Time to Flare Events (*Primary Outcome of Study 2301*)				
Number of events	11	26	NR	
Median time, days (95% CI)[a]	Not estimable	236 (141 to 449)		
HR (95% CI)[b]	0.36 (0.17 to 0.75)			
P value	*P* = 0.0032			
Time to Inactive Disease				
Number of events	41	34	NR	
Median time, days (95% CI)	30 (29 to 35)	33 (29 to 57)		
HR (95% CI)[b]	1.26 (0.79 to 1.99)			
P value	*P* = 0.1446			

CI = confidence interval; DB = double blind; HR = hazard ratio; NR = not reported; PL = placebo.
[a] Kaplan-Meier estimate. The median time to flare and median time to worsening in ACR Pedi levels were not observed for the canakinumab group, as less than 50% of patients experienced a flare event in the DB phase.
[b] Log-rank test adjusted for stratification factors prednisone (or equivalent) dose and ACR Pedi 70 response reached at the end of O/L run-in.
Sources: Clinical Study Report 2301: p.145, p 917;[14] Clinical Study Report 2305[15]

TABLE 13: ABSENCE OF SYSTEMIC FEATURES — FEVER

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Proportions of Patients with Normal Body Temperature (≤ 38°C) at Day 3				
n (%)	NR		43 (100)	33 (87)
OR (95% CI)			Not estimable	
P value			*P* = 0.0098	

CI = confidence interval; DB = double blind; NR = not reported; OR = odds ratio; PL = placebo.
Comparison of treatment groups using Cochran-Mantel-Haenszel test adjusting for stratification factors. A one-sided test was conducted with significance level 0.01612 as determined by the Pocock method for trial's overall false-positive rate of 0.025.
Sources: Clinical Study Report 2301: p.88;[14] Clinical Study Report 2305[15]

TABLE 14: ORAL STEROID TAPERING — STUDY 2301 OPEN-LABEL RUN-IN

	Study 2301 (O/L Run-In)
	Canakinumab N = 177
Patients taking steroids at baseline n (%)	**128 (72.3)**
Patients able to taper steroids	
n (%)	57 (44.5)
90% exact CI; *P* value[a]	37.1 to 52.2; *P* < 0.0001
Patients steroid free	
n (%)	42 (32.8)
95% exact CI	24.8 to 41.7

CI = confidence interval; O/L = open-label; PL = placebo.
Ability to taper oral steroids: Dose reduced from > 0.8 mg/kg/day to ≤ 0.5 mg/kg/day, or from ≥ 0.5 mg/kg/day and ≤ 0.8 mg/kg/day by at least 0.3 mg/kg, or from any initial dose to ≤ 0.2 mg/kg/day, while maintaining an ACR Pedi 30 response.
[a] *P* value from exact one-sided binomial test for percentage of patients able to taper steroids ≥ 25%.
Sources: Clinical Study Report 2301: p. 118-9;[14] Clinical Study Report 2305[15]

3. Efficacy — Health-Related Quality of Life and Functional Outcomes

TABLE 15: CHAQ DISABILITY SCORES

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Change in CHAQ Disability Score — Summary Statistics				
LS Mean ± SE	0.1184 ± 0.17592	0.1258 ± 0.18241	–0.9 ± 0.15	–0.2 ± 0.20
Difference to PL (95% CI)	–0.0073 (–0.1407 to 0.1260)		–0.69 (–1.05 to –0.32)	
P value	*P* = 0.4571[a]		*P* = 0.0002[b]	
Change in CHAQ Disability Score – Values				
Baseline				
Mean ± SD	0.3650 ± 0.67990	0.4025 ± 0.69542	1.6686 ± 0.73592	1.5091 ± 0.78431
Range	0 to 2.750	0 to 3.000	0 to 3.000	0.125 to 3.000
End of Study				
Mean ± SD	0.4600 ± 0.86582	0.5925 ± 0.83369	0.5658 ± 0.77205	1.1964 ± 1.04796
Range	0 to 3.000	0 to 3.000	0 to 2.500	0 to 2.500
Change from Baseline				
Absolute change, Mean ± SD	0.0950 ± 0.45285	0.1900 ± 0.52625	–1.1151 ± 0.73543	–0.3214 ± 0.93780
Per cent change, Mean ± SD	**–9.16% ± 100.539**	**101.48% ± 321.846**	**–68.50% ± 37.342**	**–4.83% ± 72.514**

CHAQ = Childhood Health Assessment Questionnaire; CI = confidence interval; DB = double blind; LS = least square; PL = placebo; SD = standard deviation; SE = standard error.

Note Study 2301: Repeated measures ANCOVA with treatment group, visit day, prednisone (or equivalent) dose and adapted ACR Pedi 70 response reached at the end of O/L run-in as covariates.

Note Study 2305: Mixed linear model on change from baseline in CHAQ score with treatment group, stratification factors, day of assessment and interaction between group and day as covariates.

[a] Statistically significant on one-sided significance level 0.025.

[b] A one-sided test was conducted with significance level 0.01612 as determined by the Pocock method for an overall false-positive rate of the trial at 0.025.

Sources: Clinical Study Report 2301: p.149, p.539, p.562, p.784;[14] Clinical Study Report 2305: p.91, p.192-3.[15]

TABLE 16: PAIN ASSESSMENT

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Patient's Pain Intensity (0 to 100 mm VAS) as part of CHAQ				
	Change from Baseline		**Between-Group Difference at Week 4**	
n	50	50	38	7
LS Mean ± SE	–7.1 ± 5.85	–3.6 ± 6.06	20.6 ± 5.59	62.5 ± 9.70
Difference to PL (95% CI)	–3.54 (–7.84 to 0.77)		–41.86 (–59.81 to –23.90)	
P value	*P* = 0.0536		*P* < 0.0001	

CI = confidence interval; DB = double blind; LS = least square; PL = placebo; SE = standard error; VAS = visual analogue scale.
Sources: Clinical Study Report 2301: p.2,176;[14] Clinical Study Report 2305: p.89.[15]

TABLE 17: CHQ-PF50 SCORES IN PATIENTS 5 TO 18 YEARS

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
A. Change in CHQ-PF50 Physical Health Score				
Summary Statistics				
n	39	37	28	34
LS Mean ± SE	3.9 ± 2.54	–0.3 ± 2.53	16.9 ± 3.46	4.9 ± 3.97
Difference to PL (95% CI)	**4.2 (–0.1 to 8.4)**		**12.07 (4.65 to 19.48)**	
P value	***P* = 0.0280 (ns)**		***P* = 0.0012**	
Values				
Baseline				
Mean ± SD	43.1536 ± 14.82221	44.3434 ± 14.79160	16.9190 ± 13.35216	14.8079 ± 13.03674
Range	–4.261 to 58.374	1.783 to 60.632	–4.506 to 38.073	–4.477 to 39.223
End of Study				
Mean ± SD	43.5722 ± 17.39208	38.9628 ± 18.12759	38.9109 ± 16.27324	22.6439 ± 19.72956
Range	–6.309 to 60.782	1.884 to 62.924	–6.188 to 57.491	–1.651 to 48.888
Change from Baseline				
Absolute change, Mean ± SD	0.6201 ± 11.41387	–5.7921 ± 11.60714	22.3982 ± 11.66742	14.0642 ± 12.92442
Per cent change, Mean ± SD	**6.46% ± 38.580**	**–3.20% ± 84.382**	**–465.61% ± 1797.544**	**–50.37% ± 281.545**
B. Change in CHQ-PF50 Psychosocial Health Score				
Summary Statistics				
n	39	37	28	34
LS Mean ± SE	2.5 ± 1.88	–0.5 ± 1.86	6.2 ± 2.15	–1.1 ± 2.49
Difference to PL (95% CI)	**3.0 (–0.2 to 6.1)**		**7.28 (2.61 to 11.94)**	
P value	***P* = 0.0328 (ns)**		***P* = 0.0017**	
Values				
Baseline				
Mean ± SD	53.2835 ± 11.31783	54.6434 ± 7.66990	40.5087 ± 9.49647	44.4871 ± 11.81653
Range	7.496 to 64.205	38.501 to 65.361	22.784 to 57.383	17.654 to 64.691
End of Study				
Mean ± SD	53.6192 ± 11.34412	52.7105 ± 9.79286	50.2360 ± 8.12900	40.4731 ± 19.94779
Range	16.141 to 67.131	27.051 to 65.604	34.725 to 60.487	15.216 to 64.515
Change from Baseline				

	Study 2301 (DB Phase)		Study 2305	
	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Absolute change, Mean ± SD	0.4096 ± 8.43031	–2.1209 ± 7.89225	9.8316 ± 8.22167	2.0147 ± 12.47742
Per cent change, Mean ± SD	**4.97% ± 29.118**	**–3.52% ± 15.234**	**29.43% ± 31.119**	**2.28% ± 33.868**

