Common Drug Review
Clinical Review Report

August 2015

Drug	tocilizumab (Actemra) (162 mg/0.9 mL solution for subcutaneous injection)
Indication	Adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF antagonists
Listing request	Tocilizumab (Actemra SC) alone or in combination with methotrexate (MTX) for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF.
Manufacturer	Hoffmann-La Roche Ltd.

This review report was prepared by CADTH. In addition to CADTH staff, the review team included a clinical expert in 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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

ACE	Arthritis Consumer Experts
ACR	American College of Rheumatology
AE	adverse event
anti-CCP	anti-cyclic citrullinated peptide
bDMARD	biologic disease-modifying antirheumatic drug
BRM	biologic response modifier
CAPA	Canadian Arthritis Patient Alliance
CRA	Canadian Rheumatology Association
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CRP	C-reactive protein
DAS28	Disease Activity Score 28
DMARD	disease-modifying antirheumatic drug
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	full analysis set
HAQ-DI	Health Assessment Questionnaire−Disability Index
HRQoL	health-related quality of life
IL	interleukin
IR	inadequate response
ITT	intention-to-treat
IV	intravenous
LDAS	low disease activity state
LOCF	last observation carried forward
MCID	minimal clinically important difference
MCS	mental component summary
MTX	methotrexate
NIM	non-inferiority margin
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
PCS	physical component summary
PFS	pre-filled syringe

PP	per-protocol
RA	rheumatoid arthritis
RCT	randomized controlled trial
RF	rheumatoid factor
SAE	serious adverse event
SC	subcutaneous
SF-36	Short-Form 36 Health Survey
SJC	swollen joint count
SOC	system organ class
TCZ	tocilizumab
TJC	tender joint count
TNF	tumour necrosis factor
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality. The prevalence of RA in Canada is about 1%.[1]

The pharmacological therapy of RA aims to achieve remission and, if remission is not possible, to minimize disease activity while controlling symptoms, halting damage, preventing disability, and improving quality of life.[2] Non-biologic synthetic disease-modifying antirheumatic drugs (DMARDs) have been shown to alter the clinical course of RA and slow or halt radiographic progression when used early and aggressively in the treatment of RA.[2] Methotrexate is the preferred DMARD with respect to efficacy and safety and is recommended as first-line DMARD treatment in patients with RA unless contraindicated or not tolerated.[2] Based on Canadian Rheumatology Association guidelines, if patients do not attain the desired target within three to six months of non-biologic DMARD therapy, treatment with a biologic therapy should be initiated.[2]

Tocilizumab (TCZ) is a recombinant humanized anti-human interleukin (IL)-6 receptor monoclonal antibody. It blocks the pleiotropic cytokine IL-6, which is found at high levels in the joints affected by RA.[3] In Canada, TCZ is available as 162 mg/0.9 mL solution in single-use pre-filled syringes for subcutaneous (SC) injection, and in single-use vials containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL for intravenous (IV) infusion. The IV formulation of TCZ was previously reviewed by the Canadian Drug Expert Committee for the treatment of RA and received a recommendation to be listed for adults with moderate to severely active RA who have failed to respond to an adequate trial of both DMARDs and a tumour necrosis factor (TNF) alpha inhibitor.[4]

The objective of this review was to evaluate the beneficial and harmful effects of the SC formulation of TCZ at recommended doses alone or in combination with methotrexate (MTX) or other DMARDs in adult patients with moderately to severely active RA with an inadequate response to one or more DMARDs and/or TNF alpha inhibitor therapies.

Indication under review
Adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF antagonists
Listing criteria requested by sponsor
Tocilizumab (Actemra SC) alone or in combination with methotrexate (MTX) for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF.

Results and Interpretation

Included Studies

Three randomized controlled trials (RCTs) were included in this review. The SUMMACTA trial (N = 1,262) was a double-blind, double-dummy, non-inferiority trial comparing TCZ-SC once weekly in combination with non-biologic DMARDs with TCZ-IV 8 mg/kg every four weeks in combination with non-biologic DMARDs. The MUSASHI trial (N = 348) was a double-blind, double-dummy, non-inferiority trial

comparing TCZ-SC monotherapy every two weeks with TCZ-IV 8 mg/kg monotherapy every four weeks. The BREVACTA trial (N = 656) was a double-blind superiority trial comparing TCZ-SC 162 mg every two weeks in combination with non-biologic DMARDs with placebo every two weeks in combination with non-biologic DMARDs. Patients in SUMMACTA and BREVACTA were stratified by geographic region (Europe, North America, South America, and rest of world) and body weight (< 60 kg, 60 kg to < 100 kg, and ≥ 100 kg). Patients in MUSASHI were stratified by weight at enrolment (< 60 kg or ≥ 60 kg) and by whether they had been previously treated with a TNF alpha inhibitor. All studies were blinded during the first 24 weeks. At week 24, all patients were re-randomized to open-label treatment.

Adult patients with moderately to severely active RA who had an inadequate response to DMARD therapy, approximately 20% of whom had failed at least one TNF alpha inhibitor, were included in the trials. The primary efficacy end point for all studies was the American College of Rheumatology (ACR) 20 response rate at week 24. In SUMMACTA and MUSASHI, no formal comparisons and no tests for non-inferiority were performed for secondary outcomes; therefore, results from these comparisons should be interpreted with caution. In addition, no statistical analyses were performed for the subgroup analyses in any of the included trials. Another potential limitation was the frequency at which TCZ was administered, both subcutaneously and intravenously, in the included trials, which differed somewhat from the regimens recommended in the product monographs for each product. The dose recommended by Health Canada for TCZ-SC is 162 mg every two weeks, increased to 162 mg every week based on clinical response for patients < 100 kg and every two weeks for patients ≥ 100 kg, while starting dose for TCZ-IV is 4 mg/kg every four weeks, increased up to 8 mg/kg every four weeks based on clinical response. By contrast, flexible dose adjustments were not permitted in the included trials, which may compromise the generalizability of the results to clinical practice. Finally, patients enrolled in all three studies had more severe disease activity than typically seen in clinical practice, which might limit the generalizability of the results to RA patients who exhibit less severe disease activity.

Efficacy

In SUMMACTA, the proportion of patients achieving an ACR20 response at week 24 was 69.4% in the TCZ-SC every-week group and 73.4% in the TCZ-IV group, resulting in a between-treatment difference of −4.0% (95% confidence interval [CI], −9.2 to 1.2). Based on these results, TCZ-SC every week was considered non-inferior to TCZ-IV, given that the lower bound of the 95% CI did not cross the pre-specified non-inferiority margin of −12%. The same conclusion was reached for both the per-protocol (PP) and intention-to-treat (ITT) populations. Similarly, there were no statistically significant differences between treatments for the secondary outcomes, including the proportion of patients achieving ACR50, ACR70, remission (defined as a Disease Activity Score [DAS] 28 < 2.6 based on erythrocyte sedimentation rate [ESR]), or a minimum 0.3 improvement in the Health Assessment Questionnaire–Disability Index [HAQ-DI]). Results of the health-related quality of life measurement, assessed using Short-Form (36) Health Survey (SF-36) scores, were similar for both treatment groups, both for the mental component summary (MCS) and physical component summary (PCS) domains; specifically, improvements from baseline (week 0) in the TCZ-SC every week and TCZ-IV groups were 6.2 and 6.5 for the MCS scores, and 9.5 and 9.7 for the PCS scores, respectively. The change in scores from baseline exceeded the established minimal clinically important difference (MCID) of 2.5 to 5 points for both treatment groups.

In MUSASHI, the proportion of patients achieving an ACR20 response at week 24 was 79.2% in the TCZ-SC every-two-weeks group and 88.5% in the TCZ-IV group, resulting in a between-treatment difference of −9.4% (95% CI, −17.6 to −1.2). Based on these results, TCZ-SC every two weeks was considered to be non-inferior to TCZ-IV, given that the lower bound of the 95% CI did not cross the pre-specified non-

inferiority margin of −18%. The same conclusion was reached for both the PP and ITT populations. However, although the lower bound of the 95% CI for the between-treatment difference did not cross the non-inferiority margin, the upper bound of the CI in the PP analysis was less than 0, indicating that, despite meeting the criteria for non-inferiority, the treatment effect for TCZ-SC every two weeks was statistically significantly smaller than that of TCZ-IV. As was the case for SUMMACTA, for MUSASHI there was no statistically significant difference in the proportion of patients achieving both ACR50 and ACR70 between both treatment groups. However, the percentage of patients achieving remission (defined as DAS28-ESR < 2.6) and low disease activity (defined as DAS28-ESR < 3.2) was statistically significantly lower in the TCZ-SC every-two-weeks group when compared with the TCZ-IV group with between-treatment difference of −0.12% (95% CI, −0.23 to −0.02) for remission and −0.17% (95% CI, −0.26 to −0.07) for low disease activity (CADTH Common Drug Review calculations).

In BREVACTA, a statistically significantly greater proportion (60.9%) of patients in the TCZ-SC every-two-weeks group achieved an ACR 20 response compared with 31.5% of patients in the placebo group (between-treatment difference 29.5%; 95% CI, 22.0 to 37.0; $P < 0.0001$). In addition, the proportion of patients achieving ACR50, ACR70, DAS28-ESR < 2.6, DAS28-ESR < 3.2, a minimum 0.3 and 0.22 improvement in the HAQ-DI, was significantly greater in patients receiving TCZ-SC every two weeks versus placebo. Results of the health-related quality of life (SF-36 scores) revealed an improvement from baseline of 6.5 and 3.8 in MCS scores, and 5.3 and 2.9 in PCS scores, for the TCZ-SC every-two-weeks and placebo groups, respectively.

Subgroup analysis by body weight (< 60 kg, 60 kg to < 100 kg, and ≥ 100 kg) in SUMMACTA and BREVACTA indicated that the proportion of patients achieving an ACR20, ACR50, and ACR70 response in the heaviest weight category (≥ 100 kg) was lowest overall. However, there was no evidence of any interaction between treatment and either weight category in the analysis of ACR20.

Harms

The incidence of patients reporting adverse events (AEs) in SUMMACTA and MUSASHI was balanced between the TCZ-SC and TCZ-IV treatment groups (76.2% versus 77.0% in SUMMACTA; 89.0% versus 90.8% in MUSASHI). A slightly higher proportion of patients reported AEs in the TCZ-SC treatment group versus placebo (62.7% versus 57.8%, respectively) in BREVACTA. The incidence of serious AEs (SAEs) and death were low in all treatment groups in all studies. In SUMMACTA and MUSASHI, withdrawals due to AE (WDAE) were slightly more frequent in the TCZ-IV treatment groups (6.5% and 5.2%, respectively) than in the TCZ-SC treatment groups (4.8% and 1.7%, respectively). In BREVACTA, the incidence of WDAE was similar between TCZ-SC and placebo. Infections and infestations were the most common SAE, and these occurred at a similar frequency in all treatment groups in all studies (1.4% in the TCZ-SC every-week group versus 1.4% in the TCZ-IV group in SUMMACTA; 1.2% in the TCZ-SC every-two-weeks group versus 2.9% in the TCZ-IV group in MUSASHI; 2.1% in the TCZ-SC every-two-weeks group versus 1.8% in the placebo group in BREVACTA). There was higher rate of injection-site reactions in the TCZ-SC treatment group (10.1% and 12.1%, respectively) compared with the TCZ-IV treatment group (2.4% and 5.2%, respectively) in SUMMACTA and MUSASHI. In BREVACTA, there was slightly higher rate of injection-site reactions in the TCZ-SC treatment group (7.1%) compared with placebo group (4.1%). The higher rate in injection-site reactions in the TCZ-SC treatment likely reflects the different route of delivery for this formulation compared with the IV formulation. Rates of malignancy were low and balanced between treatment groups in all trials.

In the open-label phase of SUMMACTA trial, higher AE and SAE rates were observed in the group of patients who switched from TCZ-IV to TCZ-SC (633.9 and 20.6 per 100 patient-years) compared with the group that remained on the IV formulation (532.9 and 15.2 per 100 patient-years). In the open-label phase of BREVACTA trials, the safety profile of TCZ-SC was consistent with the results from the double-blind period. No new clinically meaningful safety signals were identified during the open-label extension phase, other than an increased rate of injection-site reactions in patients who initiated escape therapy (TCZ-SC weekly) between week 12 and week 24 of the double-blind phase and continued receiving this higher dosing frequency during the open-label phase.

Other Considerations

We were unable to identify any studies in which TCZ-SC was compared directly or indirectly with any other biologic therapy in patients with RA. Two network meta-analyses (NMAs)[5,6] that compared efficacy of TCZ-IV with other biologic therapies were identified, the results of which suggest that there are no meaningful differences between TCZ-IV and other biologics. Since the efficacy of TCZ-IV is similar to other biologic therapies, and since TCZ-IV is non-inferior to TCZ-SC, it could be hypothesized that TCZ-SC is similar to other biologics. However, in the absence of any evidence that compares TCZ-SC with other biologics, the relative efficacy of TCZ-SC versus other biologics remains uncertain.

Patient input indicated that the SC formulation of tocilizumab may enhance their freedom and control over the management of their disease; they also hope that SC administration would limit visits to the clinic, and they reported a preference for SC route of administration. The clinical expert consulted for this review suggested that patient preference would be the major driver for switching patients from TCZ-IV to TCZ-SC and that newly diagnosed patients who are candidates for TCZ would likely receive TCZ-SC rather than TCZ-IV.

Conclusions

Two double-blind, double-dummy, active-controlled, non-inferiority RCTs (SUMMACTA and MUSASHI) and one placebo-controlled superiority RCT (BREVACTA) met the inclusion criteria for this review. Each of these studies included adult patients with moderately to severely active RA who had an inadequate response to previous DMARD therapy. The results of the BREVACTA trial demonstrated that TCZ-SC every two weeks is superior to placebo with respect to the proportion of patients achieving an ACR20 response as well as all secondary outcomes, including disease activity (ACR 50 and ACR70 thresholds), remission (DAS score), physical function (HAQ-DI scores), and quality of life (SF-36 score). In SUMMACTA and MUSASHI, TCZ-SC was compared directly with TCZ-IV. In SUMMACTA, TCZ-SC (administered weekly) and TCZ-IV were administered in conjunction with non-biologic DMARDs, whereas in MUSASHI, TCZ-SC (administered every two weeks) and TCZ-IV were administered as monotherapy. In SUMMACTA, TCZ-SC every week was non-inferior to TCZ-IV with respect to the proportion of patients achieving an ACR20 response, and there were no significant differences between TCZ-SC every week and TCZ-IV in secondary outcomes, including the proportion of patients who had reduced disease activity (ACR 50 and ACR70 thresholds), disease remission (DAS score), improved physical function (HAQ-DI scores), or improved quality of life (SF-36 score). Similarly, in MUSASHI, TCZ-SC every two weeks was non-inferior to TCZ-IV with respect to the proportion of patients achieving an ACR20 response. However, although the results of the MUSASHI trial met the criteria for non-inferiority, the efficacy of TCZ-SC every two weeks was statistically significantly lower than TCZ-IV with regard to the proportion of patients achieving an ACR20 response. The SC and IV formulations of TCZ were similar with respect to the types and incidences of AEs, although more injection-site reactions occurred in patients treated with the SC formulation.

TABLE 1: SUMMARY OF RESULTS

Outcome	SUMMACTA		MUSASHI		BREVACTA[a]	
	TCZ		TCZ		TCZ	Placebo
	SC 162 mg q.w.	IV 8 mg/kg q.4w.	SC 162 mg q.2w.	IV 8 mg/kg q.4w.	SC 162 mg q.2w.	
Randomized (N)	1,262		348		656	
ACR20 response (PP)						
n/N (%)	387/558 (69.4)	394/537 (73.4)	126/159 (79.2)	138/156 (88.5)	266/437 (60.9)[b]	69/219 (31.5)[b]
Weighted difference (95% CI)[c]	−4.0 (−9.2 to 1.2)		−9.4 (−17.6 to −1.2)		29.5 (22.0 to 37.0) *P* < 0.0001	
ACR50 response (PP)						
n/N (%)	262/558 (47.0)	261/537 (48.6)	101/159 (63.5)	105/156 (67.3)	174/437 (39.8)[b]	27/219 (12.3)[b]
Weighted difference (95% CI)[c]	−1.8 (7.5 to 4.0)		−4.3 (−14.7 to 6.0)		27.9 (21.5 to 34.4) *P* < 0.0001	
ACR70 response (PP)						
n/N (%)	134/558 (24.0)	150/537 (27.9)	59/159 (37.1)	64/156 (41.0)	86/437 (19.7)[b]	11/219 (5.0)[b]
Weighted difference (95% CI)[c]	−3.8 (−9.0 to 1.3)		−3.8 (−14.5 to 6.8)		14.8 (9.8 to 19.9) *P* < 0.0001	
Remission: DAS28-ESR < 2.6 (PP)						
n/N (%)	198/516 (38.4)	184/498 (36.9)	79/159 (49.7)	97/156 (62.2)	111/347 (32.0)[b]	5/124 (4.0)[b]
Weighted difference (95% CI)[c]	0.9 (−5.0 to 6.8)		−12.5 (−23.4 to −1.6)[d]		28.6 (22.0 to 35.2) *P* < 0.0001	
LDAS: DAS28-ESR ≤ 3.2 (PP)						
n/N (%)	[redacted]		[redacted]		157/347 (45.2)[b]	19/124 (15.3)[b]
Weighted difference (95% CI)[c]	0.03 (−0.03 to 0.09)[d]		[redacted]		30.3 (22.0 to 38.6) *P* < 0.0001	
Decrease of ≥ 0.3 in HAQ-DI score (PP)						
n/N (%)	336/515 (65.2)	337/500 (67.4)	NR	NR	202/348 (58.0)[b]	58/124 (46.8)[b]
Weighted difference (95% CI)[c]	−2.3 (−8.1 to 3.4)		NR		12.1 (2.2 to 22.0) *P* = 0.0170	
Harms						
N	631	631	173	173	437	218
Patients with at least one AE, n (%)	481 (76.2)	486 (77.0)	154 (89.0)	157 (90.8)	274 (62.7)	126 (57.8)
Patients with at least one SAE, n (%)	29 (4.6)	33 (5.2)	13 (7.5)	10 (5.8)	20 (4.6)	8 (3.7)
WDAE, n (%)	30 (4.8)	41 (6.5)	3 (1.7)	9 (5.2)	9 (2.1)	3 (1.4)
Deaths, n (%)	0	1 (< 1)	0	0	3 (< 1)	0
Notable harms(s) n (%)						
Infections (all grades)	227 (36.0)	247 (39.1)			131 (30.0)	61 (28.0)
Infections (SAEs)	9 (1.4)	9 (1.4)	2 (1.2)	5 (2.9)	9 (2.1)	4 (1.8)
Malignancies	4 (< 1)	2 (< 1)	0	0	3 (< 1)	0
Hypersensitivity reactions	44 (7.0)	73 (11.6)	NR	NR	19 (4.3)	8 (3.7)
Injection-site reactions	64 (10.1)	15 (2.4)	21 (12.1)	9 (5.2)	31 (7.1)	9 (4.1)
Upper respiratory tract	46 (7.3)	73 (11.6)	16 (9.2)	13 (7.5)	28 (6.4)	14 (6.4)

Outcome	SUMMACTA		MUSASHI		BREVACTA[a]	
	TCZ		TCZ		TCZ	Placebo
	SC 162 mg q.w.	IV 8 mg/kg q.4w.	SC 162 mg q.2w.	IV 8 mg/kg q.4w.	SC 162 mg q.2w.	
infection						
Increased ALT	118 (18.7)	104 (16.5)	17 (9.8)	18 (10.4)	58 (13.3)	11 (5.0)
Increased AST	85 (13.5)	66 (10.5)	[redacted]	[redacted]	36 (8.2)	8 (3.7)

ACR = American College of Rheumatology; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; CI = confidence interval; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; HAQ-DI= Health Assessment Questionnaire−Disability Index; IV = intravenous; LDAS = low disease activity state; NR = not reported; PP = per-protocol; q.w. = every week; q.2w. = every two weeks; q.4w. = every four weeks; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab; WDAE = withdrawal due to adverse event.

[a] Intention-to-treat population.

[b] Patients who withdrew prematurely, who entered escape therapy or for whom an ACR response could not be calculated were set to "Non-Responder."

[c] In the SUMMACTA and BREVACTA studies, the difference was adjusted for the stratification factors of region and body weight at enrolment (< 60 kg, 60 to < 100 kg, or ≥ 100 kg), while in MUSASHI, the difference was adjusted for the stratification factors of body weight at enrolment (< 60 or ≥ 60 kg) and previous use of TNF alpha inhibitors.

[d] Calculated by CADTH using Review Manager; negative values indicate that fewer patients in the TCZ-SC treatment group achieved remission in comparison with patients in the TCZ-IV treatment group.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality.[1] According to a report by the Arthritis Alliance of Canada, RA is the most common inflammatory joint disease in Canada, with a prevalence of 0.9% in 2010 (272,299 patients), which is expected to increase to an estimated 1.3% (549,218 patients) of the Canadian population by 2040. More than one-half of all new RA cases occur in patients between the ages of 40 and 70 years, although all age groups are affected, and the prevalence is approximately two times higher among women than among men.[7]

1.2 Standards of Therapy

1.2.1 Non-pharmacological Management

Guidelines for the management of RA emphasize the use of non-drug interventions in addition to pharmacological therapy.[2,8] Some modalities included in non-drug care are exercise therapy, electro-physical modalities, orthoses and assistive devices, and self-management interventions. There is evidence to support the utility of non-drug care to achieve symptomatic relief, including pain control and muscle stimulation, relief of strain or load on a joint, improved patterns of motion and function, and prevention of deformity, without detrimental effects on disease activity.[8] Education on self-management strategies such as joint protection and energy conservation, exercises, or the use of assistive devices equips RA patients with tools to cope with the disease.[8]

1.2.2 Pharmacological Management

The goal of RA treatment is to achieve remission and, when that is not possible, to minimize disease activity while controlling symptoms, halting damage, preventing disability, and improving quality of life.[2] Beginning treatment early and aggressively with non-biologic synthetic disease-modifying antirheumatic drugs (DMARDs) has been shown to alter the clinical course of RA and slow or halt radiographic progression.[2]

Methotrexate (MTX) is the preferred DMARD with respect to efficacy and safety and is usually the first-line DMARD in patients with RA unless contraindicated. Therapy with MTX is individualized, with doses rapidly titrated to a usual maximum dose of 25 mg per week for intramuscular or intravenous use, and 20 mg per week for oral use.[2] The Canadian Rheumatology Association (CRA) recommends parenteral administration of MTX in patients with an inadequate response or intolerance to oral MTX.[2] The initial treatment strategy with DMARDs can include nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids (in the lowest effective dose possible) or both as bridge therapy while waiting for DMARDs to take effect, to manage flares, or for symptom control if no other options exist.[2]

Currently, all Canadian provincial formularies require failure of at least two DMARDs before accessing a biologic response modifier (BRM), and many also require failure of an adequate trial of combination DMARD therapy.[2] MTX is the preferred anchor drug in combination therapy with conventional DMARDs, unless contraindicated.[2] The CRA defines inadequate response to DMARD as moderate to high disease activity despite treatment with at least two DMARDs (including MTX unless contraindicated) in monotherapy or combination therapy after three months at target doses.