CHQ = Child Health Questionnaire; CI = confidence interval; LS = least square; ns = non-significant; PL = placebo; SD = standard deviation; SE = standard error.
Note Study 2301: Repeated measures ANCOVA change from start of part 2 with treatment group, visit day, prednisone (or equivalent) dose and adapted ACR 70 Pedi response reached at the end of part 1d as covariates. *P* values statistically significant on one-sided significance **level 0.025.** Note Study 2305: Mixed linear model on change from baseline in CHQ-PF50 score with treatment group, stratification factors, day of assessment and interaction between group and day as covariates. A one-sided test was conducted with significance level 0.01612 as determined by the Pocock method for an overall false-positive rate of the trial at 0.025.
Sources: Clinical Study Report 2301: p.150, p.797;[14] Clinical Study Report 2305: p.90, p.187.[15]

4. Harms Outcomes

TABLE 18: MORTALITY AND OTHER SERIOUS ADVERSE EVENTS

	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Mortality					
n (%)	**1 (0.6)**	**0**	**1 (2.0)[a]**	**0**	**0**
Most frequently reported reasons, n (%):					
MAS	1 (0.6)	0	1 (2.0)[a]	0	0
SAEs					
n (%)	**15 (8.5)**	**6 (12.0)**	**6 (12.0)**	**2 (4.7)**	**2 (4.9)**
Most frequently reported reasons: ≥ 2% of patients (and experienced by > 1 patient) in at least one treatment group, n (%):					
Histiocytosis hematophagic (MAS)	4 (2.3)	0	1 (2.0)	1 (2.3)	1 (2.4)
Juvenile arthritis	2 (1.1)	0	2 (4.0)	0	0

DB = double blind; MAS = macrophage activation syndrome; O/L = open-label; PL = placebo; SAE = serious adverse event.
[a] One patient in the placebo group died approximately one month after receiving the last dose of study drug (approximately five months after entering the DB phase).
Sources: Clinical Study Report 2301: p.172-3, p.176-7, p 181;[14] Clinical Study Report 2305: p.111, p.113.[15]

TABLE 19: NOTABLE OR CLINICALLY SIGNIFICANT HARMS

n (%)	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
Serious Infections					
SAEs of infection	7 (4.0)	2 (4.0)	2 (4.0)	2 (4.7)	1 (2.4)
Neutropenia					
AEs of neutropenia	3 (1.7)	0	0	0	0
SAEs of neutropenia	0	0	0	1 (2.3)	0
Malignancies					
SAEs of neoplasms benign, malignant, and unspecified	4 (2.3)	1 (2.0)	1 (2.0)	1 (2.3)	1 (2.4)
Most frequently reported by preferred term:					
Hematophagic histiocytosis (MAS)	4 (2.3)	0	1 (2.0)	1 (2.3)	1 (2.4)
Abnormalities of Growth					
AEs or SAEs	None reported				
MAS					
Adjudicated cases of MAS[a]	4 (2.3)	0	1 (2.0)	2 (4.7)	4 (9.8)
Uveitis					
AEs of uveitis	0	0	1 (2.0)	0	1 (2.4)

AE = adverse event; DB = double blind; MAS = macrophage activation syndrome; O/L = open-label; PL = placebo; SAE = serious adverse event.

[a] MAS is also referred to in the trials as hematophagic histiocytosis.

Sources: Clinical Study Report 2301: p. 181, p 185-6;[14] Clinical Study Report 2305: p. 113.[15]

TABLE 20: ADVERSE EVENTS

	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
AEs					
n (%)	**138 (78)**	**40 (80)**	**35 (70)**	**24 (56)**	**16 (39)**
Most frequently reported AEs: ≥ 5% of patients in at least one treatment group, n (%):					
Arthralgia	10 (5.6)	12 (24.0)	5 (10.0)	0	0
Cough	20 (11.3)	8 (16.0)	6 (12.0)	1 (2.3)	0
Nasopharyngitis	27 (15.3)	7 (14.0)	7 (14.0)	3 (7.0)	1 (2.4)
Pyrexia	18 (10.2)	7 (14.0)	5 (10.0)	2 (4.7)	0
Upper respiratory tract infection	18 (10.2)	6 (12.0)	5 (10.0)	3 (7.0)	0
Abdominal pain	17 (9.6)	6 (12.0)	4 (8.0)	2 (4.7)	0
Pain in extremity	7 (4.0)	6 (12.0)	4 (8.0)	1 (2.3)	1 (2.4)
Rhinitis	17 (9.6)	5 (10.0)	7 (14.0)	1 (2.3)	0
Urticaria	0	4 (8.0)	2 (4.0)	0	0
Musculoskeletal pain	2 (1.1)	4 (8.0)	0	0	0
Oral herpes	0	4 (8.0)	0	0	1 (2.4)
Headache	23 (13.0)	3 (6.0)	3 (6.0)	2 (4.7)	1 (2.4)
Eczema	9 (5.1)	3 (6.0)	1 (2.0)	0	0
Nausea	9 (5.1)	3 (6.0)	1 (2.0)	1 (2.3)	0
Tinea pedis	0	3 (6.0)	0	0	0
Seasonal allergy	0	2 (4.0)	4 (8.0)	0	0
Pruritus	0	2 (4.0)	3 (6.0)	1 (2.3)	0
Abdominal pain upper	9 (5.1)	2 (4.0)	2 (4.0)	1 (2.3)	1 (2.4)
Vomiting	18 (10.2)	1 (2.0)	4 (8.0)	1 (2.3)	1 (2.4)
Diarrhea	17 (9.6)	1 (2.0)	3 (6.0)	3 (7.0)	1 (2.4)
Pharyngitis	9 (5.1)	1 (2.0)	2 (4.0)	0	0
Gastroenteritis	14 (7.9)	1 (2.0)	1 (2.0)	1 (2.3)	2 (4.9)

AE = adverse events; DB = double blind; O/L = open-label; PL = placebo.
Sources: Clinical Study Report 2301: p.167, p.4079;[14] Clinical Study Report 2305: p.108.[15]

TABLE 21: WITHDRAWAL DUE TO ADVERSE EVENTS

	Study 2301			Study 2305	
	O/L Run-in	DB Phase			
	Canakinumab N = 177	Canakinumab N = 50	PL N = 50	Canakinumab N = 43	PL N = 41
WDAEs					
n (%)	**5 (2.8)**	**0**	**6 (12.0)**	**0**	**0**
Most frequently reported reasons: > 1 patient in at least one treatment group, n (%):					
Histiocytosis hematophagic[a]	2 (1.1)	0	1 (2.0)	0	0
Pneumonia	0	0	2 (4.0)	0	0

DB = double blind; O/L = open-label; PL = placebo; WDAE = withdrawal due to adverse events.
[a] Macrophage activation syndrome.
Sources: Clinical Study Report 2301: p. 184-5;[14] Clinical Study Report 2305: p. 111.[15]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- American College of Rheumatology Pediatric (ACR Pedi) criteria
- Childhood Health Assessment Questionnaire (CHAQ)
- Childhood Health Questionnaire (CHQ)
- Pain Measures

Findings

ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi 90:

Following ACR criteria for adult RA (rheumatoid arthritis), a preliminary core set of response variables was defined for pediatric arthritis,[35] referred to as ACR-Pediatric criteria for juvenile idiopathic arthritis (JIA).[36,37]

Of note, 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), the definition of improvement in adult RA is not considered appropriate for use in JIA. There are several reasons for this: JIA is considered a different disease entity; some core variables are less often abnormal or have lower scores in children than in adults; and their measurement is compromised due to age-related cognitive problems (e.g., self-reported pain). Therefore, Giannini et al.[38] developed a definition of improvement specific for 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 3 of any 6 variables in the core set, while no more than 1 of the remaining variables can worsen by > 30%. The variables included in the core set are: physician global assessment of disease activity; parent/patient global assessment of overall well-being (each scored on a 10 cm visual analogue scale [VAS]); functional ability; number of joints with active arthritis; number of joints with limited range of motion; and erythrocyte sedimentation rate (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.[38]

There are two important characteristics of the ACR Pedi 30 criteria. First, it includes the number of joints with limited motion as a parameter; this is relevant since, in patients with short disease duration, this count can improve significantly through physical therapy. In contrast, patients with longstanding 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 variable has worsened by >30% (but not more than one).

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 3 of the 6 core set variables, with no more than one of the remaining variables worsening by > 30%.

Importantly, the authors indicated that prospective validation of the improvement criteria is necessary, but results of such a validation have not been reported.[39] 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 meaningful degree of progress.[40]

CHAQ

The Health Assessment Questionnaire (HAQ) was originally developed in 1978 at Stanford University for use in adults.[41] It was one of the first self-reported functional status (disability) measures and has become the dominant instrument in many disease areas, including RA.[42,43]

The Childhood Health Assessment Questionnaire (CHAQ) is a 30-item, self or parent-administered instrument used to measure the physical functional status in children with JIA.[28,29] It takes less than 10 minutes to complete, and scoring is easily obtained in less than 2 minutes. The CHAQ was developed by Singh et al. as an adaptation of the Stanford HAQ for use in children 1 to 19 years old.[28] It has two indices (disability and discomfort)[29] and has several new questions compared with HAQ, 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 4-point Likert 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 8 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 8 functional areas and 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 evaluation of overall well-being.[28]

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 JIA patients. The instrument showed excellent internal reliability, strong correlations of the disability index (average of scores on all functional areas) with Steinbrocker functional class, number of involved joints, morning stiffness, and a very high test-retest reliability for the disability index. 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.[28] Moderate correlation has been observed with the CHQ PhS, but poor correlation with the CHQ PsS.[31]

Further validity testing of the CHAQ was completed by Pouchot et al.[44] 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 8 out of 30 items of the CHAQ depends on the responder'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 to 3). The authors therefore concluded that the design and scoring system of CHAQ adequately remove most of the expected physical development bias.[44]

The CHAQ is thought to have advantages over other measures of physical function due to such aspects as its multidimensionality (it assesses eight domains of physical function).[45] The CHAQ is in use internationally and cross-cultural adaptations were recently validated in 32 countries.[46] One of its drawbacks is that with zero 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 zero).[29,47] The ceiling effect makes the scale intrinsically less sensitive to milder levels of disability, in which case false-negative outcomes may ensue.[48]

Few studies are available to evaluate the minimal clinically important difference (MCID) in functional ability of children with JIA.[49] Based on a study involving 131 parents of JIA patients, Dempster et al.[50]

found that the median CHAQ scores corresponding to mild, mild-to-moderate, and moderate disability were 0.13, 0.63, and 1.75, respectively. The minimal clinically important improvement was a reduction in score of 0.13 (–4.3%); whereas, the MCID deterioration 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.[50] In a similar study with a comparable population, Brunner et al.[51] proposed that the smallest potential difference in the CHAQ score of individuals is 0.125. The MCID was defined as the median change of the CHAQ scores of individual patients who had a minimally important improvement or worsening between visits. CHAQ scores were calculated for parent (n = 92) and patient ratings (children age ≥ 8 years only; n = 67) between subsequent clinic visits. Patients with a MCID improvement had a decrease in CHAQ no greater than 0.188, while patients with MCID worsening had an increase in CHAQ that was no greater than 0.125. Based on these findings, the authors concluded that CHAQ is relatively insensitive to important short-term changes in children with JIA.

CHQ

The CHQ is a generic quality of life measure that assesses the physical, emotional, and social aspects of health status in children aged five years and older and has been used to assess health-related quality of life (HRQoL) in patients with JIA.[29] The questionnaire includes 14 domains and provides a physical score (PhS) and the psychosocial score (PsS) as its two summary measures.[29,30] Two separate forms exist; one for the parent (which includes 50 or 28 items depending on the version) and one for the child (which includes 87 items).[31] It is a self-administered questionnaire with children self-administering once they are 10 years of age.[31] Scores range between 0 and 100, with higher scores indicating better HRQoL.[29,31] The domains covered in the CHQ include physical health, mental health, pain, school, social, and family, and include varying response categories with measuring descriptions of 0 = poor well-being and 100 = excellent well-being.[31]

The reliability, validity, and responsiveness of the CHQ have been ascertained in one systematic review by van Mater et al.[31] When assessing functional status or disability, the interrater reliability between parent and child was determined to be either moderate or strong, with PhS ranging from 0.69 to 0.87. Interrater reliability correlations were lower between parent and child for the PsS (range 0.38 to 0.53).[31] The CHAQ and the CHQ PhS were observed to be moderately correlated; however, poor correlation was noted between the CHAQ and the CHQ PsS.[31] The CHQ is able to differentiate between children with JIA and children that are healthy; however, no evidence was ascertained indicating that the CHQ could discriminate between disease extent in children with JIA.[31] Overall, the
CHQ demonstrates poor responsiveness. When reporting on disease state separately, the CHQ was observed to be highly responsive with regard to disease improvement but lower in those with worsening of disease.[31] No MCID was identified for the CHQ.

TABLE 22: SUMMARY OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
ACR Pedi 30[a]	• Defined as at least 30% improvement from baseline in 3 of any 6 variables in the core set, while no more than 1 of the remaining variables can worsen by > 30%. • Core set includes: o Physician global assessment of disease activity o Parent/patient global assessment of overall well-being (each scored on a 10 cm VAS) o Functional ability o Number of joints with active arthritis o Number of joints with limited range of motion o ESR.	Yes	NA	35-38
CHAQ	• 30-item, self- or parent-administered instrument • 2 indices; disability and discomfort • 8 functional areas measured by CHAQ are: o dressing and grooming o arising o eating o walking o hygiene o reach o grip o activities. • Responses for the 30 items are recorded using 4-point Likert scales: o 0 = no difficult o 1 = some difficulty o 2 = much difficulty o 3 = unable to do. • Activities that the child is unable to do because he/she is too young are marked as	Yes	According to Dempster et al.:[49] • MCID improvement reduction in score of 0.13 (or –4.3%). • MCID deterioration median change in score of 0.75 (or 25%). According to Brunner et al.:[51] • MCID improvement reduction in score of no greater than 0.188. • MCID worsening of an increase in CHAQ and no greater than 0.125.	28,29,49,51,52

Instrument	Type	Validated	MCID	References
	"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. • The global disability index obtained by calculating mean of the 8 functional areas and 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 evaluation of overall well-being.			
CHQ	• Includes 14 domains (which involved physical health, mental health, pain, school, social, and family) and provides 2 summary measures: the PhS and PsS. • There are two forms available that are self-administrated: o Parent (includes 50 or 28 items, depending on version) o Child (includes 87 items) • Scores range between 0 and 100; higher scores indicating better HRQoL: o 0 = poor well-being o 100 = excellent well-being.	Yes	None	29-31

ACR = American College of Rheumatology; CHAQ = Childhood Health Assessment Questionnaire; CHQ = Childhood Health Questionnaire; ESR = erythrocyte sedimentation rate; HRQoL = health-related quality of life; MCID = minimal clinically important difference; NA = not applicable; PhS = physical score; PsS = psychosocial score; VAS = visual analogue scale.

[a] ACR Pedi 50, 75, or 100 are also available and correspond the percentage change from baseline, e.g., ACR Pedi 50 corresponds to a 50% improvement.

APPENDIX 6: SUMMARY OF LONG-TERM DATA

[redacted]

[redacted]

[redacted]

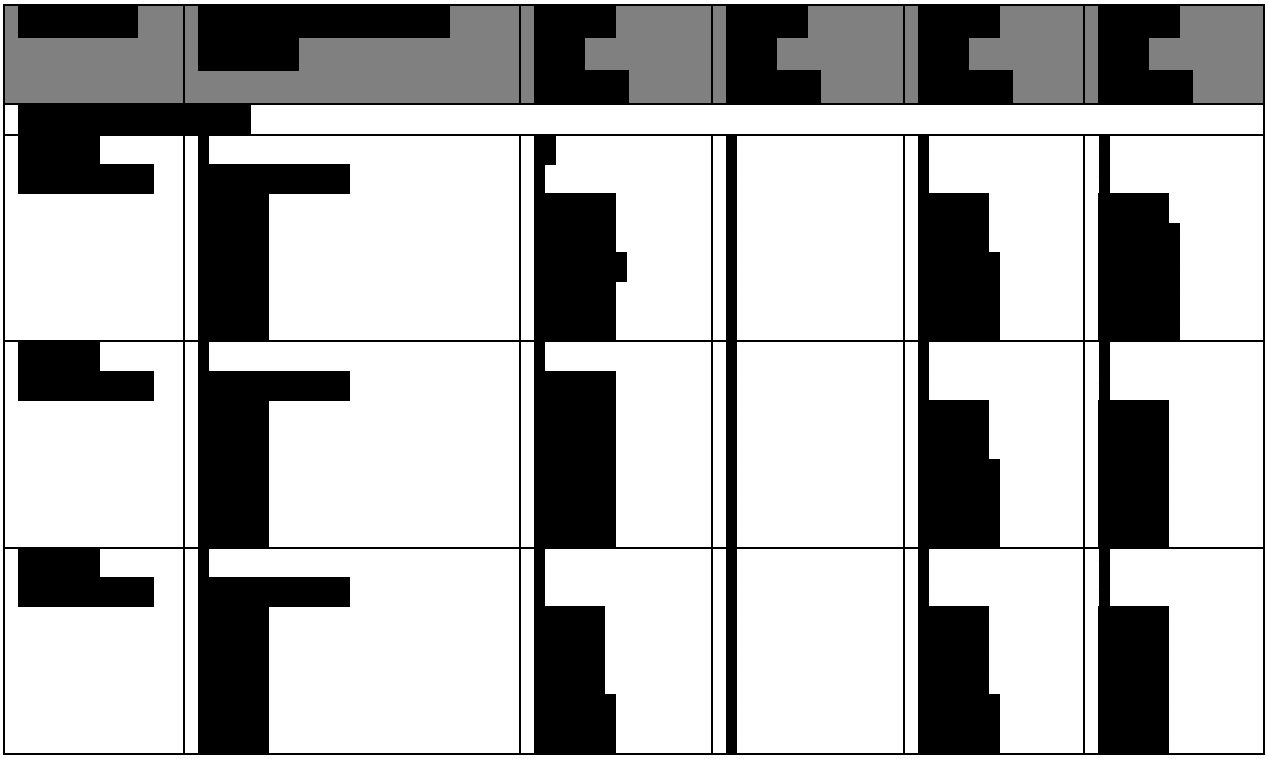
[redacted]