Most BRMs currently approved for use in Canada belong to the tumour necrosis factor (TNF) alpha inhibitor class and include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. Other approved BRMs are abatacept (T cell co-stimulatory inhibitor), rituximab (B lymphocyte-depleting drug), tocilizumab (TCZ; interleukin 6 [IL-6] receptor inhibitor), and anakinra (IL-1 receptor inhibitor).[2] Although co-administration of MTX with BRMs (i.e., adalimumab, certolizumab, etanercept, abatacept, and TCZ) is recommended for improved efficacy, each has an indication for use as monotherapy.[2,3,9-11] This is an important distinction, as not all patients tolerate MTX. In recently diagnosed patients who have not been previously treated with MTX, abatacept is to be used in combination with MTX.[10]

Based on the CRA guidelines,[2] patients who have failed treatment with one or two TNF alpha inhibitors due to lack of efficacy or toxicity could be switched to another TNF alpha inhibitor or to another BRM with a different mechanism of action (Table 2). Both abatacept and TCZ are indicated for the treatment of patients with RA who have had an inadequate response to one or more DMARDs or TNF alpha inhibitors or to both.[3,10] Rituximab, in combination with MTX, is indicated in RA patients who have had an inadequate response or intolerance to one or more TNF alpha inhibitors.[11] In situations of inadequate response to a TNF alpha inhibitor used as monotherapy, adding MTX or other DMARDs is recommended.[2]

According to the CRA recommendations, patients with active RA should be monitored every one to three months, and non-biologic and biologic DMARD therapy should be adjusted every three to six months if treatment targets have not been achieved.[2]

1.3 Drug

Actemra (TCZ) is a recombinant humanized anti-human IL-6 receptor monoclonal antibody. It blocks the pleiotropic cytokine IL-6, which is found at high levels in the joints affected by RA.[3] Tocilizumab is available as 162 mg/0.9 mL solution for subcutaneous (SC) injection, in ready-to-use, single-use pre-filled syringes, and in single-use vials containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of TCZ for intravenous (IV) infusion. Both the SC and IV formulations have a Health Canada indication for reducing signs and symptoms in adult patients with moderately to severely active RA who have inadequate response to one or more DMARDs or TNF alpha inhibitors or both. The IV formulation also has a Health Canada indication for the treatment of polyarticular and systemic juvenile idiopathic arthritis.[3]

The IV formulation of TCZ was previously reviewed by the Canadian Drug Expert Committee for the treatment of RA in November 17, 2010, and received a recommendation to "be listed for adults with moderate to severely active RA who have failed to respond to an adequate trial of both DMARDs and a TNF alpha inhibitor."[4]

The current review is for the SC formulation, for which the Health Canada–approved dose is 162 mg administered SC every two weeks, followed by an increase to every week based on clinical response for patients less than 100 kg weight, and 162 mg administered every week for patients at or above 100 kg weight.[3]

Indication under review
Adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF antagonists
Listing criteria requested by sponsor
Tocilizumab (Actemra SC) alone or in combination with methotrexate (MTX) for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis who have inadequate response to one or more DMARDs and/or TNF.

TABLE 2: KEY CHARACTERISTICS OF BIOLOGIC AGENTS FOR RHEUMATOID ARTHRITIS

	Mechanism of Action	Indication[a]	Route of Administration
Tocilizumab SC	IL-6 receptor inhibitor	IR to ≥ 1 DMARD or TNF alpha inhibitor in moderately to severely active RA	SC
Tocilizumab IV	IL-6 receptor inhibitor		IV
Rituximab	CD20 inhibitor (destroys B cells)	IR to ≥ 1 TNF alpha inhibitor in moderately to severely active RA	IV
Abatacept SC	T cell co-stimulation modulator	IR to ≥ 1 DMARD or TNF alpha inhibitor in moderately to severely active RA	SC
Abatacept IV	T cell co-stimulation modulator		IV
Adalimumab	TNF alpha inhibitors	Moderately to severely active RA	SC
Etanercept			
Golimumab			
Golimumab			IV
Certolizumab pegol			SC
Infliximab			IV
Anakinra	IL-1 receptor inhibitor	Active RA	SC

DMARD = disease-modifying antirheumatic drug; IL = interleukin; IR = inadequate response; IV = intravenous; RA = rheumatoid arthritis; SC = subcutaneous; TNF = tumour necrosis factor.
[a] Health Canada indication.
Source: Health Canada product monographs.[3,10-18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To evaluate the beneficial and harmful effects of the subcutaneous formulation of TCZ (Actemra) at recommended doses alone or in combination with MTX or other DMARDs in adult patients with moderately to severely active RA with an inadequate response to one or more DMARDs or TNF alpha inhibitors or both.

2.2 Methods

Studies identified as pivotal by Health Canada and submitted by the manufacturer were included in this review. In addition, studies that meet the selection criteria presented in Table 3 were included in the review.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Adults with moderate to severely active RA who have inadequate response to ≥ 1 DMARDs or TNF alpha antagonists or both. **Subgroups of interest:** • Body weight at baseline • Number and type of prior DMARDs (biologic or non-biologic) • Inadequate response to prior DMARD(s) versus TNF alpha inhibitors • MTX dose at baseline • Disease severity • RF status (+/-) • Anti-CCP (+/-)
Intervention	Tocilizumab SC at recommended doses alone or in combination with DMARDs
Comparators	Biologic DMARDs used as monotherapy or in combination with non-biologic DMARDs • Tocilizumab IV • Other biologic DMARDs (including rituximab, abatacept, etanercept, infliximab, adalimumab, certolizumab, and golimumab)
Outcomes	***Primary efficacy outcomes:*** • Disease activity (ACR20) ***Secondary efficacy outcomes:*** • Disease activity (ACR50/70, DAS28, CDAI, and SDAI) • Measure of physical function (HAQ-DI or any valid scale) • Quality of life assessment (SF-36 or any valid scale) • Radiography changes (Sharp, modified Sharp, or any valid scale) ***Harms outcomes:*** • Mortality • WDAEs • SAEs • AEs, including but not limited to: ○ fatal infections, serious infections, anaphylaxis/hypersensitivity reactions, hematologic effects, hyperlipidemia, malignancy, tuberculosis, antibody formation, respiratory tract infection, injection-site reaction, gastrointestinal perforation, neutrophil counts, and liver function tests
Study design	Published and unpublished RCTs

Anti-CCP = anti-cyclic citrullinated peptide; ACR = American College of Rheumatology; AE = adverse events; CDAI = Clinical Disease Activity Index; DAS = Disease Activity Score; DMARDs = disease-modifying antirheumatic drugs; HAQ-DI = Health Assessment Questionnaire–Disability Index; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; RF = rheumatoid factor; SAE = serious adverse events; SC = subcutaneous; SDAI = Simplified Disease Activity Index; SF-36 = Short-Form (36) Health Survey; TNF = tumour necrosis factor; WDAE = withdrawal due to adverse events.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Actemra (tocilizumab), RA, and subcutaneous route of administration.

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

The initial search was completed on September 18, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on January 21, 2015. 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 CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/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 Common Drug Review (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 Appendix 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of 73 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. There were no excluded studies.

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

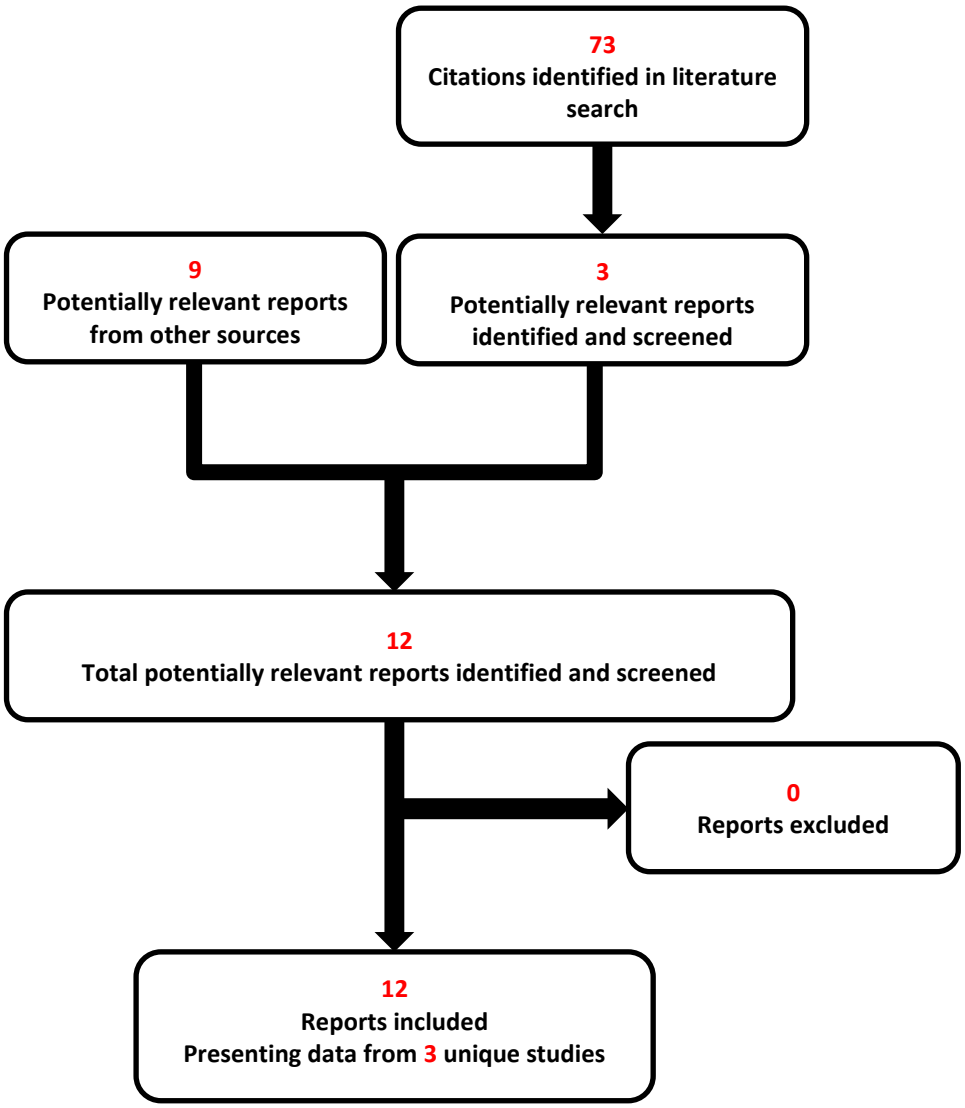


TABLE 4: DETAILS OF INCLUDED STUDIES

		SUMMACTA	MUSASHI	BREVACTA
DESIGNS & POPULATIONS	**Study design**	DB, DD, multi-centre non-inferiority RCT		DB, multi-centre placebo-controlled RCT
	Locations	Multinational: 25 countries, 209 study centres (including centres in the United States and Canada)	52 centres in Japan	Multinational: 21 countries, 124 study centres (including centres in the United States and Canada)
	Randomized (N)	1,262	348	656
	Inclusion criteria	Patients ≥ 18 years meeting the revised ACR 1987 criteria for RA (≥ 6 months from diagnosis). Had to be on at least one permitted DMARD[a] at a stable dose for 8 weeks or longer before baseline. Had an inadequate clinical response to DMARDs that included one or more TNF alpha inhibitors, with up to a maximum of 20% of patients having failed one or more TNF alpha inhibitors; and had: • ≥ 4 swollen joints (66 joint count) • ≥ 4 tender joints (68 joint count) • ESR ≥ 28 mm per hour or CRP ≥ 1.0 mg/dL	Patients aged between 20 and 75 years with diagnosis of RA based on the ACR 1987 criteria for at least 6 months before screening. Inadequate response after 12 weeks to at least one of the following drugs: MTX, salazosulfapyridine, bucillamine, leflunomide, tacrolimus, infliximab, etanercept, and adalimumab), and had: • ≥ 6 swollen joints (66 joint count) • ≥ 8 tender joints (68 joint count) • ESR ≥ 30 mm/hour or CRP ≥ 1.0 mg/dL	Patients ≥ 18 years meeting the revised ACR 1987 criteria for RA (≥ 6 months from diagnosis). Had to be on at least one permitted DMARD[a] at a stable dose for 8 weeks or longer before baseline. Had an inadequate clinical response to DMARDs that included one or more TNF alpha inhibitors, with up to a maximum of 20% of patients having failed one or more TNF alpha inhibitors; and had: • ≥ 6 swollen joints (66 joint count) • ≥ 8 tender joints (68 joint count) • ESR ≥ 28 mm/hour or CRP ≥ 1.0 mg/dL
	Exclusion criteria	• Rheumatic autoimmune disease other than RA • History of or current inflammatory joint disease other than RA • Major surgery (including joint surgery) within 8 weeks before screening • Functional class IV (ACR classification) • Current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including, but not limited to tuberculosis and atypical mycobacterial	• Class IV Steinbrocker functional activity • Previous treatment with TCZ • Been treated with infliximab, etanercept, or adalimumab within 12 weeks before treatment • Had dosage regimen of DMARDs or immunosuppressants changed, had received plasmapheresis or surgical procedures within 4 weeks of TCZ treatment	• Rheumatic autoimmune disease other than RA • History of or current inflammatory joint disease other than RA • Major surgery (including joint surgery) within 8 weeks before screening • Functional class IV (ACR classification) • Current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including, but not limited to tuberculosis and atypical mycobacterial disease, hepatitis B and C)

		SUMMACTA	MUSASHI	BREVACTA
		disease, hepatitis B and C) • Previous treatment with TCZ	• Have a history of serious allergy • Active tuberculosis • Chronic active hepatitis B or C	• Previous treatment with TCZ
DRUGS	**Intervention**	162 mg TCZ administered as SC weekly + placebo administered as IV every 4 weeks for 24 weeks + background therapy with at least one permitted non-biologic DMARD at a stable dose throughout the study[a]	162 mg TCZ administered as SC every 2 weeks + placebo administered as IV every 4 weeks for 24 weeks	162 mg TCZ administered as SC every 2 weeks for 24 weeks + background therapy with permitted non-biologic DMARD(s) at a stable dose throughout the study[a]
	Comparator(s)	8 mg/kg TCZ administered as IV every 4 weeks + placebo administered as SC weekly for 24 weeks + background therapy with at least one permitted non-biologic DMARD at a stable dose throughout the study[a]	8 mg/kg TCZ administered as IV every 4 weeks + placebo administered as SC every two weeks for 24 weeks	Placebo administered as SC every 2 weeks for 24 weeks + background therapy with permitted non-biologic DMARDs at a stable dose throughout the study[a]
DURATION	**Phase**			
	Double-blind	24 weeks	24 weeks	24 weeks Early escape criteria from 12 weeks[b]
	Open-label (long-term period)	72 weeks	84 weeks	72 weeks
OUTCOMES	**Primary end point**	The proportion of patients achieving an ACR20 response at week 24		
	Other end points	• Proportion of patients achieving the following at week 24: ○ ACR50 and ACR70 response ○ DAS28 < 2.6 (DAS remission) ○ HAQ-DI response (improvement of ≥ 0.3 from baseline) ○ Withdrew due to lack of therapeutic response	• For each time point up to 24 weeks after the initial administration: ○ Proportion of patient achieving ACR20, ACR50 and ACR70 ○ Summary statistics for DAS28 ○ Percentage of patients in each category defined according to EULAR response criteria	• Proportion of patients achieving the following at week 24: ○ ACR50 and ACR70 response ○ DAS28 < 2.6 (DAS remission) ○ DAS28 ≤ 3.2 ○ Categorical DAS28 responders (EULAR response) ○ HAQ-DI response (improvement of ≥ 0.3 from baseline) • Change from baseline (week 0) at week 24 in the: ○ van der Heijde-modified Sharp radiographic score

		SUMMACTA	MUSASHI	BREVACTA
				○ HAQ-DI ○ SF-36 subscale and summary scores
NOTES	**Publications**	Burmester et al.[19]	Ogata et al.[20]	Kivitz et al.[21]

ACR = American College of Rheumatology; CDR = CADTH Common Drug Review; CRP = C-reactive protein; DAS = Disease Activity Score; DB = double-blind; DD = double-dummy; DMARDs = disease-modifying antirheumatic drugs; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; HAQ-DI = Health Assessment Questionnaire–Disability Index; IV = intravenous; MTX = methotrexate; RCT = randomized controlled trial; SC = subcutaneous; SF-36 = Short-Form 36-Item; TCZ = tocilizumab.

[a] Permitted DMARDs: azathioprine, chloroquine, hydroxychloroquine, leflunomide, MTX, sulfasalazine.

[b] Early escape criteria = < 20% improvement in both swollen and tender joints counts.

Note: Six additional reports (SUMMACTA trial Clinical Study Report results of the long-term extension,[25] BREVACTA trial Clinical Study Report results of the long-term extension,[26] manufacturer's submission binder,[27] Health Canada Reviewer's report,[28] FDA Medical review(s),[29] FDA Statistical review(s) [30]) were used in the CDR review.

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

3.2 Included Studies

3.2.1 Description of Studies

Three randomized controlled trials (RCTs) met the criteria for inclusion in this systematic review. All were manufacturer-sponsored. All included studies were multi-centre, double-blind RCTs. Study WA22762 (also known as SUMMACTA) and Study MRA229JP (also known as MUSASHI) were double-dummy non-inferiority studies comparing TCZ administered by SC injection with TCZ administered by IV infusion, while Study NA25220 (also known as BREVACTA) compared TCZ-SC injections with placebo in adult patients with moderately to severely active RA. SUMMACTA and BREVACTA were pivotal phase 3 clinical studies, while MUSASHI trial was a supportive phase 3 study conducted exclusively in Japanese patients.

In SUMMACTA, eligible patients (N = 1,262) were randomized in a 1:1 ratio to TCZ 162 mg weekly by SC injection plus placebo IV every four weeks, or to TCZ 8 mg/kg every four weeks by IV infusion plus placebo SC every week for 24 weeks, in combination with non-biologic DMARDs. Randomization was stratified by geographic region (Europe, North America, South America, and rest of world) and body weight (< 60 kg, 60 to < 100 kg, and ≥ 100 kg). The maximum dose was capped at 800 mg for patients in the TCZ-IV group weighing ≥ 100 kg. The number of patients who failed previous TNF alpha inhibitor treatment was limited to approximately 20% of the total study population. This trial was blinded during the first 24 weeks. At week 24, all patients were re-randomized to an open-label 72 week treatment period. Data from this open-label extension phase are summarized in Appendix 6: SUMMARY OF EXTENSION STUDIES.

In MUSASHI, eligible patients (N = 348) were randomized in a 1:1 ratio to TCZ 162 mg every two weeks by SC injection plus placebo IV every four weeks, or to TCZ 8 mg/kg every four weeks by IV infusion plus placebo SC every two weeks for 24 weeks. Randomization was stratified by weight at enrolment (< 60 kg or ≥ 60 kg) and by whether the patient had been previously treated with a TNF alpha inhibitor. Subjects who completed 24 weeks of double-blind treatment continued to an 84-week open-label treatment (TCZ 162 mg SC every two weeks). Data from this open-label extension phase are not available.

In BREVACTA, eligible patients (N = 656) were randomized in a 2:1 ratio to treatment with either TCZ 162 mg every two weeks by SC injection or placebo SC every two weeks for 24 weeks in combination with non-biologic DMARDs. Randomization was stratified by geographic region (Europe, North America, South America, and rest of world) and body weight (< 60 kg, 60 to < 100 kg, and ≥ 100 kg). The number of patients who failed previous TNF alpha inhibitor treatment was limited to approximately 20% of the total study population. From weeks 12 to 48, patients initially randomized to receive either TCZ or placebo could initiate escape therapy with TCZ 162 mg SC every week if there was < 20% improvement in swollen joint count (SJC) and tender joint count (TJC) from baseline (week 0). These patients could receive open-label treatment until the completion of the trial. At week 24, all patients except those who had initiated escape therapy were re-randomized into a 72-week open-label treatment period. Data from this open-label extension phase are summarized in Appendix 6: SUMMARY OF EXTENSION STUDIES.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients were included in SUMMACTA if they were aged 18 years or older and diagnosed with moderately to severely active RA (diagnosed according to the revised 1987 American College of Rheumatology [ACR] criteria) for at least six months. Patients had to have an inadequate response to DMARD therapy that included one or more TNF alpha inhibitors. The percentage of patients who had failed one or more TNF alpha inhibitors was capped at approximately 20%. Patients had to have an SJC of four or more (66 joint count) and a TJC of four or more (68 joint count) at screening and baseline, and had to have either a C-reactive protein (CRP) level of 10 mg/L or higher (1 mg/dL or higher) or an erythrocyte sedimentation rate (ESR) of 28 mm/hour or higher at screening. Patients had to have discontinued etanercept for two weeks or more; infliximab, certolizumab, golimumab, abatacept, or adalimumab for eight weeks or more; or anakinra for one week or more before randomization. Patients had to be taking at least one permitted DMARD (azathioprine, chloroquine, hydroxychloroquine, leflunomide, MTX, or sulfasalazine), which had been at a stable dose for at least eight weeks before baseline. Patients were excluded from the study if they had had major surgery (including joint surgery) within eight weeks before screening, had rheumatic autoimmune disease other than RA, or RA with functional class IV (ACR classification), a diagnosis of juvenile idiopathic arthritis or juvenile RA or RA before the age of 16, a history of or current inflammatory joint disease other than RA, treatment with any investigational drug within four weeks of screening, previous treatment with TCZ, or history of recurrent infection.