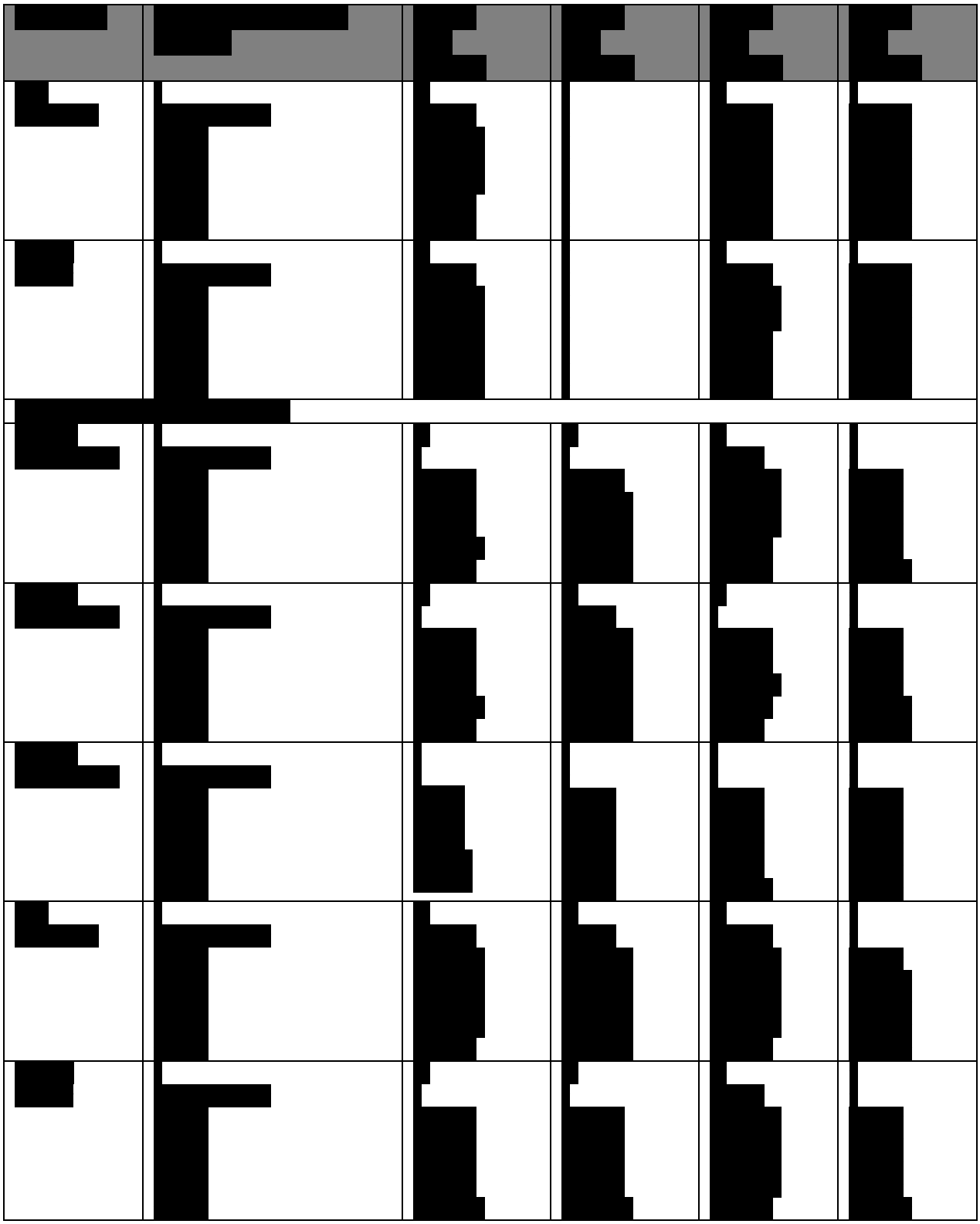
[redacted]

[redacted]

[redacted]

[redacted]



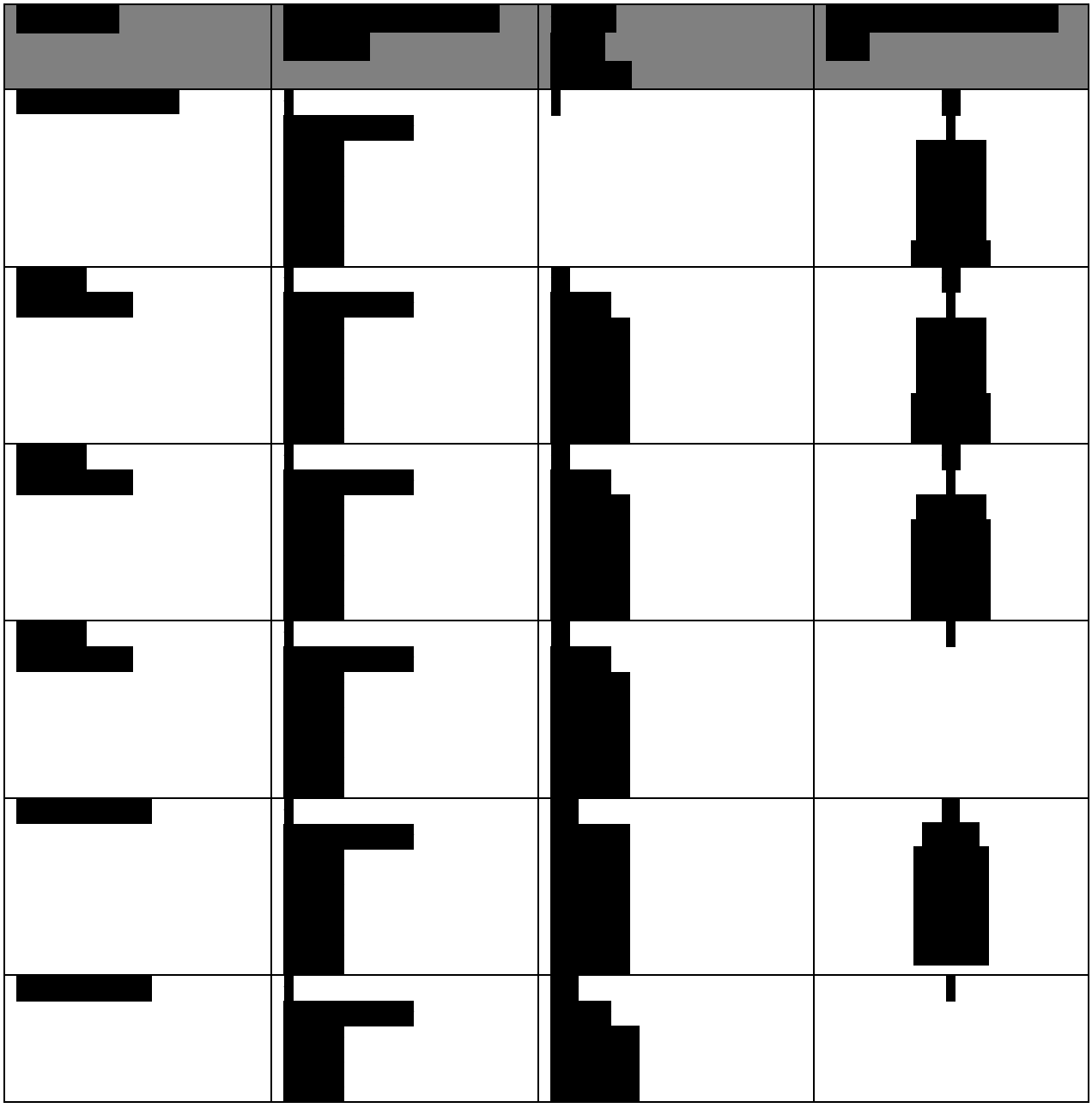


[redacted]

[redacted]

[redacted]

[redacted]