Patients were included in MUSASHI if they were between 20 and 75 years of age and diagnosed with RA (based on the 1987 ACR criteria) for at least six months. Patients had to have an inadequate response after at least one of the following drugs (MTX, salazosulfapyridine, bucillamine, leflunomide, tacrolimus, infliximab, etanercept, or adalimumab) administered for at least 12 weeks. Patients had to have an SJC of six or more (66 joint count) and a TJC of eight or more (68 joint count) at screening and baseline, and had to have either a CRP level of 10 mg/L or higher (1 mg/dL or higher) or an ESR of 30 mm per hour or higher at screening. Patients were excluded if they had been assessed as having class IV Steinbrocker functional activity (defined as confined to bed or to a wheelchair, virtually or completely unable to perform usual self-care activities) at evaluation within four weeks before treatment with the investigational product, had previous treatment with TCZ or with infliximab, etanercept, or adalimumab within 12 weeks before treatment, had dosage regimen of DMARDs or immunosuppressants changed, had received plasmapheresis, or had surgical procedures within four weeks of TCZ treatment.

Inclusion and exclusion criteria for BREVACTA trial were similar to those for the SUMMACTA trial except that patients had to have an SJC of six or more (66 joint count) and a TJC of eight or more (68 joint count) at screening and baseline in order to be included, instead of the SUMMACTA criterion of an SJC of four or more (66 joint count) and a TJC of four or more (68 joint count).

b) Baseline Characteristics

Baseline demographic and clinical disease characteristics were generally well balanced across treatment groups in each study (Table 5). Baseline characteristics were similar in SUMMACTA and BREVACTA trials, while in MUSASHI baseline characteristics were slightly different because of the difference in this population (Japanese patients). In all studies the mean age was around 52 years, and the majority (> 82%) of participants were female. In SUMMACTA and BREVACTA trials, Caucasians formed 75% of the total population. Average weight of patients in MUSASHI was at least 15 kg less than average weight of patients in SUMMACTA and BREVACTA trials. Key disease indicators — swollen and tender joints, Health Assessment Questionnaire–Disability Index (HAQ-DI), and Disease Activity Score (DAS) 28 (based on ESR) — were similar across treatment groups in each study. The mean duration of disease ranged from 8.6 to 8.7 years among treatment groups in SUMMACTA, from 8.2 to 8.4 years among those in BREVACTA, and from [redacted] among those in MUSASHI. The mean number of swollen joints ranged from 15 to 16.5 among treatment groups in SUMMACTA, from 9.9 to 10.3 among those in BREVACTA, and from [redacted], while the mean number of tender joints ranged from 27.3 to 28.6 among treatment groups in SUMMACTA, from 27.3 to 28 among those in BREVACTA, and from [redacted]. MTX was previously used in approximately 85% of patients in all treatment groups in SUMMACTA and BREVACTA, while it was previously used in more than [redacted] of patients in MUSASHI. The percentage of patients who previously failed TNF alpha inhibitor was around 21% in all treatment groups in all three trials. Based on DAS28 scores, patients had on average greater disease severity for all studies.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	SUMMACTA[a]		MUSASHI[a]		BREVACTA[a]	
	TCZ-SC 162 mg q.w. (N = 631)	TCZ-IV 8 mg/kg q.4w. (N = 631)	TCZ-SC 162 mg q.2w. (N = 173)[b]	TCZ-IV 8 mg/kg q.4w. (N = 173)[b]	TCZ-SC 162 mg q.2w. (N = 437)	Placebo (N = 218)[c]
Demographic characteristics						
Age, mean (SD)	52.7 (12.4)	52.8 (12.5)	[redacted]	[redacted]	52.1 (11.5)	52.0 (11.7)
Female, n (%)	520 (82.4)	521 (82.6)	[redacted]	[redacted]	375 (85.8)	180 (82.6)
Weight, kg, mean (SD)	74.6 (19.1)	74.4 (19.0)	[redacted]	[redacted]	70.3 (16.6)	70.0 (15.8)
< 60 kg, n (%)	144 (22.8)	146 (23.1)	[redacted]	[redacted]	119 (27.2)	58 (26.6)
60 to 100 kg, n (%)	425 (67.4)	422 (66.9)	[redacted]	[redacted]	292 (66.8)	149 (68.3)
≥ 100 kg, n (%)	62 (9.8)	63 (10.0)	[redacted]	[redacted]	26 (5.9)	11 (5.0)
RA disease characteristics						
RA duration in years, mean (SD)	8.7 (8.3)	8.6 (8.1)	[redacted]	[redacted]	11.1 (8.2)	11.1 (8.4)
Number of previous DMARDs, mean (SD)	1.4 (0.7)	1.4 (0.7)	[redacted]	[redacted]	1.3 (0.7)	1.4 (0.8)
Patients receiving glucocorticoids at baseline, n (%)	344 (54.5)	338 (53.6)	[redacted]	[redacted]	284 (65.0)	123 (56.4)
RF positive patients, n (%)	456 (73.5)	465 (74.4)	[redacted]	[redacted]	349 (80.8)	177 (81.6)
Anti-CCP positive patients, n (%)	434 (72.2)	471 (75.8)	[redacted]	[redacted]	360 (83.9)	179 (82.9)
Previously failed TNF alpha inhibitor treatment, n (%)	142 (22.5)	136 (21.6)	[redacted]	[redacted]	89 (20.4)	47 (21.6)
Previous MTX use, n (%)	531 (84.2)[d]	541 (85.7)[d]	[redacted]	[redacted]	375 (85.8)[d]	187 (85.8)[d]
DAS28 and ACR characteristics						
DAS28-ESR, mean (SD)	6.6 (1.0)	6.7 (1.0)	[redacted]	[redacted]	6.7 (0.9)	6.6 (0.9)
TJC (68 joints), mean (SD)	27.3 (15.6)	28.6 (16.2)	[redacted]	[redacted]	28.0 (15.0)	27.3 (14.3)
SJC (66 joints), mean (SD)	15.0 (9.1)	16.5 (10.8)	[redacted]	[redacted]	17.5 (10.3)	17.5 (9.9)
HAQ-DI score, mean (SD)	1.6 (0.6)	1.7 (0.6)	[redacted]	[redacted]	1.6 (0.6)	1.6 (0.6)
CRP level, mg/dL, mean (SD)	2.1 (2.2)	2.2 (2.4)	[redacted]	[redacted]	2.0 (2.6)	1.9 (2.4)

Anti-CCP = anti-cyclic citrullinated peptide; CRP = C-reactive protein; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; IV = intravenous; MTX = methotrexate; q.w. = every week; q.2w. = every two weeks; q.4w. = every 4 weeks; RF = rheumatoid factor; SC = subcutaneous; SD = standard deviation; SJC = swollen joint count; TCZ = tocilizumab; TJC = tender joint count; TNF = tumour necrosis factor.

[a] Safety population.

[b] Before start of treatment, one subject in the TCZ-SC group was withdrawn for "violation of selection criteria at entry," and one subject in the TCZ-IV group was withdrawn for "administrative/other" reason, so investigational product administration was started in 173 subjects in the TCZ-SC group and 173 subjects in the TCZ-IV group.

[c] One patient inadvertently received TCZ instead of placebo at baseline, and hence was not included in the safety population.

[d] Receiving MTX before the study or at baseline.

[e] Based on per-protocol population, 159 patients in the SC group and 156 patients in the IV group.

[f] Japanese version of the Health Assessment Questionnaire.

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

3.2.3 Interventions

In SUMMACTA, during the double-blind period, patients received an IV infusion of 8 mg/kg of TCZ every four weeks for a total of six infusions (baseline, weeks 4, 8, 12, 16, and 20) or a fixed dose of 162 mg of TCZ administered by SC injection every week until week 23. The maximum dose was capped at 800 mg for patients in the TCZ-IV group weighing 100 kg or more. To maintain the blinding, investigational products were administered using a double-dummy design in which patients in the TCZ-IV group also received placebo administered by SC injection every week until week 23, while those in the TCZ-SC group received IV infusion of placebo every four weeks. SC injections of study drug (TCZ or placebo) were given using a pre-filled syringe with a needle safety device. All patients were re-randomized for the open-label period at week 24. After a one-week dose interruption, patients assigned to receive 162 mg of TCZ-SC were to receive this dose every week, starting at week 25 until week 96, while those assigned to receive 8 mg/kg of TCZ-IV were to receive this dose every four weeks, starting at week 25 until week 93. In the double-blind period, all infusions and the first four SC injections were administered under close supervision of the investigator in a setting where medications and resuscitation facilities were available. Subsequent SC injections could be administered at home. All patients had to receive background therapy with at least one permitted non-biologic DMARD (azathioprine, chloroquine, hydroxychloroquine, leflunomide, MTX, or sulfasalazine) at a stable dose at least eight weeks before baseline and throughout the study. Patients were to remain on the same background DMARDs throughout the study. Oral corticosteroids (≤ 10 mg per day of prednisone or equivalent) and NSAIDs were permitted during the study.

In MUSASHI, during the double-blind period, patients received an IV infusion of 8 mg/kg of TCZ every four weeks for a total of six infusions (baseline, weeks 4, 8, 12, 16, and 20) or a fixed dose of 162 mg of TCZ administered by SC injection every two weeks for a total of 12 injections (baseline, weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22). To maintain the blinding, investigational products were administered using a double-dummy design in which patients in the TCZ-IV group also received placebo administered by SC injection every two weeks until week 22, while those in the TCZ-SC group received IV infusion of placebo every four weeks. The use of corticosteroids (≤ 10 mg per day as prednisolone equivalent) to treat RA and use of NSAIDs were permitted during the study, but the use of DMARDs was prohibited during the study.

In BREVACTA, during the double-blind period, patients received a fixed dose of 162 mg TCZ or matching placebo administered by SC injection every two weeks until week 24. From week 12, patients initially randomized to receive either TCZ or placebo could move to escape therapy with TCZ 162 mg SC every week if there was less than 20% improvement in SJC and TJC from baseline. These patients could receive open-label treatment until the completion of the trial. SC injections of TCZ or placebo were given using a pre-filled syringe with a needle safety device. At week 24, the open-label period began, during which all patients who did not initiate escape therapy received a fixed dose of 162 mg of TCZ-SC every two weeks. The first six SC injections of the double-blind and open-label periods were administered to patients under close supervision of the investigator in a setting where medications and resuscitation facilities were available. Subsequent injections could be administered at home. Similar to the SUMMACTA trial, all patients had to receive background therapy with at least one permitted non-biologic DMARD (azathioprine, chloroquine, hydroxychloroquine, leflunomide, MTX, or sulfasalazine) at a stable dose at least eight weeks before baseline and throughout the study. Patients were to remain on the same background DMARDs throughout the study. Oral corticosteroids (≤ 10 mg per day of prednisone or equivalent) and NSAIDs were permitted during the study.

3.2.4 Outcomes

In SUMMACTA, the primary efficacy end point was the proportion of patients achieving ACR20 response at week 24. ACR20 response was defined as an improvement (i.e., reduction) of 20% or more from baseline (week 0) in both the TJC (68 joints) and SJC (66 joints), as well as for three of the additional five ACR core set variables: patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ, and acute-phase reactant (either CRP or ESR). The major secondary end points were the proportion of patients with an ACR50 response at week 24, proportion of patients with an ACR70 response at week 24, proportion of patients with a DAS28 score of less than 2.6 at week 24, and proportion of patients achieving a decrease of 0.3 points or more in the HAQ-DI from baseline to week 24. Exploratory efficacy analyses assessed were change in DAS28 score from baseline at week 24, proportion of patients with DAS28 score of less than 3.2 at week 24, proportion of patients achieving a decrease of 0.22 points or more in the HAQ-DI from baseline at week 24, change in HAQ-DI from baseline at week 24. Health-related quality of life (HRQoL) was assessed using the change from baseline in the mental component summary (MCS) and the physical component summary (PCS) domains of the SF-36 at week 24.

In MUSASHI, the primary efficacy end point was the percentage of patients with an ACR20 response at week 24. ACR20 response was defined in the same manner as in SUMMACTA, except that a Japanese Health Assessment Questionnaire was used instead of HAQ in the assessment of the additional five ACR core set variables. The major secondary end points were proportion of patients achieving ACR20, ACR50, and ACR70 response for each time point up to 24 weeks after the initial administration, summary statistics for DAS28 for each time point up to 24 weeks after the initial administration, and percentage of patients in each category defined according to European League Against Rheumatism (EULAR) response criteria for each time point up to 24 weeks after the initial administration.

In BREVACTA, the primary efficacy end point was the percentage of patients with an ACR20 response at week 24. ACR20 response was defined in the same manner as in SUMMACTA. The major secondary end points were the proportion of patients with an ACR50 response at week 24, proportion of patients with an ACR70 response at week 24, change in DAS28 score from baseline at week 24, proportion of patients with DAS28 score of less than 2.6 at week 24, proportion of patients with DAS28 score of 3.2 or less at week 24, proportion of patients classified as categorical DAS28 responders (EULAR response) at week 24, change in the van der Heijde-modified Sharp radiographic score from baseline to week 24, proportion of patients achieving an improvement of 0.3 points or more in the HAQ-DI from baseline to week 24, change from baseline in the HAQ-DI at week 24, and change from baseline in the MCS and the PCS of the SF-36 at week 24.

a) Definitions of Efficacy Outcomes Used in the Studies

Achievement of an ACR50 and ACR70 response requires a 50% and 70% or greater improvement, respectively, relative to baseline for the same criteria as described for an ACR20 response.

A DAS28 score indicates an absolute level of disease activity, with a score of 5.1 or greater being considered high disease activity, while a DAS28 score lower than 3.2 indicates a low disease activity state, and a DAS28 score lower than 2.6 indicates remission.[31-33] In all three studies, calculation of DAS28 was based on ESR.

The HAQ-DI assesses a patient's level of functional ability. There are 20 questions in eight categories to assess a patient's physical functional status: dressing, arising, eating, walking, hygiene, reach, grip, and common activities.[34,35] For each of these categories, patients report the amount of difficulty they have in

performing specific activities on a scale from 0 (no difficulty) to 3 (unable to do). The eight category scores are averaged to yield an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled). Observational studies and RCTs have demonstrated that the HAQ-DI possesses face, content, construct, predictive, and discriminant validity. There is evidence suggesting that baseline HAQ scores are predictive of radiographic damage, work disability, and HRQoL.[36,37] A number of investigators have suggested that the minimal clinically important difference (MCID) is 0.22; however, differences as small as 0.10 have been suggested as clinically important.[34]

The Short-Form (36) Health Survey (SF-36) is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. It consists of eight sub-domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems.[38] The SF-36 also provides two component summaries, the PCS and the MCS. The eight sub-domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[39-41]

For more detailed description of study outcomes, see Appendix 5: VALIDITY OF OUTCOME MEASURES.

In SUMMACTA, adverse events (AEs) were defined as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether the event was considered drug-related. An AE was considered serious (SAE) if it was fatal; life-threatening; necessitated or prolonged hospitalization; resulted in persistent or significant disability, or a congenital anomaly/birth defect; or was medically significant or required intervention to prevent one or other of these outcomes. All safety analyses were performed using the population of all patients who received at least one dose of study drug and had at least one post-dose safety assessment.

In MUSASHI, AEs were defined as any undesirable or unintended sign, symptom, or disease occurring during or after treatment with the investigational product, whether the event was considered drug-related. An AE was considered serious (SAE) if it was fatal, life-threatening; necessitated or prolonged hospitalization; was or may be permanently incapacitating; or is a congenital anomaly/birth defect. All safety analyses were performed using the population of all patients who received at least one dose of TCZ.

In BREVACTA, AEs and SAEs were defined similar to the way they were defined in SUMMACTA. All safety analyses were based on the safety population (all patients who received at least one dose of study drug and had at least one post-dose safety assessment), including patients who received escape therapy, up to the point at which they received escape therapy.

3.2.5 Statistical Analysis

a) SUMMACTA Trial

A non-inferiority design was used to compare the efficacy of TCZ-SC every week + non-biologic DMARD with that of TCZ-IV + non-biologic DMARD. The manufacturer selected a non-inferiority margin (NIM) of 12%, based on the desire to preserve a minimum of 65% of the expected ACR20 response benefit of TCZ-IV compared with placebo, which had been previously shown to be 34.3%. Thus, non-inferiority of TCZ-SC administered every week was claimed if the lower boundary of the two-sided 95% CI of the difference between the response rates (TCZ-SC every week minus TCZ-IV) did not fall below –12%. If the NIM of 12% was met, the 95% CI would then be tested against a 10% NIM. This NIM of 10% was defined to ensure that at least 70% of the treatment effect was maintained.

For the primary efficacy end point, the 95% CI of the difference in ACR20 responses between the groups at week 24 was performed using the extended Mantel–Haenszel statistic. This difference was adjusted for the stratification factors applied at randomization (weight category and region). The primary analysis was performed on the per-protocol (PP) population. An analysis on the intention-to-treat (ITT) population was performed to confirm the findings from the PP analysis.

For the analysis of the binary response variables (the proportion of patients with an ACR50/70, DAS28 < 2.6, and a decrease of 0.3 points or more in the HAQ-DI), the treatment groups were compared using 95% CIs for the difference in proportions using the extended Mantel–Haenszel test. The difference was adjusted for the stratification factors applied at randomization. The analyses were carried out using the PP population. No formal comparisons and no tests for non-inferiority were performed.

Subgroup analyses for the primary end point using the PP population were performed based on weight and on patients with an inadequate response (IR) to DMARD versus to TNF alpha inhibitors; however, no statistical analyses were performed to compare treatment groups for any of these analyses. On the other hand, a logistic regression analysis was performed on the primary end point to study the interaction between treatment and the stratification factors applied at randomization (weight category and region). If the *P* value associated with a particular interaction term was less than 0.1, it was concluded that the interaction term being tested was significant at the 10% level.

Analyses for all exploratory end points (proportion of patients with DAS28 score of less than 3.2, proportion of patients achieving a decrease of 0.22 points or more in the HAQ-DI, change in DAS28 score, and change in HAQ-DI), and for the change from baseline in the MCS and the PCS of the SF-36, were based on the PP population. No statistical analyses were performed to compare treatment groups for any of these analyses.

Missing values for the TJC and SJC were imputed using the post-baseline last observation carried forward (LOCF) imputation. CRP was used as the acute-phase reactant for the calculation of the ACR response; however, the percentage change from baseline for ESR was used when the percentage change from baseline for CRP was missing. For the additional five ACR core set variables, no imputation was used for missing data for the physician's global assessment of disease activity visual analogue scale (VAS), the patient's global assessment of disease activity VAS, the patient's assessment of pain VAS, or HAQ-DI. Patients for whom an ACR response could not be determined were considered ACR20 non-responders in the primary analysis. Patients who withdrew from the study before the assessment visit and all patients in whom an ACR response could not be determined for any reason were considered ACR20/50/70 non-responders in the primary and secondary end point analyses. For secondary end points, DAS28 remission, and HAQ-DI response, missing data due to patient withdrawal were considered missing (i.e., no imputation).

For the primary end point, assuming a 62.5% response rate in ACR20 for one of the groups and a 1% absolute difference in ACR20 response between treatment groups, 450 patients per treatment group were required to provide 90% power to rule out a 12% NIM using a two-sided significance level (alpha) of 0.05. To account for dropouts, 600 subjects per treatment group were planned.

b) MUSASHI Trial

A non-inferiority design was used to compare the efficacy of TCZ-SC every two weeks with that of TCZ-IV. The manufacturer selected an NIM of 18%, based on the desire to preserve approximately two-thirds

of the expected ACR20 response benefit of TCZ-IV compared with controls, drawn from two previous trials that had shown the ACR20 response for TCZ-IV to be 57.3% in a 24-week study compared with MTX therapy and 65.5% in a 12-week phase 2 study compared with placebo. Thus, non-inferiority of TCZ-SC every two weeks was claimed if the lower boundary of the adjusted 95% CI of the difference between the response rates of TCZ-SC every two weeks minus TCZ-IV did not fall below –18%.

The primary analysis was performed using the Mantel–Haenszel statistic, adjusting for the stratification factors applied at randomization (weight category and whether the subject had previously used a TNF alpha inhibitor).The primary analysis was performed on the PP population. An analysis on the full analysis set (FAS) was performed to confirm the findings from the PP analysis.

For analyses of the secondary end points — ACR50 response rate and ACR70 response rate at week 24 — CIs were calculated, as in the primary analysis. No formal comparisons and no tests for non-inferiority were performed. The PP population and the FAS were used in these secondary analyses.

Subgroup analyses for the primary end point using the PP population were performed based on weight, IR to DMARD versus TNF alpha inhibitors, DAS28 score, rheumatoid factor (RF) status (positive versus negative), anti-cyclic citrullinated peptide (anti-CCP; positive versus negative). However, no statistical analyses were performed to compare treatment groups for any of these analyses.

Analyses of other secondary end points (summary statistics for DAS28 and percentage of patients in each category defined according to EULAR response criteria) and exploratory end points were based on the PP population. No statistical analyses were performed to compare treatment groups for any of these analyses.

For calculation of ACR response rates, a patient was classified as a “non-responder” if any three or more of the ACR core set variables (TJC, SJC, and the other five variables) were missing. ACR core set components were imputed using LOCF. ACR response rates were calculated using CRP. If the CRP value was missing, the ESR value was used. LOCF imputations were used for other missing values.

The ACR20 response rates at 24 weeks were assumed to be 70% in both the TCZ-IV group and the TCZ-SC every-two-weeks group. To rule out an 18% NIM using one-sided significance level (alpha) of 0.025 with 90% power, 147 patients per treatment group were required; 165 subjects per treatment group were planned in order to account for dropouts.

c) BREVACTA Trial

In the BREVACTA study, the primary hypothesis was that TCZ-SC every two weeks + non-biologic DMARD has superior efficacy to placebo SC every two weeks + non-biologic DMARD in treating RA patients with moderately to severely active disease. The primary analysis was based on the ITT population, with patients analyzed according to the treatment they were originally randomized to receive regardless of the treatment they actually received. Patients who withdrew from the study or received escape therapy before week 24, and all patients in whom the week 24 ACR20 response could not be determined for any reason, were considered non-responders in the primary analysis. For intermittent missing data, a similar approach to the SUMMACTA trial was used. For secondary end points such as DAS28 remission and HAQ-DI response, missing data due to patient withdrawal were considered missing (i.e., no imputation).

Binary categorical data (e.g., the proportion of patients with an ACR20 response) were analyzed using the Cochran–Mantel–Haenszel test adjusted for the stratification factors applied at randomization

(geographical region and body weight category). For the analyses of continuous data, change from baseline to week 24 was analyzed by analysis of covariance, adjusting for the stratification factors applied at randomization (region and weight category), and by baseline value. Change from baseline in the van der Heijde-modified Sharp score at week 24 was analyzed using the van Elteren nonparametric test on the ITT population with region and weight category as stratifying factors.

Subgroup analyses for the primary end point using the ITT population were performed based on weight and on IR to DMARD versus TNF alpha inhibitors; however, no statistical analyses were performed to compare treatment groups for any of these analyses. On the other hand, a logistic regression analysis was performed on the primary end point to study the interaction between treatment and the stratification factors applied at randomization (weight category and region). If the *P* value associated with a particular interaction term was less than 0.1, it was concluded that the interaction term being tested was significant at the 10% level.

A fixed-sequence approach was applied to control multiplicity among end points. The primary end point was first analyzed. If that was statistically significant ($P < 0.05$), then the major secondary end points were tested in descending order if the previous major secondary end point was statistically significant. If the previous major secondary end point was not statistically significant, no further comparisons were made.

For the primary end point, a total of 600 patients randomized in a 2:1 ratio (400 in the TCZ-SC every-two-weeks + non-biologic DMARD group and 200 in the placebo + non-biologic DMARD group) was determined to ensure greater than 90% power to detect the difference in ACR20 response between groups, assuming a 23% response rate in the placebo group and 46% response rate in the TCZ-SC every-two-weeks group.

The CDR protocol included subgroups by number and type of prior DMARDs (biologic or non-biologic) and MTX dose at baseline; however, such subgroup analyses were not undertaken in any of the studies. Subgroup analyses based on weight and on IR to DMARD versus TNF alpha inhibitors were performed in all three studies. Subgroup analysis by disease severity (moderate disease defined as DAS28 score greater than 3.2 and up to 5.1, and severe disease defined as DAS28 score greater than 5.1), RF status (positive versus negative), and anti-CCP (positive versus negative) was performed only in MUSASHI.

d) Analysis Populations

In SUMMACTA, the following data sets were defined:

- **ITT population:** all randomized patients who received at least one dose of study drug
- **PP population:** a subset of the ITT population that excluded patients with protocol deviations deemed to have the potential to affect patient outcome in terms of efficacy
- **Safety data set:** all patients who received at least one dose of study medication and had at least one post-dose safety assessment. Patients were assigned to treatment groups according to the treatment they received at baseline.

In MUSASHI, the following data sets were defined:

- **FAS:** enrolled subjects, other than untreated subjects, ineligible subjects, and unobserved subjects
- **PP population:** a subset of the FAS that excluded patients with protocol violations, early withdrawals, and violations of the dosage and administration method
- **Safety data set:** all patients who received at least one dose of study medication.

In BREVACTA, the following data sets were defined:

- **ITT population:** all randomized patients who received at least one dose of study drug. Patients were assigned to the ITT population as randomized, irrespective of the treatment actually received.
- **Completer population:** all ITT patients who completed the double-blind treatment portion of the study and had a valid week 24 assessment. Escape patients were not included in the completer population.
- **Safety data set:** all patients who received at least one dose of study medication and had at least one post-dose safety assessment. Patients were assigned to treatment groups according to the treatment they received at baseline.

3.3 Patient Disposition

The disposition of participants in all three trials is presented in Table 6.

Overall, the percentage of participants who discontinued treatment was similar between treatment groups in all studies. Slightly more patients discontinued due to AEs in the TCZ-IV group than in the TCZ-SC group (6% versus 4%) in SUMMACTA and in MUSASHI (5.2% versus 1.7%). Also, in the SUMMACTA and MUSASHI studies, there was a slightly greater percentage of subjects who withdrew because of lack of therapeutic response in the SC group (2% and 1.7%) compared with the IV group (1% and 0.5%), respectively. In BREVACTA, 41.1% of patients in the placebo group received escape therapy versus 16.5% in TCZ-SC group.

TABLE 6: PATIENT DISPOSITION

Criteria, N (%)	SUMMACTA		MUSASHI		BREVACTA[a]	
	TCZ-SC 162 mg q.w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	Placebo
Screened	2,157		NR		1,034	
Randomized	631 (100)	631 (100)	174 (100)	174 (100)	437 (100)	219 (100)
Treated	631 (100)	631 (100)	173 (99.4)	173 (99.4)	438 (100)	218 (> 99)
Completed[b]	572 (90.6)	564 (89.4)	161 (92.5)	161 (92.5)	410 (93.8)	209 (95.4)
Completed[c]	NA	NA	NA	NA	[redacted]	[redacted]
Escaped	NA	NA	NA	NA	72 (16.5)	90 (41.1)
Withdrew from study	59 (9.4)	67 (10.6)	13 (7.5)	13 (7.5)	28 (6.4)	9 (4.1)
WDAE	28 (4)[d]	40 (6)[d]	3 (1.7)	9 (5.2)	9 (2)[d]	3 (1)[d]
ITT	631 (100)	631 (100)	NR	NR	437 (100)	219 (100)
FAS	NR	NR	173 (99.4)	173 (99.4)	NR	NR
PP	558 (88.4)	537 (85.1)	159 (91.4)	156 (89.7)	NR	NR
Safety	631 (100)	631 (100)	173 (99.4)	173 (99.4)	437 (100)	218 (> 99)

FAS = full analysis set; ITT = intention-to-treat; IV = intravenous; NA = not applicable; NR = not reported; PP = per-protocol; q.w. = every week; q.2w. = every two weeks; q.4w. = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab; WDAE = withdrawal due to adverse event.

[a] One patient inadvertently received TCZ instead of placebo at baseline in BREVACTA.

[b] Completed 24 weeks of treatment.

[c] Completed study and had a valid efficacy assessment at week 24 (escape patients are excluded).

[d] Except anaphylaxis or serious hypersensitivity reaction.

Source: SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

3.4 Exposure to Study Treatments

During the double-blind period in SUMMACTA, the extent of exposure to TCZ-SC every week in the SC group and extent of exposure to SC placebo in the IV group was comparable between the two groups: the mean duration (0.42 years in the TCZ-SC every-week group versus 0.41 years in the SC placebo group) and median duration (0.46 years in the TCZ-SC every-week group versus 0.45 years in the SC placebo group) of treatment and total number of patient-years of exposure to treatment (267.9 in the TCZ-SC every-week group versus 260.5 in the SC placebo group) were very similar. The extent of exposure to TCZ-IV in the IV group was slightly longer than the extent of exposure to IV placebo in the SC group, with mean duration (0.46 years in the TCZ-IV group versus 0.43 years in the IV placebo group) and median duration (0.51 years in the TCZ-IV group versus 0.45 years in the IV placebo group) of treatment and total number of patient-years of exposure to treatment (292.8 in the TCZ-IV group versus 271.2 in the IV placebo group). The total compliance for SC injection up to week 24 was 98.9% for patients in the SC group (receiving TCZ-SC every week) and 99.2% in the IV group (receiving SC placebo). The total compliance for IV infusions up to week 24 was 97.5% for the SC group (receiving IV placebo) and 96.5% for the IV group (receiving TCZ-IV). [redacted]

In BREVACTA, the mean exposure to study treatment was 0.39 years for TCZ and 0.35 years for placebo. [redacted]

3.5 Critical Appraisal

3.5.1 Internal Validity

All three studies used appropriate methods to conceal allocation and randomize patients. In order to maintain blinding in SUMMACTA and BREVACTA, a trial "dual assessor" approach was used to evaluate first efficacy and then safety data to prevent potential unblinding because of observed efficacy or laboratory changes. In MUSASHI, by contrast, after initiation of investigational product administration, the laboratory test and drug concentration measurement facilities did not report the measurement results for the test variables (serum tocilizumab concentration, IL-6 and soluble IL-6 receptor [sIL-6R]) to the investigator or the sponsor until after unblinding. In addition, a double-dummy was used to maintain blinding in studies SUMMACTA and MUSASHI.

The manufacturer provided an adequate rationale for its choice of NIM for studies SUMMACTA and MUSASHI. The clinical expert consulted for this review considered less than one-third of the effect is appropriate.

In SUMMACTA, no formal comparisons and no tests for non-inferiority were performed for all secondary outcomes. Hence, results from these comparisons should be interpreted with caution. In addition, no statistical analyses were performed to compare treatment groups for all exploratory end points, for the MCS and the PCS domains of the SF-36, or for the subgroup analysis of IR to DMARD versus TNF alpha inhibitors, making it impossible to conclude whether there is a difference between treatment groups for any of these analyses.

In MUSASHI, no formal comparisons and no tests for non-inferiority were performed for the secondary end points of ACR50 and ACR70 response rates. Hence, no conclusion can be drawn from the analyses of these outcomes. In addition, no statistical analyses were performed to compare treatment groups for secondary end points DAS28 and EULAR scores, for all exploratory end points, or for any of the subgroup analyses (weight, IR to DMARDs versus TNF alpha inhibitors, DAS28 score, RF status [positive versus negative], and anti-CCP [positive versus negative]). Hence, it is not possible to conclude whether there is a difference between treatment groups for any of these analyses.

In BREVACTA, no statistical analyses were performed to compare treatment groups for the subgroup analysis of IR to DMARD versus TNF alpha inhibitors. Hence, it is not possible to conclude whether there is a difference between treatment groups in these subgroups.

The design of the BREVACTA trial allowed patients in both treatment groups who demonstrated less than 20% improvement in both TJC and SJC to receive TCZ 162 mg SC weekly (escape therapy) from week 12. More than one-third (41.1%) of patients in the placebo group received escape therapy, with an additional 4% discontinuing treatment before week 24, whereas 16.5% of patients in the TCZ-SC every-two-weeks group received escape therapy before week 24, with an additional 6% discontinuing treatment. The manufacturer used the completer population (55% of patients in the placebo group and 78% of patients in the TCZ-SC every-two-weeks group) in the analysis of secondary continuous end points DAS28 score and HAQ-DI, indicating that there was a substantial amount of missing data; hence, the baseline comparability between treatment groups achieved by randomization may not been preserved. Also, the completer population may not represent the target population. In addition, the substantial amount of missing data may introduce bias and influence the results.

3.5.2 External Validity

All three studies required patients to have an ESR of 28 mm per hour or more to qualify for entry. According to the clinical expert involved in the review, a substantial proportion (approximately 50%) of patients seen in clinical practice does not have an ESR above 28. Hence, the generalizability of the study may be limited.

Baseline characteristics of enrolled patients were consistent with what has been seen in other RA trials. However, the clinical expert consulted for this review indicated that trial patients had, on average, greater disease severity than patients treated with biologic therapies in clinical practice and may not be representative of patients in the real world.[42] Thus, study results may not be generalizable to RA patients who exhibit lower disease activity.

Frequency of TCZ-SC used in all three trials and dose of TCZ-IV used in the two non-inferiority trials (SUMMACTA and MUSASHI) were different than what is recommended by Health Canada (recommended dose for TCZ-SC is 162 mg every two weeks, increased to 162 mg every week based on clinical response for patients < 100 kg weight and injected every week for patients ≥ 100 kg, while starting dose for TCZ-IV is 4 mg/kg every four weeks, increased up to 8 mg/kg every four weeks based on

clinical response), which might limit the generalizability of the results. However, the clinical expert consulted for this review was not concerned and indicated that the 162 mg SC every week mimics the 8 mg/kg IV every four weeks, and that 162 mg SC every two weeks mimics the 4 mg/kg IV every four weeks.

3.6 Efficacy

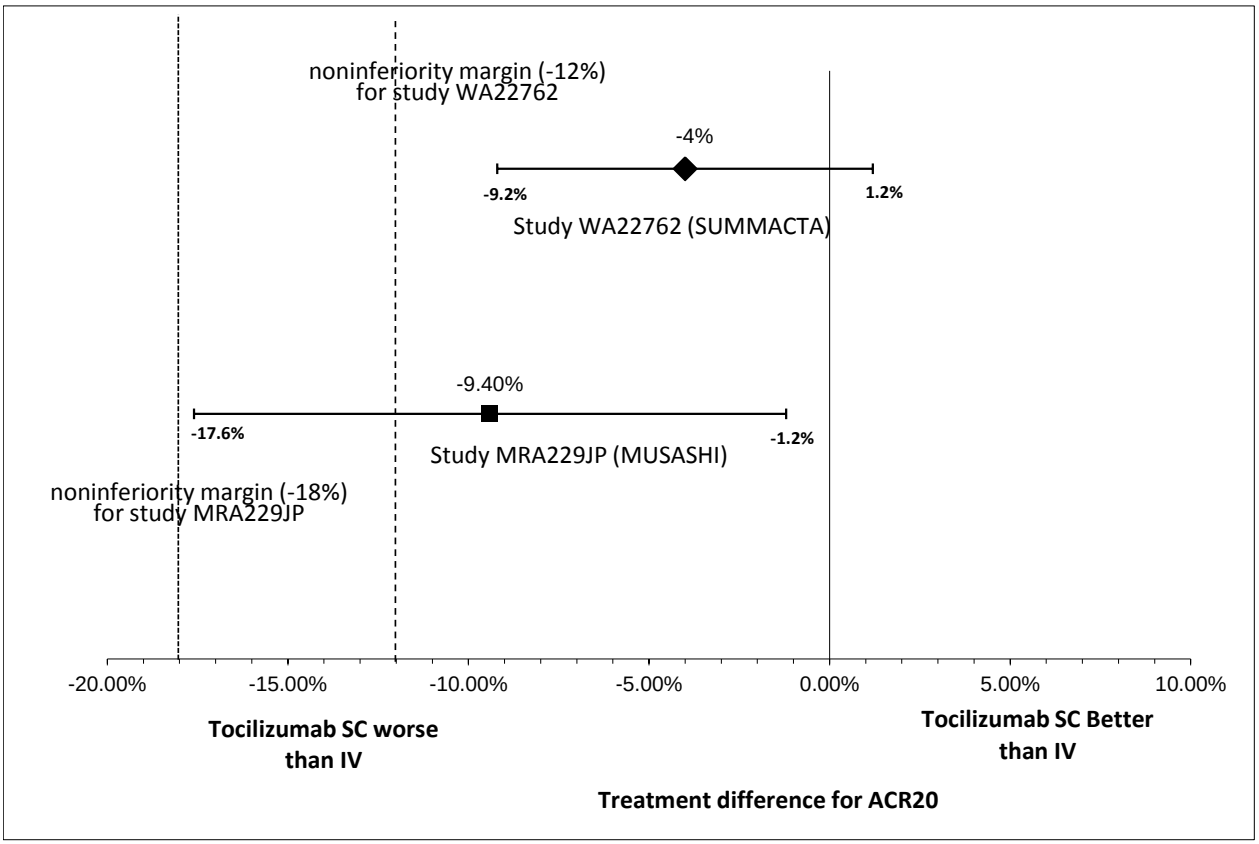
Only those efficacy outcomes identified in the review protocol are reported in this section (see also Table 3, Section 2.2). See Appendix 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Disease Activity: American College of Rheumatology Score Response

In SUMMACTA, the proportion of patients achieving an ACR20 response at 24 weeks in the PP population was 69.4% in the TCZ-SC every-week group and 73.4% in the TCZ-IV group, with a between-treatment difference of −4.0% (95% CI, −9.2 to 1.2) (Figure 2 and Table 8, Appendix 4). Given that the lower bound of the 95% CI did not fall below −12%, TCZ-SC every week was considered to be non-inferior to TCZ-IV. TCZ-SC every week was also non-inferior to TCZ-IV using a more restricted NIM of −10%. The proportion of patients achieving an ACR20 response at 24 weeks in the ITT population was 67.7% in the TCZ-SC every-week group and 70.2% in the TCZ-IV group. The between-treatment difference was less than that observed in the PP population, with the estimated difference between the TCZ-SC every-week group and TCZ-IV group being −2.7% (95% CI, −7.6 to 2.2), indicating that TCZ-SC every week is non-inferior to TCZ-IV (Table 9, Appendix 4). The proportion of patients who achieved ACR50 and ACR70 at 24 weeks in the PP population was slightly higher in the TCZ-IV group than TCZ-SC every-week group; however, between-treatment differences were not statistically significant for either end point (Table 8, Appendix 4). A plot of ACR20, ACR50, and ACR70 response over time in the PP population is shown in Figure 3, Appendix 4.

In MUSASHI, the proportion of patients achieving an ACR20 response at 24 weeks in the PP population was 79.2% in the TCZ-SC every-two-weeks group and 88.5% in the TCZ-IV group, with a between-treatment difference of −9.4% (95% CI, −17.6 to −1.2) (Figure 2 and Table 8, Appendix 4). Given that the lower bound of the 95% CI did not fall below −18%, TCZ-SC every two weeks was considered to be non-inferior to TCZ-IV; on the other hand, the 95% CI was below 0, indicating that TCZ-SC every two weeks is significantly worse than TCZ-IV. Results from the ITT analysis of ACR20 response at 24 weeks were less than those observed in the PP population, with the estimated difference between the TCZ-SC every-two-weeks group and TCZ-IV group being −7.0% (95% CI, −15.0 to 1.0), indicating that TCZ-SC every two weeks is non-inferior to TCZ-IV (Table 9, Appendix 4). The proportion of patients who achieved ACR50 and ACR70 at 24 weeks in the PP population was slightly higher in the TCZ-IV group than in the TCZ-SC every-two-weeks group; however, between-treatment differences were not statistically significant for either end point (Table 8, Appendix 4). A plot of ACR20, ACR50, and ACR70 response over time in the PP population is shown in Figure 4, Appendix 4.

FIGURE 2: FOREST PLOT FOR ACR20 RESPONSES AT WEEK 24 IN SUMMACTA AND MUSASHI STUDIES FOR THE PER-PROTOCOL POPULATION



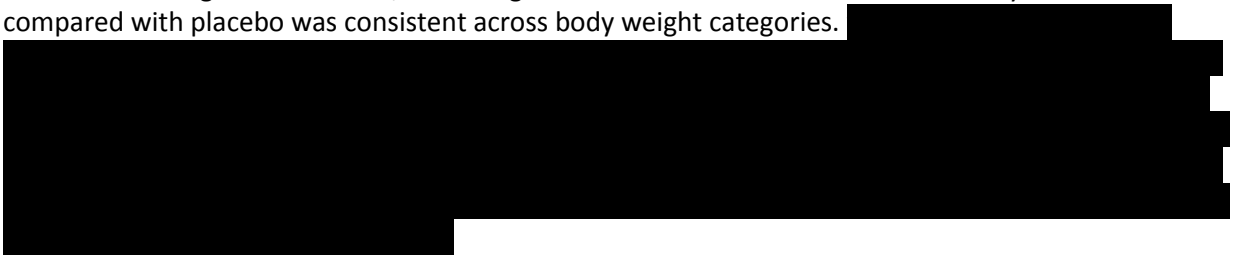
ACR = American College of Rheumatology; IV = intravenous; SC = subcutaneous.
Note: The figure was created by the CADTH Common Drug Review clinical reviewer.

In BREVACTA, a statistically significantly higher proportion of patients in the TCZ-SC every-two-weeks treatment group achieved an ACR20 response (60.9%) at week 24 compared with the placebo group (31.5%), with a between-treatment difference of 29.5% (95% CI, 22.0 to 37.0; $P < 0.0001$) (Table 8, Appendix 4). A plot of ACR20 response over time in the ITT population is shown in Figure 5, Appendix 4. A sensitivity analysis was undertaken using the completer population (those who completed the study and had a valid efficacy assessment at week 24, excluding patients who received escape therapy); the between-treatment difference from this analysis was less than that estimated in the ITT population, with a between-treatment difference of 22.4% (95% CI, 12.8 to 31.9; $P < 0.0001$) (Table 9, Appendix 4). The proportion of patients who achieved ACR 50 and ACR70 at week 24 was also greater in the TCZ-SC every-two-weeks treatment group than in the placebo-treated group (ACR50: 39.8% versus 12.3%; between-treatment difference 27.9; 95% CI, 21.5 to 34.4; $P < 0.0001$; ACR70: 19.7% versus 5.0%; between-treatment difference 14.8; 95% CI, 9.8 to 19.9; $P < 0.0001$) (Table 8, Appendix 4). Plots of ACR50 and ACR70 response over time in the ITT population are shown in Figure 6, Appendix 4, and Figure 7, Appendix 4.

In SUMMACTA, the results of subgroup analyses by body weight category at baseline (< 60 kg, 60 to < 100 kg, and ≥ 100 kg) for ACR20, ACR50, and ACR70 were similar for the TCZ-SC every-week and TCZ-IV treatment regimens. In both treatment groups, the response rate was lower for all ACR categories in patients weighing 100 kg or more. The interaction between treatment and body weight was explored by

logistic regression. The *P* value was greater than 0.1, indicating that the treatment effect of TCZ-SC every week compared with TCZ-IV was consistent across body weight categories. The proportion of patients achieving an ACR20, ACR50, and ACR70 response at week 24 for patients who were IR to DMARD and to TNF alpha inhibitors was similar for the TCZ-SC every-week and TCZ-IV treatment regimens. In both treatment groups, the response rate was lower for all ACR categories, in patients in the group IR to TNF alpha inhibitors (Table 10, Appendix 4).

In BREVACTA, the results of subgroup analyses by body weight category at baseline (< 60 kg, and 60 kg to 100 kg) for ACR20, ACR50, and ACR70 were higher in the TCZ-SC every-two-weeks treatment group than in the placebo group, with between-treatment difference (TCZ-SC every two weeks minus placebo) of 30.6%, 29.6%, and 15.9% for ACR20, ACR50, and ACR70, respectively. In patients with body weight at baseline greater than 100 kg, results were similar, with between-treatment difference (TCZ-SC every-two-weeks group minus placebo group) of 11.2%, −6.6%, and −5.2% for ACR20, ACR50, and ACR70, respectively. The interaction between treatment and body weight was explored by logistic regression. The *P* value was greater than 0.1, indicating that the treatment effect of TCZ-SC every two weeks compared with placebo was consistent across body weight categories.