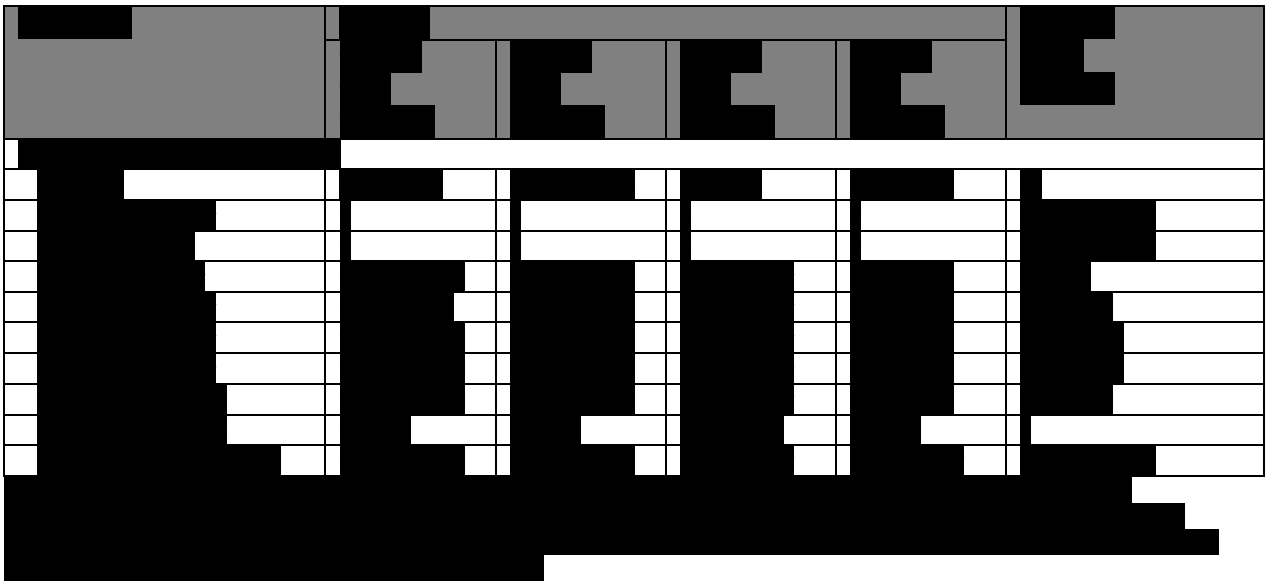
[redacted]

[redacted]

[redacted]

[redacted]

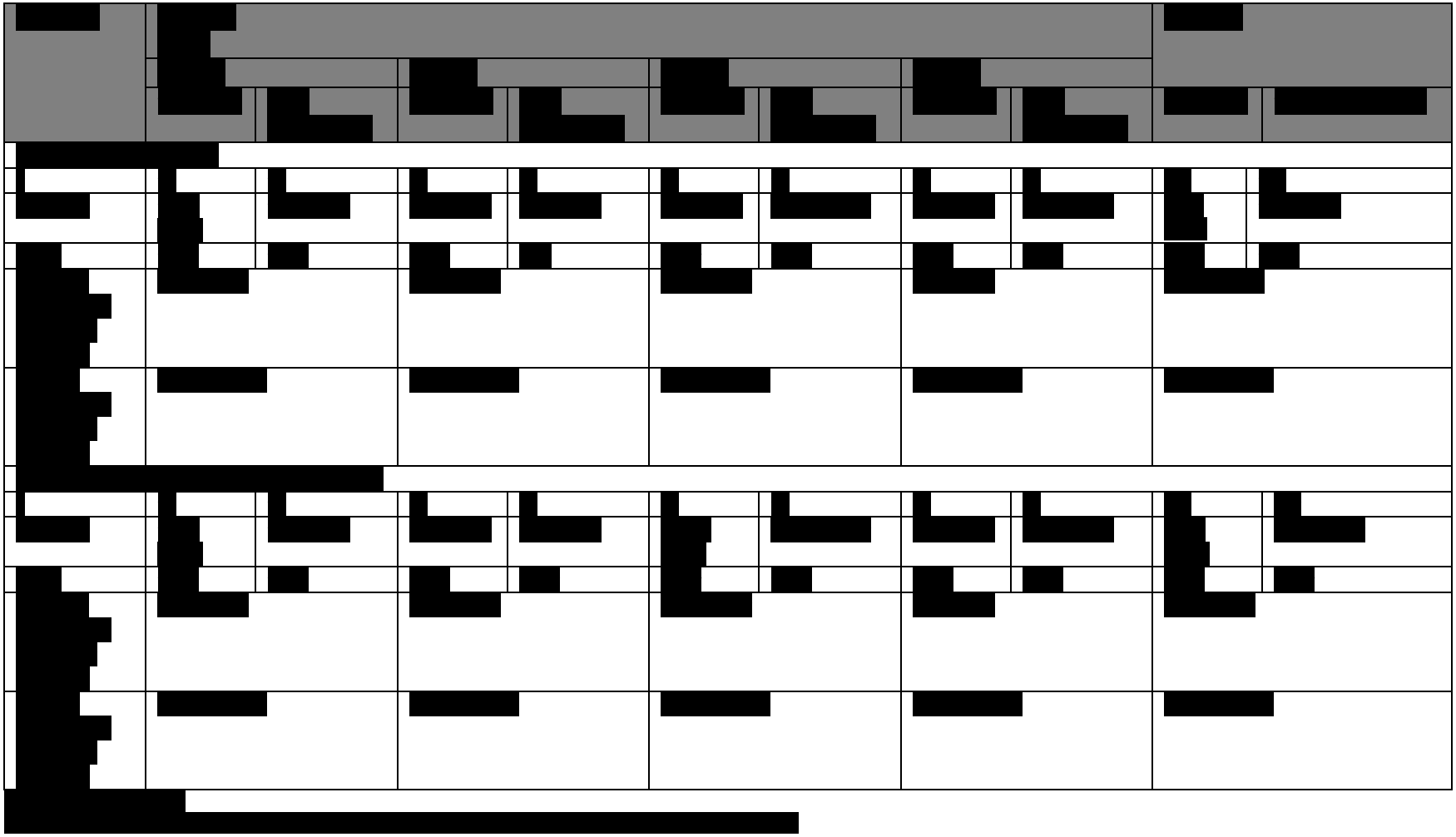
[redacted]



[redacted]

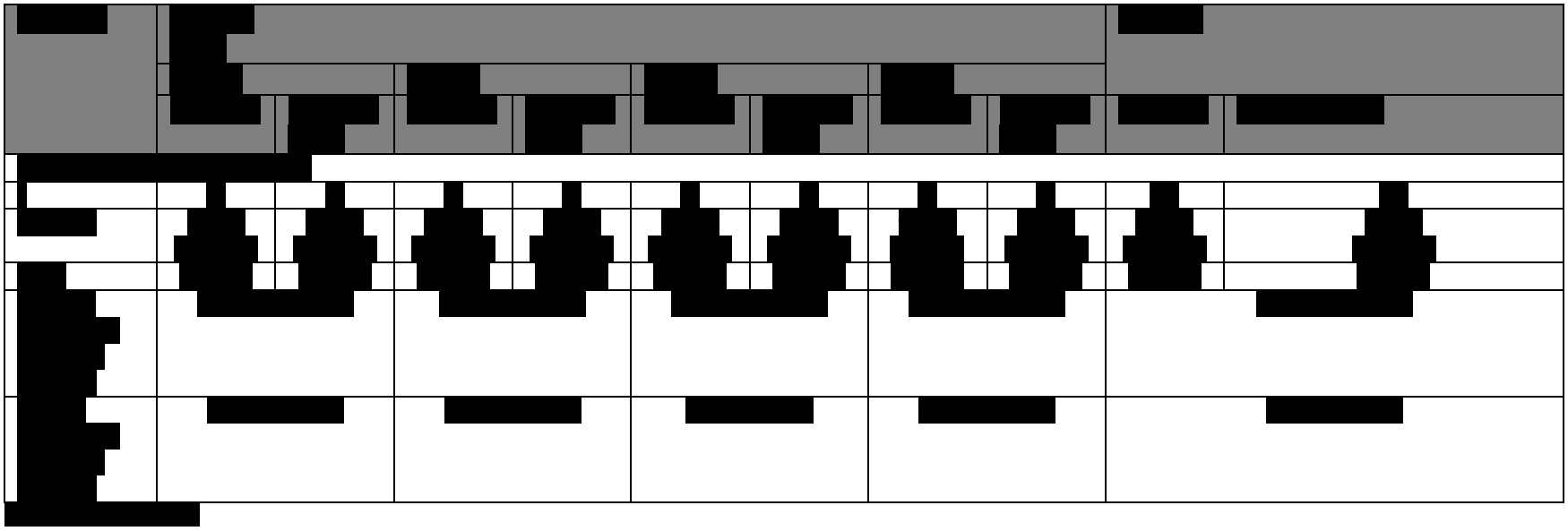
[redacted]

[redacted]