The CDR protocol included subgroups by number and type of prior DMARDs (biologic or non-biologic) and MTX dose at baseline; however, such subgroup analyses were not performed in any of the studies. Subgroup analyses based on weight and on IR to DMARD versus TNF alpha inhibitors were performed in all three studies. Subgroup analysis by disease severity (moderate disease defined as DAS28 score of more than 3.2 and up to 5.1, and severe defined as DAS28 score greater than 5.1), RF status (positive versus negative), and anti-CCP (positive versus negative) was performed only in MUSASHI.

3.6.2 Disease Activity: Disease Activity Score 28–Erythrocyte Sedimentation Rate

In SUMMACTA, the mean change (improvement) in the DAS28-ESR score, from baseline to week 24, was similar between TCZ-SC every week and TCZ-IV (−3.6 and −3.6, respectively); no statistical test was applied (Table 11, Appendix 4). There was no statistically significant difference in the proportion of patients achieving DAS remission (DAS28-ESR score less than 2.6) at week 24 between the TCZ-SC every-week group and the TCZ-IV group (38.4% versus 36.9%, respectively; Table 11, Appendix 4). The proportion of patients who achieved a low DAS (DAS28-ESR score 3.2 or less) was comparable between the TCZ-SC every-week group and the TCZ-IV group at week 24 ([redacted], respectively); no statistical test was applied for this analysis (Table 11, Appendix 4). The results of subgroup analyses by body weight category at baseline (< 60 kg, 60 to < 100 kg, and ≥ 100 kg) for DAS28-ESR score less than 2.6 were similar for the TCZ-SC every-week and TCZ-IV treatment regimens, although no statistical test was applied. In both treatment groups, the response rate was lower in patients weighing 100 kg or more relative to the other weight categories (Table 11, Appendix 4).

In MUSASHI, the mean change (improvement) in the DAS28-ESR score, from baseline to week 24, was not assessed. The proportion of patients achieving DAS remission (DAS28-ESR score less than 2.6) at week 24 was statistically significantly lower in the TCZ-SC every-two-weeks group than the TCZ-IV group: 49.7% versus 62.2%, respectively (Table 11, Appendix 4). [redacted]

In BREVACTA, the mean change (improvement) in the DAS28-ESR score, from baseline to week 24, was significantly lower in the TCZ-SC every-two-weeks group than in the placebo group at week 14 (−3.1 versus −1.7, $P < 0.0001$; Table 11, Appendix 4). The proportion of patients in the TCZ-SC every-two-weeks treatment group who achieved DAS remission (DAS28-ESR score less than 2.6) at week 24 was significantly higher than that in the placebo group (32% versus 4%, $P < 0.0001$; Table 11, Appendix 4). Similarly, the proportion of patients in the TCZ-SC every-two-weeks treatment group that achieved a low DAS (DAS28-ESR score 3.2 or less) at week 24 was significantly higher than that in the placebo group (45.2% versus 15.3%, $P < 0.0001$; Table 11, Appendix 4). Likewise, the proportion of patients who achieved good DAS28-ESR response at week 24 was higher in the TCZ-SC every-two-weeks group than in the placebo group (41.7% versus 13.8%, $P < 0.0001$; Table 11, Appendix 4). [redacted]

3.6.3 Radiography Changes

One trial (BREVACTA) examined radiographic changes. At 24 weeks, radiographic progression was statistically significantly less for patients randomized to TCZ-SC every two weeks compared with placebo; mean changes from baseline in the van der Heijde-modified total Sharp radiographic score were 0.6 and 1.2, respectively (P = 0.0145), suggesting there was less joint damage following TCZ-SC every-two-weeks treatment (Table 12, Appendix 4).

3.6.4 Physical Function: Health Assessment Questionnaire–Disability Index Response

In SUMMACTA, the percentage of patients achieving an improvement of at least 0.30 units in the HAQ-DI score from baseline to week 24 was not statistically significantly different between TCZ-SC every week and TCZ-IV (65.2% versus 67.4%, respectively; Table 13, Appendix 4). The percentage of patients achieving an improvement of at least 0.22 units in the HAQ-DI score from baseline at week 24 was 73.0% and 74.0% for the TCZ-SC every-week and TCZ-IV treatment groups, respectively (Table 13, Appendix 4). Mean change (improvement) in HAQ-DI scores from baseline to week 24 for the TCZ-SC every-week and TCZ-IV groups was the same (−0.6; Table 13, Appendix 4).

[redacted]

Table 13 [redacted]

In BREVACTA, the percentage of patients achieving an improvement of at least 0.30 points on the HAQ-DI from baseline at week 24 in the TCZ-SC every-two-weeks treatment group was statistically significantly higher than the percentage in the placebo group (58.0% versus 46.8%, P = 0.0170; Table 13, Appendix 4). The percentage of patients achieving an improvement of at least 0.22 points in the HAQ-DI from baseline at week 24 in the TCZ-SC every-two-weeks treatment group was higher than the percentage in the placebo group (67.5% versus 54.8%; Table 13, Appendix 4); no statistical test was done for this analysis. There was a statistically significantly higher mean change (improvement) in HAQ-DI scores from baseline to week 24 in the TCZ-SC every-two-weeks treatment group than in the placebo treatment group (−0.4 versus −0.3, P = 0.0054; Table 13, Appendix 4); however, patients from both treatment groups had a mean change from baseline that exceeded the established MCID of 0.22.

3.6.5 Quality of Life Assessment: Short-Form (36) Health Survey

In SUMMACTA, the mean changes from baseline to week 24 in the SF-36 PCS and the SF-36 MCS were similar between TCZ-SC every-week and TCZ-IV groups: 9.5 versus 9.7 for PCS and 6.2 versus 6.5 for MCS, respectively (Table 14, Appendix 4). The change in scores from baseline exceeded the established MCID of 2.5 to 5 points for both treatment groups.

In BREVACTA, the mean changes from baseline to week 24 in SF-36 PCS in the TCZ-SC every-two-weeks treatment group was statistically significantly higher than in the placebo group (5.3 versus 2.9, P = 0.0006; Table 14, Appendix 4). Similarly, the mean changes from baseline to week 24 in SF-36 MSC in the TCZ-SC every-two-weeks treatment group was statistically significantly higher than in the placebo group (6.5 versus 3.8, P = 0.0068; Table 14, Appendix 4). The change in scores from baseline exceeded the lower bound of the established MCID of 2.5 to 5 points for both treatment groups; however, the upper bound of the MCID was exceeded only by the TCZ-SC every-two-weeks treatment group.

3.7 Harms

Only those harms identified in the review protocol are reported in this section (see also Section 2.2.1 Protocol). See Appendix 4: DETAILED OUTCOME DATA (Table 15, Appendix 4) for detailed harms data.

3.7.1 Adverse Events

In SUMMACTA, the percentage of patients who experienced at least one AE was 76.2% in the TCZ-SC every week versus 77.0% in the TCZ-IV group (Table 7). The most common system organ class (SOC) (≥ 10% in either group) in which AEs were reported was infections and infestations (36.0% in the TCZ-SC every-week group versus 39.1% in the TCZ-IV group), investigations (23.3% in the TCZ-SC every-week group versus 21.2% in the TCZ-IV group), gastrointestinal disorders (19.2% in the TCZ-SC every-week group versus 18.5% in the TCZ-IV group), musculoskeletal and connective tissue disorders (15.4% in each group), skin and subcutaneous tissue disorders (11.6% in the TCZ-SC every-week group versus 13.0% in the TCZ-IV group), general disorders and administration-site conditions (14.9% in the TCZ-SC every-week group versus 7.0% in the TCZ-IV group), and nervous system disorders (9.4% in the TCZ-SC every-week group versus 11.6% in the TCZ-IV group).

In MUSASHI, the percentage of patients who experienced at least one AE was 89.0% in the TCZ-SC every-two-weeks group versus 90.8% in the TCZ-IV group (Table 7). The most common SOC (≥ 10% in either group) in which AEs were reported was investigations (53.8% in the TCZ-SC every-two-weeks group versus 51.4% in the TCZ-IV group), infections and infestations (41.6% in the TCZ-SC every-two-weeks group versus 45.1% in the TCZ-IV group), skin and subcutaneous tissue disorders (22.5% in the TCZ-SC every-two-weeks group versus 24.3% in the TCZ-IV group), gastrointestinal disorders (19.7% in the TCZ-SC every-two-weeks group versus 24.9% in the TCZ-IV group), general disorders and administration-site conditions (19.1% in the TCZ-SC every-two-weeks group versus 7.5% in the TCZ-IV group), and nervous system disorders (10.4% in the TCZ-SC every-two-weeks group versus 2.9% in the TCZ-IV group).

In BREVACTA, the percentage of patients who experienced at least one AE was 62.7% in the TCZ-SC every-two-weeks group versus 57.8% in the placebo group (Table 7). The most common SOC (≥ 10% in either group) in which AEs were reported was infections and infestations (30.0% TCZ-SC in the every-two-weeks group versus 28.0% in the placebo group), investigations (16.9% TCZ-SC in the every-two-weeks group versus 6.9% in the placebo group), gastrointestinal disorders (11.9% TCZ-SC in the every-two-weeks group versus 10.1% in the placebo group), and musculoskeletal and connective tissue disorders (8.7% TCZ-SC in the every-two-weeks group versus 12.4% in the placebo group).

3.7.2 Serious Adverse Events

In SUMMACTA, the percentage of patients who experienced at least one SAE was similar in both groups (4.6% in the TCZ-SC every-week group versus 5.2% in the TCZ-IV group) (Table 7). The most common SOC in which SAEs were reported was infections and infestations (1.4% in each treatment group).

In MUSASHI, the percentage of patients who experienced at least one SAE was higher in the TCZ-SC every-two-weeks group (7.5%) than in the TCZ-IV group (5.8%) (Table 7). [redacted]

In BREVACTA, the percentage of patients who experienced at least one SAE was similar in both groups (4.6% in the TCZ-SC every-two-weeks group versus 3.7% in the placebo group) (Table 7). The most common SOC in which SAEs were reported was infections and infestations (2.1 in TCZ-SC in the every-two-weeks group and 1.8% in the placebo group).

3.7.3 Withdrawals Due to Adverse Events

In SUMMACTA, the percentage of patients who prematurely discontinued study treatment because of an AE was comparable between both treatment groups (4.8% in the TCZ-SC every-week group versus 6.5% in the TCZ-IV group) (Table 7). [redacted]

[redacted]

In BREVACTA, the percentage of patients in the TCZ-SC every-two-weeks group who prematurely discontinued study treatment because of an AE was greater than in the placebo group: 2.1% versus 1.4%, respectively (Table 7).

3.7.4 Mortality

In SUMMACTA, one death occurred in the TCZ-IV treatment group. The patient died from sepsis, secondary to bacterial arthritis [redacted]

There were no deaths in MUSASHI.

In BREVACTA, three deaths occurred in the TCZ-SC every-two-weeks treatment group (one from lower respiratory tract infection and two from sepsis). No deaths occurred in the placebo group. [redacted]

3.7.5 Notable Harms

In SUMMACTA, the overall incidence of patients with infections and serious infections was similar in both groups: 36% and 1.4% in the TCZ-SC every-week treatment group, respectively, versus 39.1% and 1.4% in the TCZ-IV treatment group, respectively (Table 7). The most common type of infection in both treatment groups was upper respiratory tract infection (7.3% in the TCZ-SC every-week versus 11.6% in the TCZ-IV group). Of the other notable harms that occurred, most common were hypersensitivity reactions (7.0% in the TCZ-SC every-week group versus 11.6% in the TCZ-IV group), injection-site reactions (10.1% in the TCZ-SC every-week group versus 2.4% in the TCZ-IV group), increased alanine aminotransferase (18.7% in the TCZ-SC every-week group versus 16.5% in the TCZ-IV group), and increased aspartate transaminase (13.5% in the TCZ-SC every-week group versus 10.5% in the TCZ-IV group).

In MUSASHI, overall incidence of patients with serious infections was 1.2% in the TCZ-SC every-two-weeks group and 2.9% in the TCZ-IV group (Table 7). [redacted]

In BREVACTA, the overall incidence of patients with infections and serious infections was similar in both groups: 30.0% and 2.1% in the TCZ-SC every-two-weeks treatment group versus 28.0% and 1.8% in the placebo group (Table 7). The most common type of infection in both treatment groups was upper respiratory tract infection: 6.4% in each treatment group. Of the other notable harms that occurred, the most common were hypersensitivity reactions (4.3% in the TCZ-SC every-two-weeks group versus 3.7% in the placebo group), injection-site reactions (7.1% in the TCZ-SC every-two-weeks group versus 4.1% in the placebo group), increased alanine aminotransferase (13.3% in the TCZ-SC every-two-weeks group versus 5.0% in the placebo group), and increased aspartate transaminase (8.2% in the TCZ-SC every-two-weeks group versus 3.7% in the placebo group). Malignancies were reported in three patients in the TCZ-SC every-two-weeks treatment group versus none in the placebo group.

TABLE 7: HARMS

AEs	SUMMACTA		MUSASHI		BREVACTA[a]	
	TCZ-SC 162 mg q.w. (N = 631)	TCZ-IV 8 mg/kg q.4w. (N = 631)	TCZ-SC 162 mg q.2w. (N = 173)	TCZ-IV 8 mg/kg q.4w. (N = 173)	TCZ-SC 162 mg q.2w. (N = 437)	Placebo (N = 218)
Subjects with > 0 AEs, n (%)	481 (76.2)	486 (77.0)	154 (89.0)	157 (90.8)	274 (62.7)	126 (57.8)
SAEs						
Subjects with > 0 SAEs, n (%)	29 (4.6)	33 (5.2)	13 (7.5)	10 (5.8)	20 (4.6)	8 (3.7)
Notable SAEs[b]						
Infections and infestations	9 (1.4)	9 (1.4)	[redacted]	[redacted]	9 (2.1)	4 (1.8)
WDAEs						
WDAEs, n (%)	30 (4.8)	41 (6.5)	3 (1.7)	9 (5.2)	9 (2.1)	3 (1.4)
Notable reasons						
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	3 (0.7)	2 (0.9)
AEs leading to dose modification or interruption						
n (%)	172 (27.3)	170 (26.9)	25 (14.5)	22 (12.7)	59 (13.5)	18 (8.3)
Notable reasons						
Infections and infestations	91 (14.4)	97 (15.4)	[redacted]	[redacted]	[redacted]	[redacted]
Deaths						
Number of deaths, n (%)	0	1 (< 1)	0	0	3 (< 1)	0
Notable harms						
Infections (all grades)	227 (36.0)	247 (39.1)			131 (30.0)	61 (28.0)
Infections (SAEs)	9 (1.4)	9 (1.4)	2 (1.2)	5 (2.9)	9 (2.1)	4 (1.8)
Hypersensitivity reactions	44 (7.0)	73 (11.6)			19 (4.3)	8 (3.7)
Injection-site reactions	64 (10.1)	15 (2.4)	[redacted]	[redacted]	31 (7.1)	9 (4.1)
Hyperlipidemia	5 (0.8)	7 (1.1)	[redacted]	[redacted]	1 (0.2)	0
Upper respiratory tract infection	46 (7.3)	73 (11.6)	[redacted]	[redacted]	28 (6.4)	14 (6.4)
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased ALT	118 (18.7)	104 (16.5)	[redacted]	[redacted]	58 (13.3)	11 (5.0)
Increased AST	85 (13.5)	66 (10.5)	[redacted]	[redacted]	36 (8.2)	8 (3.7)
Blood bilirubin increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; IV = intravenous; NA = not applicable; NR = not reported; q.w. = every week; q.2w. = every two weeks; q.4w. = every four weeks; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab; WDAE = withdrawal due to adverse events.

[a] All safety analyses were based on the safety population, inclusive of patients who received escape therapy, up to the point at which they received escape therapy.

[b] Frequency > 2%.

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

4. DISCUSSION

4.1 Summary of Available Evidence

Three RCTs were included in this review. The SUMMACTA trial (N = 1,262) was a double-blind, double-dummy, non-inferiority trial comparing TCZ-SC 162 mg every week in combination with non-biologic DMARDs to TCZ-IV 8 mg/kg every four weeks in combination with non-biologic DMARDs. The MUSASHI trial (N = 348) was a double-blind, double-dummy, non-inferiority trial comparing TCZ-SC 162 mg monotherapy every two weeks with TCZ-IV 8 mg/kg monotherapy every four weeks. The BREVACTA trial (N = 656) was a double-blind superiority trial comparing TCZ-SC 162 mg every two weeks in combination with non-biologic DMARDs with placebo every two weeks in combination with non-biologic DMARDs. Adult patients with moderately to severely active RA who had an inadequate response to DMARD therapy were included in the trials, with the percentage of patients who had failed one or more TNF alpha inhibitors capped at approximately 20%. The primary efficacy end point for all studies was the ACR20 response rate at week 24. All studies were blinded during the first 24 weeks. At week 24, all patients were re-randomized to an open-label treatment period. Data from the open-label extension phase for SUMMACTA trial and BREVACTA trial are summarized in Appendix 6: SUMMARY OF EXTENSION STUDIES.

4.2 Interpretation of Results

4.2.1 Efficacy

In the BREVACTA trial, TCZ-SC every two weeks was superior to placebo in reducing the signs and symptoms of RA in patients with moderate to severe RA treated concurrently with DMARDs, as reflected by a statistically significantly greater proportion of patients treated with TCZ-SC achieving an ACR20 response at week 24 (between-treatment difference 29.5%; $P < 0.0001$). Similarly, TCZ-SC every two weeks was superior to placebo in the BREVACTA trial in achieving secondary outcomes such as ACR50, ACR70, DAS28-ESR score less than 2.6, and DAS28-ESR score less than 3.2. Statistically significantly greater improvements were observed in the MCS and PCS scores of the SF-36 among patients treated with TCZ-SC every two weeks than in those in the placebo group at week 24. Patients in both treatment groups exceeded the MCID for the SF-36 improvement, which is typically between 2.5 and 5 points for either the PCS or MCS of the SF-36, but the magnitude of the improvement in the TCZ-SC every-two-weeks treatment group was almost twice as great as that in the placebo group.

The results of the SUMMACTA trial demonstrated that TCZ-SC administered every week is non-inferior to TCZ-IV in reducing the signs and symptoms of RA in patients with moderate to severe RA treated concurrently with DMARDs, as measured by the proportion of patients achieving an ACR20 response at week 24. The NIM selected by the manufacturer was considered reasonable by both the CDR reviewer and the clinical expert consulted for this review. A second non-inferiority study, the MUSASHI trial, also demonstrated that TCZ-SC administered every two weeks as monotherapy is non-inferior to TCZ-IV monotherapy in reducing the signs and symptoms of RA in patients with moderate to severe RA, as measured by the proportion of patients achieving an ACR20 response at week 24. However, despite demonstrating non-inferiority based on a pre-specified NIM, the upper bound of the 95% CI of the between-treatment difference was less than 0; therefore, the efficacy of TCZ-SC every two weeks was statistically significantly worse than that of TCZ-IV in the MUSASHI trial. These results suggest that there is some uncertainty associated with the conclusion that TCZ-SC and TCZ-IV are equally efficacious when TCZ is administered every two weeks.

In addition to the results for the ACR20, the SUMMACTA trial also showed that there was no statistically significant difference between TCZ-SC every week and TCZ-IV in the proportion of patients achieving the ACR50 and ACR70. In addition, there was no statistically significant difference between treatments in the percentage of patients achieving remission (DAS28-ESR score less than 2.6), in improvements in function (0.30 points or greater improvement in the HAQ-DI), or in HRQoL improvements (change in SF-36 score). Despite the similarity between treatments for the aforementioned secondary outcomes, there were no formal tests for non-inferiority for these outcomes.

Similar to SUMMACTA, the results of the MUSASHI trial demonstrated no statistically significant differences between treatments in the proportion of patients achieving the ACR50 and ACR70. However, fewer patients achieved remission (DAS28-ESR score less than 2.6) and low disease activity (DAS28-ESR score less than 3.2) in the TCZ-SC every-two-weeks group compared with the TCZ-IV group. HRQoL was not assessed in the MUSASHI trial. As in the SUMMACTA trial, there were no formal tests for non-inferiority for these outcomes.

Baseline characteristics of the patients enrolled in the each of the included trials were consistent with those enrolled in previous trials for the treatment of patients with moderately to severely active RA. The clinical expert consulted for this review noted that inclusion criteria for all included trials in this review and other RA studies tend to enrol patients with more severe disease activity than typically seen in clinical practice; therefore, the results may not be generalizable to RA patients who exhibit lower disease activity.[42,43]

Subgroup analysis of the data from SUMMACTA and BREVACTA by weight stratification (< 60 kg, 60 kg to < 100 kg, and > 100 kg) demonstrated that patients in the heaviest weight category (≥ 100 kg) achieve lower responses (ACR20, ACR50, and ACR70) than other patients. This might reflect suboptimal dosing in heavier patients, as the product monograph recommends administering treatment twice as frequently (weekly) to patients > 100 kg than to patients who weigh less than 100 kg (treatment every two weeks).[3]

The frequency at which TCZ was administered, both SC and IV, in the included trials differed somewhat from the regimens recommended in the product monographs for each product. The dose recommended by Health Canada for TCZ-SC is 162 mg every two weeks, increased to 162 mg every week based on clinical response for patients < 100 kg and every week for patients ≥ 100 kg, while starting dose for TCZ-IV is 4 mg/kg every four weeks, increased up to 8 mg/kg every four weeks based on clinical response. By contrast, flexible dose adjustments were not permitted in the included trials. While this design was necessary to compare the two treatments, the generalizability of the results to clinical practice may be somewhat compromised.

Data from the open-label extension phases of SUMMACTA indicated that response rates did not change with a switch in treatment from TCZ-SC every week to TCZ-IV and vice versa. Therefore, it is likely that patients who are currently using TCZ-IV could switch to TCZ-SC every week without compromising their treatment response. It is not known whether this would also be true for patients who switch from other biologics to TCZ-SC every week.

4.2.2 Harms

TCZ-SC and TCZ-IV were associated with similar incidences of AEs, SAEs, withdrawal due to adverse events (WDAE), and death in SUMMACTA and MUSASHI. In both of these trials, the incidence of injection-site reactions was higher in patients treated with TCZ-SC than with those treated with TCZ-IV. The higher incidence of injection-site reactions in the SC-treated patients likely reflects the different

routes of delivery in the different treatment groups (SC injection versus IV infusion) and was not associated with a higher rate of discontinuations; in fact, there were more WDAE in the TCZ-IV groups than in the TCZ-SC groups. Malignancy rates were low in the SUMMACTA trial (six cases in total) and absent from the MUSASHI trial. Similar results were reported for the placebo-controlled BREVACTA trial.