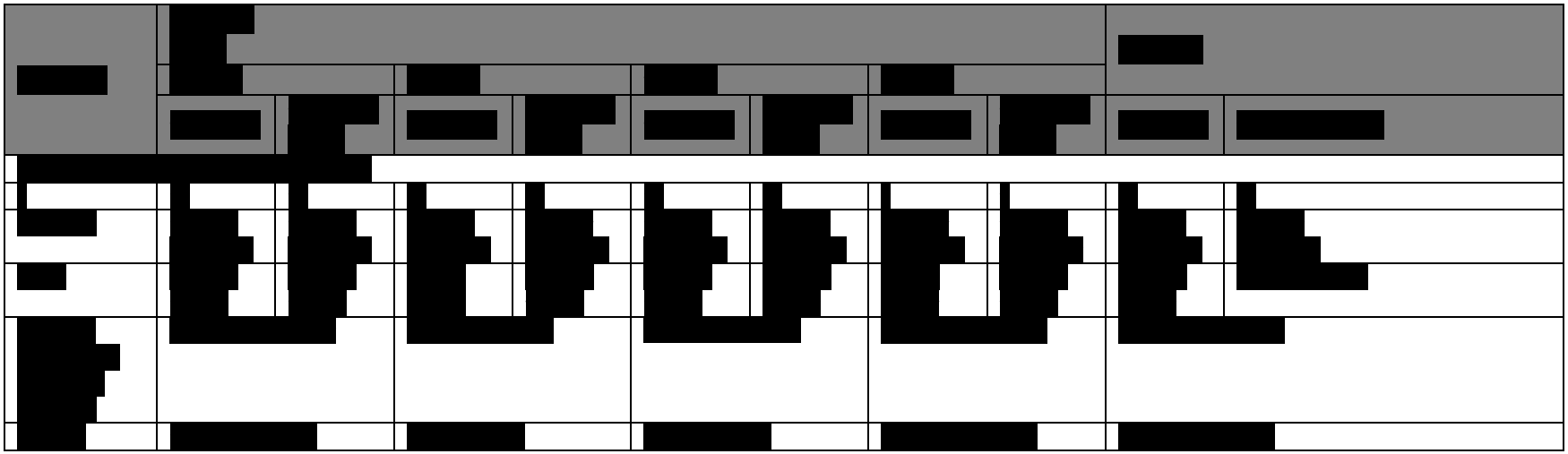


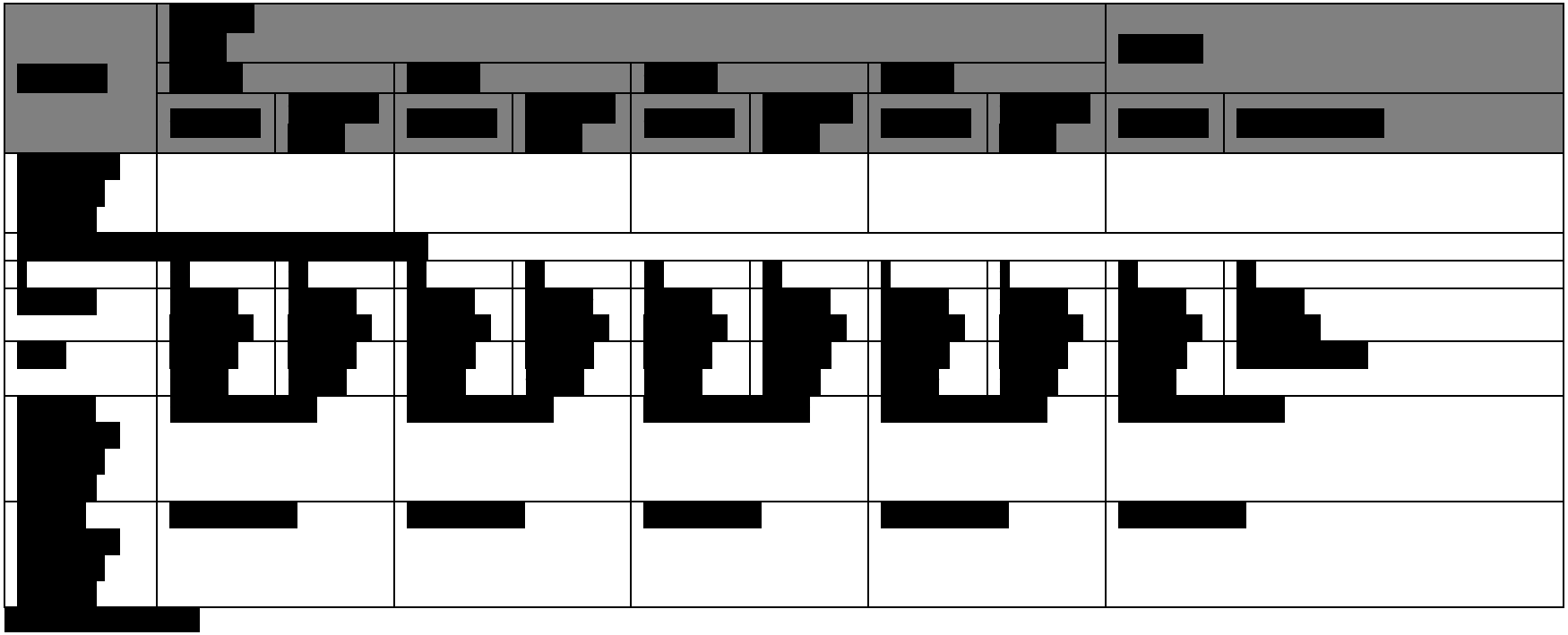
[redacted]

[redacted]



[redacted]





APPENDIX 7: SUMMARY OF INDIRECT TREATMENT COMPARISONS

1. Introduction

1.1 Background

There is a lack of evidence with which to directly compare canakinumab with other drugs used in the management of sJIA. In order to inform this evidence gap, the CADTH CDR reviewed and critically appraised available indirect evidence.

1.2 Methods

A literature search was undertaken by CDR to identify any relevant published indirect treatment comparisons (ITCs). One relevant publication,[13] presenting data from one unique ITC, is included in this section, in addition to one manufacturer-provided, unpublished ITC.

2. Description of ITCs identified

Both ITCs assessed the comparative efficacy of canakinumab versus tocilizumab as treatment for sJIA. Studies were selected for inclusion based on the selection criteria presented in.

TABLE 26: INCLUSION CRITERIA (PICOS) FOR THE ITCS

	Otten et al. 2013[13]	Manufacturer ITC[9]
Patient Population	Patients with sJIA	Patients with sJIA who have responded inadequately to NSAIDs and systemic corticosteroids
Intervention	Canakinumab	Canakinumab
Relevant Comparators	Tocilizumab Anakinra	Tocilizumab
Relevant Outcomes	Disease flares; ACR Pedi30 Response; Inactive disease	ACR Pedi Response 30, 50, 70 and 90 levels; physician's assessment of disease activity; parent/patient assessment of overall well-being; CHAQ; joints with active disease; joints with limited range of motion; change from baseline in pain on VAS; absence of fever.
Study Design	RCTs with parallel study design	RCTs with parallel study design

CHAQ = Childhood Health Assessment Questionnaire; ITC = indirect treatment comparison; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; sJIA = systemic juvenile idiopathic arthritis; VAS = visual analogue scale.

2.1 Review and Appraisal of ITCs

2.1.1 Objectives and rationale

Otten et al. 2013[13] had the objective of comparing the efficacy of canakinumab and other biologic drugs (anakinra and tocilizumab) used in the management of sJIA. The objective of the manufacturer's analysis was to determine the relative clinical efficacy of canakinumab compared with tocilizumab in patients with sJIA who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. The only comparator selected was tocilizumab; together with canakinumab, these interleukin inhibitors are the only therapeutic options with a Health Canada indication for sJIA.

2.2 Methods

2.2.1 Study eligibility and selection process

The authors of Otten et al. 2013[13] performed a systematic search using several databases (PubMed, Embase, and Cochrane clinical trials), including studies up to January 2012. The study selection process involved independent duplicate reviewers. In the manufacturer-provided analysis, Study 2305 was selected as the data source for canakinumab. A literature review was performed to identify published RCTs for tocilizumab, but the detailed search strategy was not reported.

2.2.2 Data extraction

Studies were selected for inclusion in the two included ITCs based on the selection criteria presented in Table 26. In Otten et al. 2013,[13] data extraction was performed by independent duplicate reviewers. A total of three RCTs were included in the systematic review: Ruperto et al.[12] (canakinumab Study 2305; n = 84), De Benedetti et al.[54] (tocilizumab; n = 112), and Quartier[55] (anakinra; n = 24).

The manufacturer-provided ITC included two RCTs, which were also included in Otten et al. 2013: Ruperto et al. (canakinumab) and De Benedetti (tocilizumab). No information was provided with regard to the data extraction process. Details for all included studies are presented in Table 27.

All included trials exclusively enrolled patients with sJIA. The mean disease duration ranged between 3.4 years for the canakinumab trial and 5.2 years for the tocilizumab trial. The trial duration was 4 weeks for the canakinumab and anakinra trials, and 12 weeks for the tocilizumab trial. All studies included a proportion of patients who had prior experience with a biological drug.

TABLE 27: CHARACTERISTICS OF THE INCLUDED STUDIES AND POPULATION IN OTTEN ET AL. 2013 AND MANUFACTURER ITC

Studies	Included in the Following ITC	Interventions and Duration	Population	Outcome
Ruperto et al. 2011 (Study 2305)	Otten et al. 2013[13] AND Manufacturer ITC [9]	Canakinumab versus placebo For a duration of 4 weeks (Primary analysis at day 15)	• Patients with sJIA (n = 84). • Mean disease duration of 3.4 years. • Prior use of biologic drug: 40% interleukin inhibitor; 36% other.	Primary outcome: Adapted ACR Pedi 30 response
De Benedetti 2010-2011 (TENDER)	Otten et al. 2013[13] AND Manufacturer ITC [9]	Tocilizumab versus placebo For a duration of 12 weeks	• Patients with sJIA (n = 112). • Mean disease duration of 5.2 years. • Prior use of biologic drug in 82% of patients.	Primary outcome: Adapted ACR Pedi 30 response
Quartier 2010 (ANAJIS)	Otten et al. 2013[13] only	Anakinra versus placebo For a duration of 4 weeks	• Patients with sJIA (n = 24). • Mean disease duration of 3.7 years. • Prior use of biologic drug in 54% of patients.	Primary outcome: Adapted ACR Pedi 30 response

ITC = indirect treatment comparison; sJIA = systemic juvenile idiopathic arthritis.
Source: [9,13]

2.2.3 Comparators

Comparators in the included studies were tocilizumab and anakinra. Included comparators are the ones that were of most interest to Canadian decision-makers.