The open-label extension phases of the SUMMACTA and BREVACTA trials did not reveal any harms that were not already detected in the double-blind phases of these trials. However, in the extension phase of SUMMACTA, higher AE and SAE rates were observed in the group of patients who switched from IV to SC administration of TCZ, compared with the group that remained on IV administration, while there was an increased rate of injection-site reactions in patients who initiated escape therapy (TCZ-SC every week) between week 12 and week 24 of the double-blind phase and continued receiving this higher dosing frequency during the open-label phase.

4.3 Other Considerations

CDR reviewers were unable to identify any published studies in which TCZ-SC has been compared directly or indirectly with any other biologic therapy in RA patients. Two network meta-analyses[5,6] were identified in which the efficacy of TCZ-IV was compared with other biologic therapies (see Appendix 7: SUMMARY AND APPRAISAL OF NETWORK META-ANALYSES). An appraisal of these studies by CDR revealed that there are no consistent or meaningful differences between TCZ-IV and other biologics in RA patients (within the limitations of the indirect comparisons). Since the efficacy of TCZ-IV is similar to other biologic therapies, and since TCZ-IV is non-inferior to TCZ-SC, it could be hypothesized that TCZ-SC is similar to other biologics. However, in the absence of any direct or indirect evidence that compares TCZ-SC with other biologics, whether TCZ-SC is similar to other biologics remains uncertain.

Patient input for TCZ-SC revealed that patients hope that the SC formulation of tocilizumab would enhance their freedom and improve management of their disease. Patients also hope that SC administration would be more comfortable than IV administration and would limit visits to the clinic, and therefore patients would prefer the SC route of administration. The results of this review suggest that, while the SC formulation might be less restrictive in terms of the logistics of delivery, it comes at a cost of potentially higher rates of injection-site reactions. The clinical expert consulted for this review suggested that patient preference would be the major driver for switching patients from TCZ-IV to TCZ-SC, and that newly diagnosed patients who are candidates for TCZ would likely receive TCZ-SC rather than TCZ-IV.

5. CONCLUSIONS

Two double-blind, double-dummy, active-controlled, non-inferiority RCTs (SUMMACTA and MUSASHI) and one placebo-controlled superiority RCT (BREVACTA) met the inclusion criteria for this review. Each of these studies included adult patients with moderately to severely active RA who had an inadequate response to previous DMARD therapy. The results of the BREVACTA trial demonstrated that TCZ-SC every two weeks is superior to placebo with respect to the proportion of patients achieving an ACR20 response as well as all secondary outcomes, including the proportion of patients who had reduced disease activity (ACR 50 and ACR70 thresholds), disease remission (DAS score), improved physical function (HAQ-DI scores), and improved HRQoL (SF-36 score). In SUMMACTA and MUSASHI, TCZ-SC was compared directly with TCZ-IV. In SUMMACTA, TCZ-SC (administered weekly) and IV were administered in conjunction with non-biologic DMARDs, whereas in MUSASHI, TCZ-SC (administered every two weeks) and TCZ-IV were administered as monotherapy. In SUMMACTA, TCZ-SC every week was non-inferior to TCZ-IV with respect to the proportion of patients achieving an ACR20 response, and there were no significant differences between TCZ-SC every week and TCZ-IV in secondary outcomes, including the proportion of patients who had reduced disease activity (ACR 50 and ACR70 thresholds), disease remission (DAS score), improved physical function (HAQ-DI scores), and improved HRQoL (SF-36 score). Similarly, in MUSASHI, TCZ-SC every two weeks was non-inferior to TCZ-IV with respect to the proportion of patients achieving an ACR20 response. However, although the results of the MUSASHI trial met the criteria for non-inferiority, the efficacy of TCZ-SC every two weeks was statistically significantly lower than TCZ-IV with regard to the proportion of patients achieving an ACR20 response. The SC and IV formulations of TCZ were similar with respect to the types and incidences of AEs, although more injection-site reactions occurred in patients treated with the SC formulation.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group(s) Supplying Input
Three patient groups representing people with rheumatoid arthritis (RA) provided input.

The Arthritis Society is a national charity that provides education and programs for people with arthritis, as well as funding for arthritis research. It is accredited by Imagine Canada's Standards Program. The Arthritis Society receives funding from individual donors, and during the past 12 months it has received funding from many pharmaceutical companies, including AbbVie, Amgen, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche, and UCB. The Society follows all Canada Revenue Agency and Imagine Canada requirements and declares it believes there was no conflict of interest in the preparation of the patient input submission.

The Canadian Arthritis Patient Alliance (CAPA) is an independent, national organization that seeks to improve the quality of life for patients with arthritis through patient education and advocacy. In the past year, CAPA has received both restricted and unrestricted funding and in-kind support from AbbVie, Amgen, Janssen, Novartis, Pfizer, UCB Pharma, the Ontario Rheumatology Association, the Canadian Rheumatology Association, and The Arthritis Society. CAPA declared no conflicts of interest in the preparation of the submission.

Arthritis Consumer Experts (ACE) is a national organization committed to educating and empowering people with arthritis to improve their quality of life. It also provides evidence-based information and research decision-making training to people with arthritis to help them participate meaningfully in research organizations and government consultation. ACE has received unrestricted grants from several pharmaceutical companies, including AbbVie Corporation, Amgen Canada, Arthritis Research Centre of Canada, BIOTECanada, Bristol-Myers Squibb Canada, the Canadian Rheumatology Research Consortium, Canadian Institutes of Health Research, Celgene Inc., GlaxoSmithKline, Hoffman-La Roche Canada Ltd., Janssen Inc., Pfizer Canada, Purdue Pharma L.P., Takeda Canada Inc., and UCB. It declares no conflicts of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information
This information was collected through online surveys, one-on-one conversations and correspondence with patients and caregivers, and printed sources.

RA is a chronic, disabling, autoimmune disease that greatly affects every aspect of patients' lives. RA causes severe inflammation leading to joint destruction, which sometimes necessitates major joint surgery. People with RA experience daily debilitating pain and fatigue. Patients commonly reported that pain is the most important aspect of RA to control, as it hinders participation in normal activities. Swollen and stiff joints restrict range of motion and dexterity, which can affect daily tasks including personal hygiene, dressing, walking, meal preparation, and housework. Mobility may become so impaired that patients require the aid of bath lifts, canes or wheelchairs, modifications to their house or car, or the use of paratransit to participate in daily activities. People with RA may become unable to work, attend school, exercise, or socialize with family and friends. At the very least, patients must make

substantial adjustments to their way of life to compensate for their pain and reduced mobility and dexterity; individual patients have reported restricting travel plans (e.g., limiting duration, selecting accommodations and attractions without steps) or wardrobe choices (e.g., clothes with few zippers and buttons). Patients can experience frustration with others' misperceptions of the extent and implications of RA; one patient reported being told to "take a Tylenol and get on with it."

Caregivers of those living with RA also face significant demands. Caregivers must perform all the household tasks that their loved ones are unable to help with, which may add stress to the relationship or cause patients to feel guilty. Caregivers may need to administer medications by injection and thus may have concerns about correct administration and risk of hurting the patient. Emotional suffering also comes from the knowledge that caregivers cannot always alleviate the pain that their loved ones are experiencing, especially when the current treatment regime does not provide the desired outcomes. Time demands and need for flexibility were also identified as significant challenges for caregivers when they need to care for patients incapacitated by adverse effects or accompany them to medical appointments.

Current treatments for RA include disease-modifying antirheumatic drugs (DMARDs; including biologics and methotrexate), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and analgesics. Patients often require multiple drugs in combination to manage their RA. When patients respond to treatment, it can be very effective, yet, for others, current therapies are only partially effective or completely ineffective. Even when current treatment is effective, patients often fear that at some point it will stop working for them, and they may not be able to find a suitable replacement. For this reason, the availability of a variety of treatment options is important, especially for young patients who will require treatment for the rest of their lives. Some patients reported success with Actemra for their disease management. However, currently only the intravenous (IV) form is reimbursed, and this route of administration places a burden on patients. Actemra IV must be delivered at a clinic, which requires a significant time investment for travel and leave from work in addition to administration time, and limits travel plans. Inserting the IV needle can be painful, may cause bruising, and may be difficult to accomplish due to extensive vein scarring.

Currently available RA medications have several adverse effects, including nausea, vomiting, tiredness, easy bruising or bleeding, dizziness, itching, reactions at injection sites, fever, night sweats, weight loss, feeling full after eating a small amount, stomach pain, pale skin, shortness of breath, rapid heart rate, loss of appetite, dark urine, clay-coloured stools, and jaundice. RA medications are very expensive and, as a result, patients need to have private insurance or take on extra work to cover this cost. There is also a significant paperwork burden with provincial drug plans to approve requests for drug coverage. The patient groups emphasized that having a range of treatment options increases the likelihood that patients will have better access to affordable and effective medication with fewer side effects.

3. Related Information About the Drug Being Reviewed

Patients hope that Actemra SC will effectively reduce pain and improve quality of life. Patients without experience with this drug cannot be certain that it would improve their lives but reported a preference for subcutaneous route of administration because the drug can be self-administered; this would enhance their freedom and control over the management of their disease. Patients also hope that subcutaneous administration would be more comfortable than IV administration and would limit visits to the clinic, which would be more convenient for patients and may reduce the burden on their caregivers and the health care system. Patients said that they would be willing to experience short-term, non–life-threatening adverse events.

One patient recently initiated treatment with Actemra SC and experienced colds, a sore throat, and an eye infection, although it is unclear whether this was related to the drug. This patient has received only two doses of Actemra SC and cannot comment on its effectiveness, but reported fewer side effects from the subcutaneous form of Actemra than the IV form.

4. Additional Information

It was suggested that use of the term "condition" in the CADTH Patient Group Input Template is not medically accurate and should be replaced with "disease" or at least "disease or condition" throughout the document. One group strongly disagreed with calling for patient input on queued drugs without providing an indication of how long it could be until this drug may be accessible to patients.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 18, 2014
Alerts:	Weekly search updates until (date of CDEC meeting)
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1 (Actemra* or RoActemra* or tocilizumab or atlizumab or R-1569 or R1569).ti,ot,ab,sh,rn,hw,nm. 2 ("monoclonal antibody" adj2 MRA).ti,ab. 3 (Chugai adj2 MRA).ti,ab. 4 375823-41-9.rn,nm. 5 or/1-4 6 exp arthritis rheumatoid/ use pmez 7 exp *rheumatoid arthritis/ use oemezd 8 ((rheumatoid or inflammatory or rheumatic) adj2 arthritis).ti,ab. 9 ((chronic or rheumatic) adj2 (polyarthritis or poly-arthritis)).ti,ab. 10 (arthritis deformans or arthrosis deformans or Beauvais disease or rheumarthritic or rheumatism or rheumatic or RA).ti,ab. 11 ((still* or felty* or caplan* or sicca* or sjogren* or chauffard*) adj2 (syndrome* or disease*)).ti,ab. 12 or/6-11 13 "Injections, Subcutaneous"/ use pmez 14 subcutaneous drug administration/ use oemezd 15 (subcutaneous* or autoinjector or auto-injector or SC or SQ or sub-cu or sub-Q or (subcut adj3 SQ) or (self adj3 administ*) or (self adj3 inject*)).ti,ab. 16 (Subcutaneous adj1 (inject* or administration or administer or administering or "SCIT" or shot or shots)).ti,ab. 17 or/13-16 18 5 and 12 and 17 19 5 and 17 20 18 or 19 21 remove duplicates from 20 22 21 not conference abstract.pt.

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

Grey Literature

Dates for Search:	September, 2014
Keywords:	Actemra® (tocilizumab), rheumatoid arthritis, subcutaneous
Limits:	No date or language limits used

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

- Health technology assessment agencies
- Health economics
- Clinical practice guidelines
- Drug and device regulatory approvals
- Advisories and warnings
- Drug class reviews
- Databases (free)
- Internet search

APPENDIX 3: EXCLUDED STUDIES

No studies were excluded.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 8: PROPORTION OF PATIENTS WITH ACR20, ACR50, AND ACR70 RESPONSES AT WEEK 24

	SUMMACTA[ab]		MUSASHI[ab]		BREVACTA[cde]	
	TCZ-SC 162 mg q.w. (N = 558)[a]	TCZ-IV 8 mg/kg q.4w. (N = 537)[a]	TCZ-SC 162 mg q.2w. (N = 159)[a]	TCZ-IV 8 mg/kg q.4w. (N = 156)[a]	TCZ-SC 162 mg q.2w. (N = 437)	Placebo (N = 219)
ACR20						
n (%)	387 (69.4)	394 (73.4)	126 (79.2)	138 (88.5)	266 (60.9)	69 (31.5)
Weighted difference (95% CI)	−4.0 (−9.2 to 1.2)		−9.4 (−17.6 to −1.2)		29.5 (22.0 to 37.0) *P* < 0.0001	
ACR50						
n (%)	262 (47.0)	261 (48.6)	101 (63.5)	105 (67.3)	174 (39.8)	27 (12.3)
Weighted difference (95% CI)	−1.8 (−7.5 to 4.0)		−4.3 (−14.7 to 6.0)		27.9 (21.5 to 34.4) *P* < 0.0001	
ACR70						
n (%)	134 (24.0)	150 (27.9)	59 (37.1)	64 (41.0)	86 (19.7)	11 (5.0)
Weighted difference (95% CI)	−3.8 (−9.0 to 1.3)		−3.8 (−14.5 to 6.8)		14.8 (9.8 to 19.9) *P* < 0.0001	

ACR = American College of Rheumatology; CI = confidence interval; IV = intravenous; q.w. = every week; q.2w. = every two weeks; q.4w. = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] Per-protocol population.

[b] Analysis was stratified by weight (< 60 kg, ≥ 60 kg) and previous TNF alpha inhibitor (YES, NO). Weighted difference calculated using extended Mantel–Haenszel method.

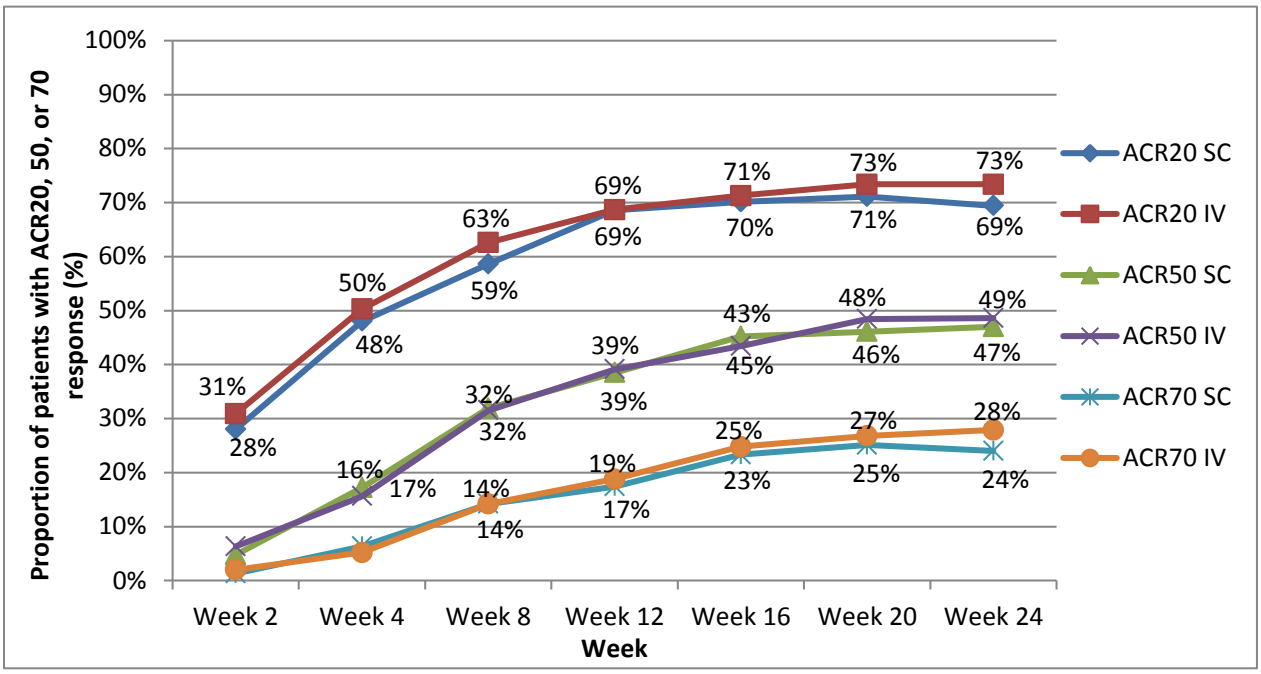
[c] Intention-to-treat population.

[d] The stratification factors region and weight were included in the model.

[e] Patients who withdrew prematurely, who entered escape therapy or in whom an ACR response could not be calculated were set to "Non-Responder."

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

FIGURE 3: PROPORTION OF PATIENTS ACHIEVING ACR20, ACR50, AND ACR70 RESPONSES OVER TIME IN SUMMACTA (PER-PROTOCOL POPULATION)



ACR = American College of Rheumatology; IV = intravenous tocilizumab 8 mg/kg every four weeks; SC = subcutaneous tocilizumab 162 mg once weekly.
Source: SUMMACTA trial Clinical Study Report.[22]

FIGURE 4: PROPORTION OF PATIENTS ACHIEVING ACR20, ACR50, AND ACR70 RESPONSES OVER TIME IN MUSASHI (PER-PROTOCOL POPULATION)

[Confidential data regarding the Proportion of Patients Achieving ACR20, ACR50, and ACR70 Responses Over Time in MUSASHI were removed at the manufacturer's request.]

ACR = American College of Rheumatology; IV = intravenous tocilizumab 8 mg/kg every 4 weeks; SC = subcutaneous tocilizumab 162 mg every other week.
Source: MUSASHI trial Clinical Study Report.[23]

FIGURE 5: PROPORTION OF PATIENTS ACHIEVING AN ACR20 RESPONSE OVER TIME IN BREVACTA (INTENTION-TO-TREAT POPULATION)

[Confidential data regarding the Proportion of Patients Achieving ACR20 Response Over Time in BREVACTA were removed at the manufacturer's request.]

ACR = American College of Rheumatology; ITT = intention-to-treat; SC = subcutaneous tocilizumab 162 mg every other week.
Source: BREVACTA trial Clinical Study Report.[24]

FIGURE 6: PROPORTION OF PATIENTS ACHIEVING ACR50 RESPONSE OVER TIME IN BREVACTA (INTENTION-TO-TREAT POPULATION)

[Confidential data regarding the Proportion of Patients Achieving ACR50 Response Over Time in BREVACTA were removed at the manufacturer's request.]

ACR = American College of Rheumatology; ITT = intention-to-treat; SC = subcutaneous tocilizumab 162 mg every other week.
Source: BREVACTA trial Clinical Study Report.[24]

FIGURE 7: PROPORTION OF PATIENTS ACHIEVING ACR70 RESPONSE OVER TIME IN BREVACTA (INTENTION-TO-TREAT POPULATION)

[Confidential data regarding the Proportion of Patients Achieving ACR70 Response Over Time in BREVACTA were removed at the manufacturer's request.]

ACR = American College of Rheumatology; ITT = intention-to-treat; SC = subcutaneous tocilizumab 162 mg every other week.
Source: BREVACTA trial Clinical Study Report.[24]

TABLE 9: SENSITIVITY ANALYSIS ON THE PROPORTION OF PATIENTS WITH ACR20 AT WEEK 24

	SUMMACTA[ab]		MUSASHI[b]		BREVACTA[ac]	
	TCZ-SC 162 mg q.w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	Placebo
ITT population						
N	631	631	173[d]	172[d]		
ACR20 responders, n (%)	427 (67.7)	443 (70.2)	137 (79.2)	148 (86.0)		
Weighted difference (95% CI)	−2.7 (−7.6 to 2.2)[a]		−7.0 (−15.0 to 1.0)[b]			
ACR50 responders, n (%)	NR	NR	[redacted]	[redacted]		
Weighted difference (95% CI)	NR		[redacted]			
ACR70 responders, n (%)	NR	NR	[redacted]	[redacted]		
Weighted difference (95% CI)	NR		[redacted]			
Completer population[e]						
N					347	124
ACR20 responders, n (%)					266 (76.7)	69 (55.6)
Weighted difference (95% CI)					22.4 (12.8 to 31.9)[c] *P* < 0.0001	

ACR = American College of Rheumatology; CI = confidence interval; ITT = intention-to-treat; IV = intravenous; NR = not reported; q.w. = every week; q.2w. = every two weeks; q.4w. = every 4 weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] The stratification factors region and weight were included in the model.

[b] Analysis was stratified by weight (< 60 kg, ≥ 60 kg) and previous TNF alpha inhibitor (YES, NO). Weighted difference calculated using extended Mantel–Haenszel method.

[c] Patients who withdrew prematurely or for whom an ACR response could not be calculated were set to "Non-Responder."

[d] Full analysis set.

[e] Patients who completed the double-blind treatment portion of the study and who had a valid week 24 assessment.