2.2.4 Outcomes

The primary outcome in all included trials was the adapted ACR Pedi 30 response, and this was the only outcome reported in Otten et al. 2013. The manufacturer-provided ITC also included secondary outcomes of the trials, including other levels of ACR Pedi response, as well as HRQoL and functional outcomes.

2.2.5 Quality assessment of included studies

In Otten et al. 2013,[13] the authors evaluated the risk of bias in the included studies. Independent duplicate reviewers performed study assessment using the Jadad scale criteria. Assessment of trial quality could not be completed for most included studies due to the lack of information available from the publications. No quality assessment of the trials was reported in the manufacturer-provided analysis.

2.3 Indirect Treatment Comparison Methods

Otten et al. 2013 indicate that indirect between-drug comparisons were conducted using the Bucher method. Through standard meta-analysis techniques, this method uses the effect measure comparing two treatments within an RCT rather than the individual results for each treatment group, which partially maintains the strength of randomization. Heterogeneity assessment was performed for all included studies regarding trial design and baseline characteristics. Results for the adjusted ITCs were reported using the relative risk (RR) with associated 95% confidence intervals (95% CI) and two-sided *P* values with a significance level of 0.05.

The manufacturer-provided ITC compared indirectly canakinumab with tocilizumab using the Bucher method as well. The authors adjusted the clinical efficacy of canakinumab using trial data in order to match the length of follow-up and outcome definition of the tocilizumab study. In order to align the efficacy evaluation time points to 12 weeks, the clinical response of patients randomized to canakinumab in Study 2305, and who continued to receive canakinumab as part of another manufacturer-sponsored RCT, was estimated at 12 weeks. An assumption was made for the placebo group that the 4-week efficacy results would remain constant over time and be representative of a potential 12-week outcome assessment had the placebo group been followed for an additional 8 weeks.

As for outcome definition, the tocilizumab trial (De Benedetti 2012)[54] used as primary outcome an absence of fever combined with a conventional ACR Pedi 30 response. The canakinumab study used an adapted ACR Pedi response by adding no intermittent fever in the preceding week to the conventional ACR Pedi measures, and using C-reactive protein (CRP) instead of erythrocyte sedimentation rate (ESR) as a measurement of inflammation levels. The manufacturer-provided ITC makes an assumption on the correlation between changes in CRP and ESR. In addition, the authors changed the ACR definition of Study 2305 to make it comparable across the trials. As a result, ACR Pedi response criteria for canakinumab were re-estimated using patient-level data to provide a conventional ACR Pedi response with no reference to systemic features such as fever. Since the primary outcome in the tocilizumab trial included the absence of fever, the reasons supporting this adjustment, as well as its impact on the analysis, are unclear. Results for the ITCs were reported using the RR with associated 95% CIs.

2.4 Results

The primary outcome in the ITCs and in the included trials was the adapted ACR Pedi 30 response. The main ITC findings are presented in Table 28. In Otten et al. 2013, there was no statistically significant difference between canakinumab and anakinra, as well as between canakinumab and tocilizumab. Results favoured canakinumab in both comparisons, but statistical significance was not reached.
The manufacturer-provided ITC reported results for the modified outcome of ACR Pedi 30 response (non-adapted for the systemic features of sJIA). [redacted]

TABLE 28: MAIN ITC RESULTS

	Otten et al. 2013[13]	Manufacturer ITC [9]
Primary Outcome	**Adapted ACR Pedi Response**	[redacted]
Comparison	Tocilizumab versus canakinumab	[redacted]
RR (95% CI), *P* value	0.41 (0.14 to 1.23), *P* = 0.11	[redacted]
Comparison	Anakinra versus canakinumab	[redacted]
RR (95% CI), *P* value	0.93 (0.11 to 7.91), *P* = 0.95	

ACR Pedi = American College of Rheumatology, Pediatric score; CI = confidence interval; RR = relative risk.
* No *P* value reported.
Sources: CDR submission;[9] Otten et al. 2013[13]

2.5 Critical Appraisal

Otten et al. 2013 was likely conducted with methodological rigour, with adequate reporting quality, but was not without limitations. Outcomes included in the ITC were limited to ACR Pedi 30 response with no fever; no ITCs were reported for clinical outcomes directly relevant to patients such as HRQoL and functional outcomes. Whether the ITCs provide a valid estimate of the relative effect of two interventions depends on the fulfillment of the primary assumption of comparability of treatments, patients, and methodology. There were a few imbalances in baseline characteristics between studies, some of which may be considered a significant source of concern, especially in terms of length of follow-up. The impact on the ITC findings is uncertain. The patient characteristics reflect the profile of sJIA patients with a high degree of disease activity and refractory to initial therapeutic options. Canakinumab and tocilizumab dosing strategies were in line with the Health Canada-approved labels for the products; the anakinra dosage could not be assessed as the drug has no Health Canada indication for sJIA.

The studies included in the manufacturer-provided ITC were also included in Otten et al. 2013; therefore, the same limitations regarding these studies also apply. In addition, the ITC had insufficient reporting quality with regard to methodology, which was obviously non-systematic. No detail was provided on the literature search strategy, study selection process, data extraction methods and sources of the included data. A layer of uncertainty was added due to the fact that results for the canakinumab

study were converted to align with the tocilizumab study for length of follow-up and outcome definition, requiring the authors to make assumptions. Adjustment of clinical efficacy at the 12-week time point appeared a conservative approach, as it may bias results against canakinumab; however, the reasons supporting the outcome definition adjustment and potential impact on the analysis are unclear, considering the similarity between the primary outcome definitions in both studies. There is also a potential for conflicts of interest, as the analysis was manufacturer-provided.

The main limitation of both ITCs was the small number of studies included, all with a relatively small sample size. Only one study was included in the evidence network for each drug, resulting in a high degree of uncertainty around the ITC findings. In addition, no ITCs were reported for safety outcomes, which are directly relevant to patients. The ITCs did not provide assessment of whether the monthly subcutaneous administration of canakinumab is a significant benefit to patients compared with the intravenous administration of tocilizumab every two weeks, and the daily subcutaneous administration of anakinra.

3. Conclusion

There is a lack of evidence with which to directly compare canakinumab to other drugs used in managing sJIA, especially the interleukin inhibitor tocilizumab. In order to inform this evidence gap, CDR reviewed and critically appraised available indirect evidence. A literature search was undertaken to identify relevant published ITCs. One relevant publication was included, in addition to one manufacturer-provided, unpublished ITC. Otten et al. 2013[13] assessed the comparative efficacy of canakinumab, anakinra, and tocilizumab in the management of sJIA; the manufacturer's ITC focused on canakinumab and tocilizumab in a population of patients with sJIA including patients who have responded inadequately to NSAIDs and corticosteroids. [redacted] Safety outcomes were not assessed. The main limitation was the small number of studies included and the small sample sizes, which results in a high degree of uncertainty surrounding the findings. [redacted]

REFERENCES

1. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, Dewitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) [Internet]. 2011 Apr [cited 2016 Jan 27];63(4):465-82. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3222233/pdf/nihms322240.pdf
2. Chedeville G. Petit guide de l'arthrite juvenile idiopatique. Le Rhumatologue. 2011;9:1-12.
3. Gowdie PJ, Tse SM. Juvenile idiopathic arthritis. Pediatr Clin North Am. 2012 Apr;59(2):301-27.
4. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet. 2011 Jun 18;377(9783):2138-49.
5. Ringold S, Weiss PF, Beukelman T, Dewitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Care Res (Hoboken) [Internet]. 2013 Oct [cited 2016 Jan 27];65(10):1551-63. Available from: http://onlinelibrary.wiley.com/doi/10.1002/acr.22087/epdf
6. Ringold S, Weiss PF, Beukelman T, Dewitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum [Internet]. 2013 Oct [cited 2016 Jan 28];65(10):2499-512. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.38092/epdf
7. Grom AA, Ilowite NT, Pascual V, Brunner HI, Martini A, Lovell D, et al. Rate and clinical presentation of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis treated with canakinumab. Arthritis rheumatol [Internet]. 2016 Jan [cited 2016 Feb 1];68(1):218-28. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.39407/epdf
8. Woerner A, von Scheven-Gete A, Cimaz R, Hofer M. Complications of systemic juvenile idiopathic arthritis: risk factors and management recommendations. Expert Rev Clin Immunol. 2015 May;11(5):575-88.
9. CDR submission: Ilaris® (canakinumab) 150 mg powder for solution for subcutaneous injection. Company: Novartis Pharmaceuticals Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2015 Dec 16.
10. Ilaris® (canakinumab) 150 mg powder for solution for subcutaneous injection [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2014 Jul 14.
11. Kimura Y. Systemic juvenile idiopathic arthritis: treatment. 2015 Sep 28 [cited 2016 Jan 27]. In: UpToDate [Internet]. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.
12. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012 Dec 20;367(25):2396-406.
13. Otten MH, Anink J, Spronk S, van Suijlekom-Smit LW. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013 Nov;72(11):1806-12.