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

TABLE 10: SUBGROUP ANALYSIS OF PROPORTION OF PATIENTS WITH ACR20, ACR50, AND ACR70 RESPONSES AT WEEK 24

	SUMMACTA[a]		MUSASHI[a]		BREVACTA[b]	
	TCZ-SC 162 mg q.w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	Placebo
By Body Weight at Baseline						
ACR20						
< 60 kg, n/N (%)	99/131 (75.6)	100/129 (77.5)	[redacted]	[redacted]	75/119 (63.0)	17/58 (29.3)
60 kg to 100 kg, n/N (%)	260/374 (69.5)	264/358 (73.7)	[redacted]	[redacted]	181/292 (62.0)	49/150 (32.7)
≥ 100 kg, n/N (%)	28/53 (52.8)	30/50 (60.0)	[redacted]	[redacted]	10/26 (38.5)	3/11 (27.3)
ACR50						
< 60 kg, n/N (%)	66/131 (50.4)	71/129 (55.0)	[redacted]	[redacted]	52/119 (43.7)	6/58 (10.3)
60 kg to 100 kg, n/N (%)	176/374 (47.1)	177/358 (49.4)	[redacted]	[redacted]	119/292 (40.8)	19/150 (12.7)
≥ 100 kg, n/N (%)	20/53 (37.7)	13/50 (26.0)	[redacted]	[redacted]	3/26 (11.5)	2/11 (18.2)
ACR70						
< 60 kg, n/N (%)	31/131 (23.7)	47/129 (36.4)	[redacted]	[redacted]	28/119 (23.5)	2/58 (3.4)
60 kg to 100 kg, n/N (%)	96/374 (25.7)	100/358 (27.9)	[redacted]	[redacted]	57/292 (19.5)	8/150 (5.3)
≥ 100 kg, n/N (%)	7/53 (13.2)	3/50 (6.0)	[redacted]	[redacted]	1/26 (3.8)	1/11 (9.1)
By DMARD IR Versus TNF IR						
ACR20						
DMARD IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNF IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR50						
DMARD IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNF IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR70						
DMARD IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TNF IR, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
By DAS28						
ACR20						
> 3.2 to ≤ 5.1, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 5.1, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR50						
> 3.2 to ≤ 5.1, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SUMMACTA[a]		MUSASHI[a]		BREVACTA[b]	
	TCZ-SC 162 mg q.w.	**TCZ-IV 8 mg/kg q.4w.**	**TCZ-SC 162 mg q.2w.**	**TCZ-IV 8 mg/kg q.4w.**	**TCZ-SC 162 mg q.2w.**	**Placebo**
> 5.1, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR70						
> 3.2 to ≤ 5.1, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
> 5.1, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
By Rheumatoid Factor (Positive Versus Negative)						
ACR20						
RF positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR50						
RF positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR70						
RF positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RF negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
By Anti-CCP Antibody (Positive Versus Negative)						
ACR20						
Anti-CCP positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR50						
Anti-CCP positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ACR70						
Anti-CCP positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; anti-CCP = anti-cyclic citrullinated peptide; DAS = Disease Activity Score; DMARDs = disease-modifying antirheumatic drugs; IR = inadequate responder; IV = intravenous; NR = not reported; q.w. = every week; q.2w. = every two weeks; q.4w. = every four weeks; RF = rheumatoid factor; SC = subcutaneous; TCZ = tocilizumab; TNF = tumour necrosis factor.

[a] Per-protocol population.

[b] Intention-to-treat population.

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

TABLE 11: DAS28 SCORES

	SUMMACTA[ab]		MUSASHI[a]		BREVACTA[c]	
	TCZ-SC 162 mg q.w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	TCZ-IV 8 mg/kg q.4w.	TCZ-SC 162 mg q.2w.	Placebo
DAS28 < 2.6 (REMISSION) AT WEEK 24						
N	516	498	159	156	347[b]	124
n (%)	198 (38.4)[d]	184 (36.9)	79 (49.7)	97 (62.2)	111 (32.0)[d]	5 (4.0)
Weighted difference (95% CI)	0.9 (−5.0 to 6.8)		−12.5 (−23.4 to −1.6)[e]		28.6 (22.0 to 35.2) *P* < 0.0001	
DAS28 < 3.2 (LOW DISEASE ACTIVITY) AT WEEK 24						
N	516	498	159	156	347[b]	124
n (%)[d]	[redacted]		[redacted]		157 (45.2)	19 (15.3)
Weighted difference (95% CI)	NR		[redacted]		30.3 (22.0 to 38.6) *P* < 0.0001	
CHANGE FROM BASELINE IN DAS28 SCORED[f]						
Baseline, n	551	533			434	217
Baseline, mean (SD)	6.6 (1.0)	6.7 (1.0)			6.7 (0.9)	6.6 (0.9)
Week 24, n	509	496			344	123
Change from baseline at week 24	−3.6 (1.4)	−3.6 (1.4)			−3.1[gh]	−1.7[gh]
Weighted difference (95% CI)	NR				−1.4 (−1.7 to −1.1) *P* < 0.0001	
PROPORTION OF PATIENTS WITH DAS28 REMISSION (DAS28 SCORE < 2.6) AT WEEK 24 BY WEIGHT AT BASELINE						
< 60 kg, n/N (%)	[redacted]				[redacted]	
60−100 kg, n/N (%)	[redacted]				[redacted]	
≥ 100 kg, n/N (%)	[redacted]				[redacted]	
PROPORTION OF PATIENTS CLASSED AS CATEGORICAL DAS28 RESPONDERS (EULAR RESPONSE) AT WEEK 24						
N	NR	NR	159	155	374[bi]	138[bi]
Good response, n (%)	NR	NR	104 (65.4)	128 (82.6)	156 (41.7)	19 (13.8)
Moderate response, n (%)	NR	NR	[redacted]		[redacted]	
No response, n (%)	NR	NR	[redacted]		[redacted]	
P value	NR		NR		*P* < 0.0001	

ACR = American College of Rheumatology; CI = confidence interval; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; IV = intravenous; LOCF = last observation carried forward; NR = not reported; q.2w. = every two weeks; q.w. = every week; q.4w. = every 4 weeks; SC = subcutaneous; SD = standard deviation; TCZ = tocilizumab.

[a] Per-protocol population.

[b] The stratification factors region and weight were included in the model.

[c] Intention-to-treat population. Patients who withdrew prematurely, who entered escape therapy, or in whom an ACR response could not be calculated were set to "Non-Responder." Imputation was performed for missing DAS28 score.

[d] LOCF used for tender and swollen joint counts; no imputation used for ESR and Patient's Global Assessment of Disease Activity visual analogue scale.

[e] Calculated by CADTH using Review Manager; negative values indicate that fewer patients in the TCZ-SC treatment group achieved remission than those in the TCZ-IV treatment group.

[f] No data imputation is applied, and patients who had missing data are excluded.

[g] Adjusted mean.

[h] Covariance analysis adjusted for the randomization stratification factors applied at baseline and baseline score.

[i] Escape patients were included until time of escape, when they were classed as withdrawn. Patients who withdrew are excluded.

Source: Burmester et al.,[19] Kivitz et al.,[21] Ogata et al.,[20] SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

TABLE 12: CHANGE FROM BASELINE IN MODIFICATION OF THE SHARP SCORE AT WEEK 24

	SUMMACTA		MUSASHI		BREVACTA	
	TCZ-SC 162 mg q.w.	**TCZ-IV 8 mg/kg q.4w.**	**TCZ-SC 162 mg q.2w.**	**TCZ-IV 8 mg/kg q.4w.**	**TCZ-SC 162 mg q.2w.**	**Placebo**
Linear Extrapolation Method Using van Elteren Analysis and ANOVA Analysis						
Baseline, n					391	186
Baseline, mean (SD)					59.0 (65.9)	60.4 (66.5)
Week 24, n					391	186
Change from baseline at week 24, mean (SD)					0.6 (2.7)	1.2 (2.8)
P value					0.0145	
Including Post-Withdrawal and Escape Data, Linear Extrapolation Using van Elteren Analysis						
Baseline, n					408	203
Baseline, mean (SD)					60.3 (66.6)	58.7 (66.4)
Week 24, n					408	203
Change from baseline at week 24, mean (SD)					0.5 (2.5)	1.1 (2.4)
P value					0.0039	

ANOVA = analysis of variance; IV = intravenous; q.w. = every week; q.2w. = every two weeks; q.4w. = every four weeks; SC = subcutaneous; SD = standard deviation; TCZ = tocilizumab.
Source: BREVACTA trial Clinical Study Report.[24]

TABLE 13: HEALTH ASSESSMENT QUESTIONNAIRE–DISABILITY INDEX SCORE

	SUMMACTA[ab]		MUSASHI[ac]		BREVACTA[bd]	
	TCZ-SC 162 mg q.w.	**TCZ-IV 8 mg/kg q.4w.**	**TCZ-SC 162 mg q.2w.**	**TCZ-IV 8 mg/kg q.4w.**	**TCZ-SC 162 mg q.2w.**	**Placebo**
% of Patients Achieving a Decrease of ≥ 0.3 in HAQ-DI Score from Baseline at Week 24						
N	515	500			348	124
n (%)[e]	336 (65.2)	337 (67.4)			202 (58.0)	58 (46.8)
Weighted difference (95% CI)	−2.3 (−8.1 to 3.4)				12.1 (2.2 to 22.0) *P* = 0.0170	
% of Patients Achieving a Decrease of ≥ 0.22 in HAQ-DI Score from Baseline at Week 24						
N	515	500			[redacted]	
n (%)[e]	376 (73.0)	373 (74.6)			[redacted]	
Change from Baseline in HAQ-DI						
N	515	500	[redacted]		348	124
Change from Baseline at week 24, mean (SD)	−0.6 (0.6)	−0.6 (0.6)	[redacted]		−0.4	−0.3
Weighted difference (95% CI)	NR		NR		−0.2 (−0.3 to 0.0) *P* = 0.0054	

ACR = American College of Rheumatology; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire−Disability Index; IV = intravenous; NR = not reported; q.2w. = every two weeks; q.w. = every week; q.4w. = every 4 weeks; SC = subcutaneous; SD = standard deviation; TCZ = tocilizumab.

[a] Per-protocol population.

[b] The stratification factors region and weight were included in the model.

[c] Analysis was stratified by weight (< 60 kg, ≥ 60 kg) and previous TNF alpha inhibitor (YES, NO). Weighted difference calculated using extended Mantel–Haenszel method.

[d] Patients who withdrew prematurely, who entered escape therapy, or in whom an ACR response could not be calculated were set to "Non-Responder."

[e] No imputation of missing scores was made other than for missing baseline scores, for which last score prior to baseline was carried forward.

Source: SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

TABLE 14: SHORT-FORM (36) HEALTH SURVEY SCORE

	SUMMACTA[ab]		MUSASHI		BREVACTA[bc]	
	TCZ-SC 162 mg q.w. (N = 558)	**TCZ-IV 8 mg/kg q.4w. (N = 537)**	**TCZ-SC 162 mg q.2w. (N = 159)**	**TCZ-IV 8 mg/kg q.4w. (N = 156)**	**TCZ-SC 162 mg q.2w. (N = 437)**	**Placebo (N = 219)**
SF-36 Mental Component Summary Score						
Baseline, n	555	532			[redacted]	[redacted]
Baseline, mean (SD)	39.7 (11.6)	39.0 (12.1)			[redacted]	[redacted]
Week 12, n	521	501			[redacted]	[redacted]
Change from baseline at Week 12	5.8 (11.0)	6.6 (10.6)			[redacted]	[redacted]
Week 24, n	511	495			347	123
Change from baseline at week 24	6.2 (11.3)	6.5 (11.1)			6.5	3.8
Mean difference (95% CI)	NR				2.7 (0.7 to 4.6) *P* = 0.0068	
SF-36 Physical Component Summary Score						
Baseline, n	555	532			[redacted]	[redacted]
Baseline, mean (SD)	30.2 (7.2)	30.2 (7.5)			[redacted]	[redacted]
Week 12, n	521	501			[redacted]	[redacted]
Change from baseline at week 12	8.1 (8.0)	7.1 (8.1)			[redacted]	[redacted]
Week 24, n	511	495			347	123
Change from baseline at week 24	9.5 (8.2)	9.7 (8.2)			5.3	2.9
Mean difference (95% CI)	NR				2.4 (1.0 to 3.8) *P* = 0.0006	

ACR = American College of Rheumatology; CI = confidence interval; IV = intravenous; NR = not reported; q.w. = every week; q.2w. = every two weeks; q.4w. = every 4 weeks; SC = subcutaneous; SD = standard deviation; SF-36 = Short-Form (36) Health Survey; TCZ = tocilizumab.

[a] Per-protocol population.

[b] Missing SF-36 data were replaced by the last valid post-baseline assessment.

[c] Patients who withdrew prematurely, who entered escape therapy, or in whom an ACR response could not be calculated were set to "Non-Responder."

Source: SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

TABLE 15: MOST COMMON SOCS IN WHICH AES WERE REPORTED (≥ 10% IN EITHER GROUP IN ANY OF THE TRIALS) AND THE MOST COMMONLY REPORTED AE IN EACH CLASS IN EACH TRIAL

AEs	SUMMACTA		MUSASHI		BREVACTA	
	TCZ-SC 162 mg q.w. (N = 631)	TCZ-IV 8 mg/kg q.4w. (N = 631)	TCZ-SC 162 mg q.2w. (N = 173)	TCZ-IV 8 mg/kg q.4w. (N = 173)	TCZ-SC 162 mg q.2w. (N = 437)	Placebo (N = 218)
Subjects with > 0 AEs, N (%)	481 (76.2)	486 (77.0)	154 (89.0)	157 (90.8)	274 (62.7)	126 (57.8)
Most common AEs						
Infections and infestations	**227 (36.0)**	**247 (39.1)**	**72 (41.6)**	**78 (45.1)**	**131 (30.0)**	**61 (28.0)**
Upper respiratory tract infections	46 (7.3)	73 (11.6)	[redacted]	[redacted]	28 (6.4)	14 (6.4)
Nasopharyngitis	36 (5.7)	36 (5.7)	31 (17.9)	36 (20.8)	19 (4.3)	5 (2.3)
Urinary tract infections	26 (4.1)	32 (5.1)			18 (4.1)	7 (3.2)
Pharyngitis			[redacted]	[redacted]		
Investigations	**147 (23.3)**	**134 (21.2)**	**93 (53.8)**	**89 (51.4)**	**74 (16.9)**	**15 (6.9)**
Increased ALT	118 (18.7)	104 (16.5)	17 (9.8)	18 (10.4)	58 (13.3)	11 (5.0)
Increased AST	85 (13.5)	66 (10.5)			36 (8.2)	8 (3.7)
Blood cholesterol increased			31 (17.9)	33 (19.1)		
Low-density lipoprotein increased			24 (13.9)	30 (17.3)		
Blood triglycerides increased			18 (10.4)	18 (10.4)		
Gastrointestinal disorders	**121 (19.2)**	**117 (18.5)**	**34 (19.7)**	**43 (24.9)**	**52 (11.9)**	**22 (10.1)**
Nausea	25 (4.0)	29 (4.6)			6 (1.4)	2 (0.9)
Diarrhea	27 (4.3)	26 (4.1)			8 (1.8)	3 (1.4)
Dyspepsia					9 (2.1)	2 (0.9)
Stomatitis			[redacted]	[redacted]		
Dental caries			[redacted]	[redacted]		
Musculoskeletal and connective tissue disorders	**97 (15.4)**	**97 (15.4)**	**14 (8.1)**	**11 (6.4)**	**38 (8.7)**	**27 (12.4)**
Arthralgia	9 (1.4)	16 (2.5)			10 (2.3)	1 (0.5)
Back pain	8 (1.3)	15 (2.4)	[redacted]	[redacted]	5 (1.1)	3 (1.4)
RA					5 (1.1)	4 (1.8)
Skin and subcutaneous tissue disorders	**73 (11.6)**	**82 (13.0)**	[redacted]	[redacted]	**30 (6.9)**	**13 (6.0)**
Rash	18 (2.9)	17 (2.7)	[redacted]	[redacted]	6 (1.4)	1 (0.5)
Pruritus	15 (2.4)	11 (1.7)	[redacted]	[redacted]	6 (1.4)	0
Eczema			[redacted]	[redacted]		

AEs	SUMMACTA		MUSASHI		BREVACTA	
	TCZ-SC 162 mg q.w. (N = 631)	**TCZ-IV 8 mg/kg q.4w. (N = 631)**	**TCZ-SC 162 mg q.2w. (N = 173)**	**TCZ-IV 8 mg/kg q.4w. (N = 173)**	**TCZ-SC 162 mg q.2w. (N = 437)**	**Placebo (N = 218)**
General disorders and administration-site conditions	**94 (14.9)**	**44 (7.0)**	**33 (19.1)**	**13 (7.5)**	**43 (9.8)**	**13 (6.0)**
Injection-site erythema	28 (4.4)	5 (0.8)	17 (9.8)	5 (2.9)	10 (2.3)	1 (0.5)
Peripheral edema	11 (1.7)	9 (1.4)				
Injection-site pain	12 (1.9)	5 (0.8)			11 (2.5)	5 (2.3)
Pyrexia			[redacted]	[redacted]		
Nervous system disorders	**59 (9.4)**	**73 (11.6)**	**18 (10.4)**	**5 (2.9)**	**37 (8.5)**	**17 (7.8)**
Headache	28 (4.4)	33 (5.2)	[redacted]	[redacted]	23 (5.3)	13 (6.0)
Dizziness	13 (2.1)	15 (2.4)	[redacted]	[redacted]	3 (0.7)	3 (1.4)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate transaminase; IV = intravenous; q.w. = every week; q.2w. = every two weeks; q.4w. = every 4 weeks; RA = rheumatoid arthritis; SC = subcutaneous; SOC = system organ class; TCZ = tocilizumab.
Source: SUMMACTA trial Clinical Study Report,[22] MUSASHI trial Clinical Study Report,[23] BREVACTA trial Clinical Study Report.[24]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To summarize the characteristics, validity, limitations, and minimal clinically important differences of the following outcome measures used in trials of rheumatoid arthritis (RA) included in the CADTH Common Drug Review systematic review of subcutaneous (SC) tocilizumab:

- American College of Rheumatology (ACR) 20, ACR50, and ACR70
- Disease Activity Score (DAS) 28
- Health Assessment Questionnaire–Disability Index (HAQ-DI)
- Short-Form (36) Health Survey (SF-36).

Findings

ACR criteria, DAS28, HAQ-DI, and SF-36 are briefly summarized in Table 16.

TABLE 16: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
ACR20 ACR50 ACR70	ACR20, ACR50, and ACR70 responses represent at least a 20%, 50%, and 70% improvement, respectively, in tender and swollen joint counts and in three of the five additional criteria: • Patient global assessment of disease activity • Physician global assessment of disease activity • Patient assessment of pain • Health assessment questionnaire • CRP or ESR.	Yes	Unspecified	van Riel and van Gestel (2000)[44] Cohen et al. (2006)[36] Bansback et al. (2008)[45] ACR criteria (2007)[46] Chung et al. (2006)[47]
DAS28	DAS28 is an abbreviated version of the DAS, based on a 28-joint count that omits the feet and ankle joints.	Yes	Unspecified	Wells et al. (2009)[32] Crowson et al. (2009)[48]
HAQ-DI	HAQ-DI is the disability assessment component of the HAQ.	Yes	0.22	Bruce and Fries (2003)[34,35]
SF-36	The SF-36 consists of eight sub-domains. The SF-36 provides two component summaries, PCS and MCS. The eight sub-domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status.	Yes	2.5 to 5.0	Gallagher et al. (2001)[38] Hays and Morales (2001)[39] Samsa et al. (1999)[40] Strand and Singh (2008)[41]

ACR = American College of Rheumatology; CRP = C-reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; MCID = minimal clinically important difference; MCS = mental component summary; PCS = physical component summary; SF-36 = Short-Form (36) Health Survey.

American College of Rheumatology Response Criteria

The ACR criteria for assessing joint status were initially developed for patients with RA.[44] ACR criteria provide a composite measure of improvement in both swollen and tender joint counts and at least three of five additional disease criteria:

- patient global assessment of disease activity
- physician global assessment of disease activity
- patient assessment of pain
- HAQ
- either C-reactive protein (CRP) level or erythrocyte sedimentation rate (ESR).

The ACR joint count for RA assesses 68 joints for tenderness and 66 joints for swelling. Patient and physician assessments are conducted using visual analogue scale (VAS) or Likert scale measurements. ACR 20, 50, or 70 responses represent at least a 20%, 50%, or 70% improvement, respectively, in tender and swollen joint counts as well as in three of the five additional core measures listed above. This core set of measures included in the ACR response criteria was established through a consensus process of clinical experts. Individual criteria were selected based on their construct, face, content, criterion, and discriminant validity.[49] In the assessment of criterion validity, standards for comparison included death, physical disability, and radiologic evidence of joint damage. Physical functioning capacity as measured by the HAQ was considered a strong predictor of mortality, and many other risk factors for premature mortality were insignificant after adjusting for functional capacity. Predictors of radiographic progression included swollen joint counts and levels of acute-phase reactants such as ESR and CRP.[49] When considering the ability of an outcome measure to detect change, pain assessments, global assessments, tender joint counts, and HAQ scores all had strong discriminant validity.

The ACR20 is most commonly used as the primary end point in randomized controlled trials (RCTs) evaluating biologics used in RA. The US FDA considers ACR20 a well-validated composite end point for assessing the signs and symptoms of RA, as noted in guidance provided to industry on the conduct of trials in RA patients.[50] ACR50 and ACR70 are often reported in clinical trials and are considered more stringent outcome measures.

Chung et al.[47] conducted a meta-analysis of 21 RCTs of RA therapies published between 1997 and 2004 to compare the discriminant capabilities of the ACR50 and ACR20 responses and to determine whether ACR50 is as informative as ACR20 in distinguishing between active therapies and control groups. While both measures have the ability to distinguish an active therapy, the levels of improvement captured by ACR20 response do not generally represent an optimal clinical improvement. Furthermore, since the development of the ACR20 response criteria, much more aggressive therapies have been introduced in the treatment of RA and larger clinical responses can be expected. This meta-analysis concluded that ACR20 and ACR50 are similar in distinguishing between active and control therapies but that ACR50 represents a more robust clinical response and may be a preferred end point in clinical trials.[47]

ACR70 is considered even more rigorous than ACR50. It is a component of the definitions established by the FDA in order to satisfy labelling requirements for RA drugs. Specifically, a “major clinical response” as defined by the FDA refers to a statistically significant increase in the proportion of patients achieving an ACR70 response, maintained for six months, with active therapy compared with the control group.[50]

With widespread use of the ACR criteria during the past 20 years, limitations associated with them have been identified. For example, while ACR response indicates the change from baseline, it does not indicate the final level of disease severity that the patient attains. This limitation also means that

patients who are classified as ACR responders could have very different levels of disease.[45] Other criticisms of the ACR criteria are that most of its component measures are subjective, that dichotomous measures such as ACR lack sensitivity to change compared with continuous measures of response, and that the ACR20 response threshold is too low relative to treatment goals applied in clinical practice.[46] In response to these criticisms, attempts have been made to develop improved outcome measures for RA, although none have widespread acceptance or are consistently used in clinical trials.[46,51]

Disease Activity Score 28

The DAS is a measure of RA disease activity and includes the Ritchie Articular Index (0 to 78), which grades tenderness based on physical examination of 53 joints, a swollen joint count based on examination of 44 joints (0 to 44), ESR or CRP level, and a general health item using a VAS (0 to 100).[52] DAS28 is an abbreviated version of the DAS, based on a 28-joint count that omits the feet and ankle joints. Thus, one obvious criticism of this scale is that a patient who had inflammation only at the feet and ankles would be counted as in remission.[53] The DAS components correlate well with each other and with the ACR criteria.[54-57] The DAS28 is a composite score derived using the following formula:

$$DAS28 = 0.56 \times \sqrt{(t28)} + 0.28 \times \sqrt{(sw28)} + 0.70 \times \ln(ESR) + 0.014 \times GH$$

where DAS28 = Disease Activity Score 28, ESR = erythrocyte sedimentation rate, ln(ESR) = natural logarithm of ESR value, sw28 = swollen joint count of 28 joints, t28 = tender joint count of 28 joints, GH = general health measured by Patient's Global Assessment of Disease Activity on a VAS of 100 mm.