14. Clinical Study Report: CACZ885G2301. A randomized, double-blind, placebo controlled, withdrawal study of flare prevention of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations [**CONFIDENTIAL** internal manufacturer's report]. [Basel (Switzerland)]: Novartis; 2012 Sep 20.
15. Clinical Study Report: CACZ885G2305. A randomized, double-blind, placebo controlled, single-dose study to assess the initial efficacy of canakinumab (ACZ885) with respect to the adapted ACR Pediatric 30 criteria in patients with Systemic Juvenile Idiopathic Arthritis (sJIA) and active systemic manifestations [**CONFIDENTIAL** internal manufacturer's report]. [Basel (Switzerland)]: Novartis; 2012 Sep 19.
16. Grom A. Juvenile idiopathic arthritis: epidemiology and immunopathogenesis. 2012 Oct 31 [cited 2013 Feb 14]. In: UpToDate [Internet]. Waltham (MA): UpToDate; 1992 - . Available from: www.uptodate.com Subscription required.
17. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2009 -. Nonsteroidal anti-inflammatory drugs (NSAIDs); 2014 [cited 2016 Feb 2]. Available from: https://www.e-therapeutics.ca Subscription required.
18. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2009 -. Corticosteroids: systemic (CPhA monograph); 2011 Oct [cited 2016 Mar 7]. Available from: https://www.e-therapeutics.ca Subscription required.
19. Actemra® (tocilizumab): 20 mg/mL concentrate solution for infusion, 162 mg/0.9 mL solution for injection [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2015 Oct 29.
20. Woerner A, Uettwiller F, Melki I, Mouy R, Wouters C, Bader-Meunier B, et al. Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. Rmd open [Internet]. 2015 [cited 2016 Jan 29];1(1):e000036. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4613174/pdf/rmdopen-2014-000036.pdf
21. Methotrexate: methotrexate tablets USP, methotrexate injection USP [product monograph]. Kirkland (QC): Pfizer Canada, Inc.; 2011.
22. Humira® (adalimumab): 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneuous injection [product monograph]. St-Laurent (QC): AbbVie Corporation; 2015 Dec 31.
23. Enbrel (etanercept): solution for injection in a prefilled syringe 50 mg/mL and lyophilized powder for reconstitution in a vial 25 mg/vial [product monograph]. Thousand Oaks (CA): Immunex Corporation; 2012.
24. Remicade (infliximab): powder for solution, sterile, lyophilized, 100 mg/vial [product monograph]. Toronto: Janssen Inc.; 2013.
25. Orencia (abatacept): intravenous injection 250 mg/15 mL vial [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2012.
26. Kineret® (anakinra): solution for injection in prefilled syringe, 100 mg per syringe (150 mg/mL) [product monograph]. Stockholm (Sweden): Swedish Orphan BioVitrum AB (publ); 2015.
27. Health Canada reviewer's report: Ilaris® (canakinumab) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2015 Sep.
28. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum. 1994 Dec;37(12):1761-9.

29. Sawhney S, Agarwal M. Outcome measures in pediatric rheumatology. Indian J Pediatr. 2010 Oct;77(10):1183-9.

30. Luca NJ, Feldman BM. Disease activity measures in paediatric rheumatic diseases. Int J Rheumatol [Internet]. 2013 [cited 2016 Mar 8];2013:715352. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3781994

31. van Mater HA, Williams JW Jr, Coeytaux RR, Sanders GD, Kemper AR. Psychometric characteristics of outcome measures in juvenile idiopathic arthritis: a systematic review. Arthritis Care Res (Hoboken). 2012 Apr;64(4):554-62.

32. Brunner HI, Ruperto N, Quartier P, Constantin T, Berkun Y, Calvo-Penedes I, et al. Efficacy of canakinumab in systemic juvenile idiopathic arthritis patients previously exposed to biologics. Arthritis Rheum [Internet]. 2015 [cited 2016 Apr 27];67(S10):1255-6. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.39448/pdf

33. Ruperto N, Quartier P, Wulffraat N, Woo P, Ravelli A, Mouy R, et al. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum. 2012 Feb;64(2):557-67.

34. Canakinumab (Ilaris) for systemic juvenile idiopathic arthritis. Med Lett Drugs Ther. 2013 Aug 19;55(1423):65-6.

35. Giannini EH, Lovell DJ, Felson DT, Goldsmith DP. Preliminary core of set of outcome variables for use in JRA clinical trials [abstract]. Arthritis Rheum. 1994;37 Suppl 9:S428.

36. Brewer EJ, Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, et al. Current proposed revision of JRA Criteria. JRA Criteria Subcommittee of the Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Section of The Arthritis Foundation. Arthritis Rheum. 1977 Mar;20(2 Suppl):195-9.

37. Cassidy JT, Levinson JE, Bass JC, Baum J, Brewer EJ, Fink CW, et al. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum. 1986 Feb;29(2):274-81.

38. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997 Jul;40(7):1202-9.

39. Lurati A, Pontikaki I, Teruzzi B, Desiati F, Gerloni V, Gattinara M, et al. A comparison of response criteria to evaluate therapeutic response in patients with juvenile idiopathic arthritis treated with methotrexate and/or anti-tumor necrosis factor alpha agents. Arthritis Rheum [Internet]. 2006 May [cited 2016 Feb 25];54(5):1602-7. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.21784/pdf

40. Reiff A. Childhood quality of life in the changing landscape of pediatric rheumatology. J Pediatr (Rio J). 2008 Jul;84(4):285-8.

41. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.

42. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20.

43. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 -- status and review. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1996. p. 227-37.

44. Pouchot J, Ecosse E, Coste J, Guillemin F. Validity of the childhood health assessment questionnaire is independent of age in juvenile idiopathic arthritis. Arthritis Rheum. 2004 Aug 15;51(4):519-26.

45. Tennant A, Kearns S, Turner F, Wyatt S, Haigh R, Chamberlain MA. Measuring the function of children with juvenile arthritis. Rheumatology (Oxford, England) [Internet]. 2001 Nov [cited 2016 Feb 25];40(11):1274-8. Available from: http://rheumatology.oxfordjournals.org/cgi/reprint/40/11/1274

46. Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, et al. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clin Exp Rheumatol. 2001 Jul;19(4 Suppl 23):S1-S9.

47. Ruperto N, Ravelli A, Migliavacca D, Viola S, Pistorio A, Duarte C, et al. Responsiveness of clinical measures in children with oligoarticular juvenile chronic arthritis. J Rheumatol. 1999 Aug;26(8):1827-30.

48. McHorney CA. Generic health measurement: past accomplishments and a measurement paradigm for the 21st century. Ann Intern Med. 1997 Oct 15;127(8 Pt 2):743-50.

49. Ruperto N. Is minimal clinically important difference relevant for the interpretation of clinical trials in pediatric rheumatic diseases? J Rheumatol. 2007 Mar;34(3):463-5.

50. Dempster H, Porepa M, Young N, Feldman BM. The clinical meaning of functional outcome scores in children with juvenile arthritis. Arthritis Rheum. 2001 Aug;44(8):1768-74.

51. Brunner HI, Klein-Gitelman MS, Miller MJ, Barron A, Baldwin N, Trombley M, et al. Minimal clinically important differences of the childhood health assessment questionnaire. J Rheumatol. 2005 Jan;32(1):150-61.

52. Amine B, Rostom S, Benbouazza K, Abouqal R, Hajjaj-Hassouni N. Health related quality of life survey about children and adolescents with juvenile idiopathic arthritis. Rheumatol Int. 2009 Jan;29(3):275-9.

53. Clinical Study Report: CACZ885G2301E1. An open-label extension study of canakinumab (ACZ885) in patients with Systemic Juvenile Idiopathic Arthritis (SJIA) and active systemic manifestations who participated in studies ACZ885G2301 and ACZ885G2305; and response characterization study in canakinumab treatment-naïve patients with active SJIA with and without fever [**CONFIDENTIAL** internal manufacturer's report]. [Basel (Switzerland)]: Novartis; 2015 May 19.

54. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med [Internet]. 2012 Dec 20 [cited 2016 Mar 11];367(25):2385-95. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1112802

55. Quartier P, Grom A, Ruperto N, Brunner HI, Schikler K, Erguven M, et al. Efficacy of canakinumab in biologic-naïve versus previously biologic-exposed SJIA patients: a 12 week pooled post-hoc analysis. Pediatric Rheumatology [Internet]. 2014 [cited 2016 Feb 26];12(Suppl 1):P66. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4184290/pdf/1546-0096-12-S1-P66.pdf