The formula was developed by comparing serial assessments of tender and swollen joint counts, ESR, and patient global assessment (global health or GH) for a panel of RA patients at times of poorly controlled and well-controlled RA.[58] A DAS28 score indicates an absolute level of disease activity, with a score of 5.1 or greater being considered high disease activity, while a DAS28 score lower than 3.2 indicates low disease activity state (LDAS), and a DAS28 score lower than 2.6 indicates remission.[31-33]

In recent years, CRP has been used in place of ESR to calculate the DAS28. The trend toward using CRP levels rather than ESR is mainly driven by greater availability, reduced cost, and increased sensitivity of CRP to short-term changes of in disease activity.[32,48] The formula used to calculate the DAS28-CRP is as follows:

$$DAS28\text{-}CRP = 0.56 \times \sqrt{(t28)} + 0.28 \times \sqrt{(sw28)} + 0.014 \times GH + 0.36 \times \ln(CRP+1) + 0.96$$

where CRP = C-reactive protein, DAS28 = Disease Activity Score 28, ln(CRP + 1) = natural logarithm of (CRP value +1), sw28 = swollen joint count of 28 joints, t28 = tender joint count of 28 joints, GH = general health measured by Patient's Global Assessment of Disease Activity on a VAS of 100 mm.

A DAS28 score indicates an absolute level of disease activity, with a score of 5.1 or greater being considered high disease activity, while a DAS28 score lower than 3.2 indicates LDAS, and a DAS28 score lower than 2.6 indicates clinical remission.[31-33] Overall, the DAS28-CRP correlates well with the original ESR-based DAS28 (DAS28-ESR), and both are validated measures for assessing disease activity in RA.[31,32,59-61] However, studies have shown that the DAS28-CRP score value is usually lower than the DAS28-ESR score.[31,59-62] The difference (DAS28-CRP minus DAS28-ESR) ranges from −0.2[59] to −0.8.[62] Because the definitions of remission (score lower than 2.6) are the same for both DAS28-CRP and DAS28-ESR, it was concluded that DAS28-CRP underestimates disease activity and overestimates the

improvement in disease activity and the remission rate compared with DAS28-ESR. It was also suggested that DAS28-CRP should be evaluated using different criteria from that for DAS28-ESR.[61] Furthermore, the European League Against Rheumatism (EULAR) recommended that the clinical implications of the DAS28 score (such as good response, moderate response, or no response) should be determined based on the baseline DAS28 scores (Table 17).[63] Finally, no MCID for change in DAS28 scores exists.

TABLE 17: THE EUROPEAN LEAGUE AGAINST RHEUMATISM IMPROVEMENT RESPONSE CRITERIA (DAS28)

Baseline DAS28 Score	DAS28 Improvement Over Time Points		
	> 1.2	0.6 to 1.2	< 0.6
< 3.2	Good response	Moderate response	No response
3.2 to 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

DAS = Disease Activity Score.
Source: Matsui et al. (2007).[61]

Health Assessment Questionnaire and Disability Index

The HAQ was originally developed in 1978 at Stanford University.[64] It was one of the first self-reported functional status (disability) measures and has become the dominant instrument in many disease areas, including arthritis.[65] The HAQ has been widely validated in patients with RA.[65] The full HAQ collects data on five generic patient-centred health dimensions: 1) to avoid disability, 2) to be free of pain and discomfort, 3) to avoid adverse treatment effects, 4) to keep dollar costs of treatment low, and 5) to postpone death.[34]

The HAQ Disability Index (HAQ-DI) is the disability assessment component of the HAQ. It assesses a patient's level of functional ability. There are 20 questions in eight categories to assess a patient's physical functional status: dressing, arising, eating, walking, hygiene, reach, grip, and common activities.[34,35] For each of these categories, patients report the amount of difficulty they have in performing specific activities, and their responses are made on a scale from 0 (no difficulty) to 3 (unable to do). The eight category scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled). Observational studies and RCTs have demonstrated that the HAQ-DI possesses face validity, content validity, construct validity, predictive validity and discriminant validity. There is evidence suggesting that baseline HAQ scores are predictive of radiographic damage, work disability and quality of life.[36,37] A number of investigators have suggested that the minimal clinically important difference (MCID) is 0.22; however, differences as small as 0.10 have been suggested as clinically important.[34]

Short-Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. The SF-36 consists of eight sub-domains: physical functioning, pain, vitality, social functioning, psychological functioning, general health perceptions, and role limitations due to physical and emotional problems.[38] The SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS). The eight sub-domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 and 5 points.[39-41]

Summary

The ACR criteria and DAS28 scores are commonly used and accepted measures of disease activity. The ACR 20, 50, and 70 indicate a percentage improvement from baseline (but not a final level of disease activity). ACR20 is most commonly reported in clinical trials; however, ACR50 or ACR70 are often cited as evidence of a more robust treatment effect. The use of ACR responses in clinical trials may result in participants who are classified as "responders" having different levels of disease activity that may not meet the current goals of therapy. DAS28 uses a 28 joint count that does not include the feet, which is a limitation of the scale. DAS28 measures an absolute rather than relative level of disease activity and thus may be preferred to the ACR responder rates. The DAS28 components correlate well with each other and with the ACR components. However, it has been reported that DAS28-CRP underestimates disease activity and overestimates the improvement in disease activity and the remission rate compared with DAS28-ESR. The MCID for a change in DAS28 scores has not been specified. The HAQ is a comprehensive measure of the patient's perception of functional status and has been widely validated in RA. The HAQ-DI is one of five components (the disability component) of the full HAQ. The HAQ-DI score ranges from 0 to 3, with higher scores indicating greater disability. A suggested MCID in patients with RA is 0.22; however, differences as small as 0.10 have also been suggested. The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life. The suggested MCID for either component summary of the SF-36 is typically from 2.5 to 5 points.[39-41]

APPENDIX 6: SUMMARY OF EXTENSION STUDIES

SUMMACTA (Study WA22762) LONG-TERM EXTENSION STUDY[25]

Objectives

To summarize the clinical efficacy and harms of weekly subcutaneous (SC) administration of tocilizumab (TCZ) 162 mg through 72 weeks in patients with rheumatoid arthritis (RA) reported during the open-label extension period of the pivotal study WA22762, also known as SUMMACTA.[25]

Findings

SUMMACTA included a 24-week phase 3 double-blind randomized controlled trial (RCT) of patients with active RA, designed to test the non-inferiority of TCZ-SC to TCZ-intravenous (TCZ-IV) in combination with disease-modifying antirheumatic drugs (DMARDs), followed by a 72 week open-label extension in which patients were re-randomized within their groups to either continue on the same treatment received for the first 24 weeks or to switch treatments. Re-randomization and a one-week dose interruption occurred at the end of the double-blind study period (week 24), and the first dose of the open-label treatment started at week 25. Blinding was maintained for investigators and patients until the results of the primary analysis from the double-blind period were reported.

A total of 1,135 patients, 572 (91%) from the original TCZ-SC group, and 563 (89%) from the original TCZ-IV group, continued into the open-label extension study. The TCZ-SC group was re-randomized in blocks of 12 at a ratio of 11:1 to SC or IV, respectively. The TCZ-IV group was re-randomized in blocks of six at a ratio of 2:1 to IV or SC, respectively. As in the 24-week double-blind study period, patients continued to receive at least one permitted non-biologic DMARD throughout the open-label period. At the clinical cut-off date of January 16, 2012, 550 of the 572 (96.2%) patients in the original TCZ-SC group and 539 of the 563 (95.7%) patients in the original TCZ-IV group who entered the open-label extension had completed treatment. The disposition of patients for the SUMMACTA open-label extension phase is summarized in Table 18.

TABLE 18: PATIENT DISPOSITION OF SUMMACTA OPEN-LABEL EXTENSION STUDY

	SUMMACTA LTE			
	TCZ-SC 162 mg q.w. → TCZ-SC (n = 524)	**TCZ-SC 162 mg q.w. → TCZ-IV (n = 48)**	**TCZ-IV 8 mg/kg q.4w. → TCZ-SC (n = 186)**	**TCZ-IV 8 mg/kg q.4w. → TCZ-IV (n = 377)**
Completed to Week 24	572		563	
Re-randomized ITT (%)	524 (100)	48 (100)	186 (100)	377 (100)
Re-randomized PP (%)	473 (90.3)	44 (91.7)	161 (86.6)	338 (89.7)
Safety population[a]	631	48	186	631
Completed to clinical cut-off (%)	503 (95.6)	47 (97.9)	179 (96.2)	360 (95.5)
Withdrew from study (%)	21 (4.0)	1 (2.1)	7 (3.8)	17 (4.5)
Adverse event (%)	10 (1.9)	0	2 (1.1)	7 (1.9)
Anaphylaxis or serious hypersensitivity (%)	1 (0.2)	0	0	1 (0.3)
Death (%)	1 (0.2)	0	0	0
Insufficient response (%)	4 (0.8)	0	1 (0.5)	3 (0.8)
Patient withdrawal (%)	3 (0.6)	0	1 (0.5)	4 (1.1)
Physician withdrawal (%)	1 (0.2)	0	0	1 (0.3)
Protocol violation (%)	0	0	1 (0.5)	0
Lost to follow-up (%)	0	1 (2.1)	1 (0.5)	0
Pregnancy (%)	0	0	1 (0.5)	0
Other (%)	1 (0.2)	0	0	1 (0.3)

ITT = intention-to-treat; IV = intravenous; LTE = long-term extension; PP = per-protocol; q.w. = every week; q.4w. = every four weeks; SC = subcutaneous; TCZ = tocilizumab.

[a] The safety population consisted of all 1,262 patients who were enrolled in the study. The SC and IV groups included all patients who received TCZ-SC and TCZ-IV, respectively, during the double-blind part of the study (631 per group); data are included up to the clinical cut-off for patients who were re-randomized at week 24 to continue receiving SC and IV therapy, respectively, in the open-label period but only up to the point of switch for patients who were re-randomized to switch therapy for the open-label period. TCZ-SC → TCZ-IV and TCZ-IV → TCZ-SC groups include all patients who were re-randomized to switch therapy; data are included from the point of switch (i.e., open-label data only).

Source: SUMMACTA long-term extension Clinical Study Report.[25]

The maximum duration of open-label exposure was 72 weeks. Duration of study treatment was variable by design and depended on re-randomization at week 24; duration of treatment for patients re-randomized at week 24 to continue on the same treatment included the double-blind and open-label phases, while duration of treatment for those re-randomized to switch treatment at week 24 included only the open-label phase. Details of treatment exposure are summarized in Table 19.

TABLE 19: DURATION OF SUMMACTA OPEN-LABEL EXTENSION STUDY TREATMENT (SAFETY POPULATION)

Duration of Open-Label Phase Treatment,[a] Years	SUMMACTA LTE			
	TCZ-SC 162 mg q.w. → TCZ-SC (n = 631)	TCZ-SC 162 mg q.w. → TCZ-IV (n = 48)	TCZ-IV 8 mg/kg q.4w. → TCZ-SC (n = 186)	TCZ-IV 8 mg/kg q.4w. → TCZ-IV (n = 631)
Mean (SD)	0.65 (0.26)	0.34 (0.22)	0.31 (0.21)	0.62 (0.27)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range (min–max)	[redacted]	[redacted]	[redacted]	[redacted]

IV = intravenous; LTE = long-term extension; PP = per-protocol; q.w. = every week; q.4w. = every four weeks; SC = subcutaneous; SD = standard deviation; TCZ = tocilizumab.

[a] If patients were re-randomized at week 24 to receive the same study treatment, then the duration of study treatment includes both the double-blind and the open-label extension study phases. For patients re-randomized to switch study treatments at week 24, the duration of study treatment refers only to treatment received during the open-label extension phase.

Source: SUMMACTA long-term extension Clinical Study Report.[25]

Efficacy

The per-protocol population was used for all efficacy analyses. Efficacy results were presented for weeks 24 (end of the double-blind study phase), 37, and 49, since results beyond the week 49 time point were limited. American College of Rheumatology (ACR) 20/50/70 response rates, change in the Health Assessment Questionnaire–Disability Index (HAQ-DI) scores, and mean Disease Activity Score (DAS) 28 scores were generally similar among all treatment groups at each time point and are presented in Table 20. Furthermore, the ACR response rates were similar to those observed during the double-blind period. Variability between groups was occasionally seen as the sample size in the groups decreased. This suggests that the efficacy of TCZ-SC was comparable to TCZ-IV and sustained from weeks 24 to 49 with respect to these outcome measures, and that the efficacy was unaffected by switching treatment at week 24.

TABLE 20: OVERVIEW OF SUMMACTA OPEN-LABEL EXTENSION PHASE EFFICACY RESULTS UP TO WEEK 49 (PER-PROTOCOL POPULATION)

Time Point	SUMMACTA LTE			
	TCZ-SC 162 mg q.w. → TCZ-SC (n = 473)	TCZ-SC 162 mg q.w. → TCZ-IV (n = 44)	TCZ-IV 8 mg/kg q.4w. → TCZ-SC (n = 161)	TCZ-IV 8 mg/kg q.4w. → TCZ-IV (n = 338)
ACR 20 response rate, n (%)				
Week 24	355/473 (75%)	29/44 (66%)	130/161 (81%)	263/338 (78%)
Week 37	203/274 (74%)	21/28 (75%)	71/97 (73%)	155/203 (76%)
Week 49	84/115 (73%)	8/12 (67%)	28/41 (68%)	63/92 (69%)
ACR 50 response rate, n (%)				
Week 24	238/473 (50%)	22/44 (50%)	85/161 (53%)	176/338 (52%)
Week 37	146/274 (53%)	14/28 (50%)	49/97 (51%)	96/203 (47%)
Week 49	59/115 (51%)	5/12 (42%)	14/41 (34%)	38/92 (41%)
ACR 70 response rate, n (%)				
Week 24	127/473 (27%)	7/44 (16%)	45/161 (28%)	105/338 (31%)
Week 37	80/274 (29%)	10/28 (36%)	26/97 (27%)	60/203 (30%)
Week 49	39/115 (34%)	4/12 (33%)	7/41 (17%)	27/92 (29%)
Decrease in HAQ-DI ≥ 0.22, n (%)				
Week 24	343/468 (73%)	30/43 (70%)	123/161 (76%)	249/337 (74%)
Week 37	209/267 (78%)	18/25 (72%)	63/92 (69%)	142/196 (72%)
Week 49	84/107 (79%)	5/9 (56%)	29/38 (76%)	62/88 (71%)
Decrease in HAQ-DI ≥ 0.30, n (%)				
Week 24	307/468 (66%)	26/43 (61%)	107/161 (67%)	229/337 (68%)
Week 37	176/267 (66%)	16/25 (64%)	56/92 (61%)	129/196 (66%)
Week 49	76/107 (71%)	5/9 (56%)	25/38 (66%)	58/88 (66%)
DAS-ESR remission (< 2.6), n (%)				
Week 24	180/467 (39%)	16/43 (37%)	61/160 (38%)	122/335 (36%)
Week 37	110/260 (42%)	13/26 (50%)	37/90 (41%)	77/193 (40%)
Week 49	47/105 (45%)	8/10 (80%)	18/37 (49%)	30/87 (35%)

DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire–Disability Index; IV = intravenous; LTE = long-term extension; q.w. = every week; q.4w. = every four weeks; SC = subcutaneous; TCZ = tocilizumab.
Source: SUMMACTA long-term extension Clinical Study Report.[25]

Harms

The safety population was used for the adverse event (AE) analyses, which included all patients who received at least one dose of study medication, regardless of re-randomization, and who had at least one post-dose safety assessment. For analysis purposes, patients were assigned to treatment groups according to the first dose they received at the beginning of the double-blind period, and safety data were collected for patients up until week 24 if they switched treatments or through the open-label phase for patients who continued on the same treatment. For those who switched treatment at week 24, safety data were collected under the new treatment group assignment for the duration of the open-label phase. Therefore, safety data were presented primarily as patient-year–adjusted rates to reduce the impact of varying patient numbers and treatment exposure durations. Summaries of AEs and notable harms are presented in Table 21 and Table 22.

Three deaths were reported throughout the study until the clinical cut-off date. One death was reported in the IV group during the double-blind period (due to sepsis), one in the intravenous group during the open-label period (due to idiopathic pulmonary fibrosis), and one in the SC group during the open-label period (due to shock); no deaths were reported for patients who switched treatment assignments at week 24. The rates of AEs and serious AEs (SAEs) were similar in the SC and IV groups. The rates of AEs and SAEs were higher in the IV-to-SC switch group and lower in the SC-to-IV switch group; however, the confidence intervals for the SAE rates were wide and overlapped with those of the groups that did not switch treatment. The most commonly reported types of AEs and SAEs were infections and infestations (SC, IV, and SC-to-IV switch groups) or injection-site reactions (IV-to-SC switch group). The high rate of injection-site reactions in the IV-to-SC switch group was attributed to four patients in this group who experienced injection-site reaction symptoms after most SC injections. These patients also experienced injection-site reactions while receiving SC placebo during the double-blind phase.

TABLE 21: SUMMARY OF ADVERSE EVENTS IN THE SUMMACTA OPEN-LABEL EXTENSION STUDY (SAFETY POPULATION)

	SUMMACTA LTE			
	TCZ-SC 162 mg q.w. (n = 631)	**TCZ-SC 162 mg q.w. → TCZ-IV (n = 48)**	**TCZ-IV 8 mg/kg q.4w. → TCZ-SC (n = 186)**	**TCZ-IV 8 mg/kg (n = 631)**
Total PY	454.2	13.0	58.4	401.0
AEs	2501	39	370	2137
AEs per 100 PY (95% CI)	550.6 (529.3 to 572.7)	300.5 (213.7 to 410.8)	633.9 (570.9 to 701.9)	532.9 (510.5 to 556.0)
SAEs	66	1	12	61
SAEs per 100 PY (95% CI)	14.5 (11.2 to 18.5)	7.7 (0.2 to 42.9)	20.6 (10.6 to 35.9)	15.2 (11.6 to 19.5)
WDAEs	58	0	3	68
WDAEs per 100 PY (95% CI)	12.8 (9.7 to 16.5)	0	5.1 (1.1 to 15.0)	17.0 (13.2 to 21.5)
Deaths	1	0	0	2
Deaths per 100 PY (95% CI)	0.2 (0.01 to 1.2)	0	0	0.5 (0.1 to 1.8)

AE = adverse event; CI = confidence interval; IV = intravenous; LTE = long-term extension; PY = patient-years; q.w. = every week; q.4w. = every four weeks; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab; WDAE = withdrawal due to adverse event.
Source: SUMMACTA long-term extension Clinical Study Report.[25]

TABLE 22: ADVERSE EVENTS OF SPECIAL INTEREST PER 100 PATIENT-YEARS IN THE SUMMACTA OPEN-LABEL EXTENSION STUDY (SAFETY POPULATION)

AESIs per 100 PY (95% CI)	SUMMACTA LTE			
	TCZ-SC 162 mg q.w. (n = 631)	TCZ-SC 162 mg q.w. → TCZ-IV (n = 48)	TCZ-IV 8 mg/kg q.4w. → TCZ-SC (n = 186)	TCZ-IV 8 mg/kg (n = 631)
Total PY	454.2	13.0	58.4	401.0
Infections and infestations	126.6 (116.5 to 137.4)	92.5 (47.8 to 161.5)	118.2 (92.0 to 149.6)	121.4 (110.9 to 132.7)
Infections and infestations (SAEs)	3.5 (2.0 to 5.7)	0	6.9 (1.9 to 17.6)	3.0 (1.6 to 5.2)
Malignancies	1.3 (0.5 to 2.9)	7.7 (0.2 to 42.9)	1.7 (0.04 to 9.6)	0.8 (0.2 to 2.2)
Malignancies (SAE)	0.9 (0.2 to 2.3)	7.7 (0.2 to 42.9)	1.7 (0.04 to 9.6)	0.3 (0.01 to 1.4)
Anaphylaxis events[a]	0	0	0	0
Hypersensitivity reactions	19.2 (15.3 to 23.6)	0	15.4 (7.1 to 29.3)	31.2 (26.0 to 37.1)
Hypersensitivity reactions (SAEs)	0.9 (0.2 to 2.3)	0	0	0.8 (0.2 to 2.2)
Injection-site reactions	51.3 (44.9 to 58.3)	0	248.4 (209.6 to 292.3)	22.7 (18.3 to 27.9)
Hepatic events (SAEs)	0	0	0	NR[b]
Stroke (SAEs)	0.7 (0.1 to 1.9)	0	0	1.00 (0.3 to 2.6)
Myocardial infarction (SAEs)	0.2 (0.01 to 1.2)[b]	0	0	0
Gastrointestinal perforations (SAEs)	0	0	0	0
Bleeding events (SAEs)	0.9 (0.2 to 2.3)	0	0	1.0 (0.3 to 2.6)
Demyelinating disorders (SAEs)	0	0	0	0

AE = adverse event; AESIs = adverse events of special interest; CI = confidence interval; IV = intravenous; LTE = long-term extension; NR = not reported; PY = patient-years; q.w. = every week; q.4w. = every four weeks; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab.

[a] Two anaphylaxis AEs occurred in the IV group during the open-label period more than 24 hours after an infusion and therefore were not recorded in this category.

[b] One event occurred during the double-blind study period, previously reported in main SUMMACTA Clinical Study Report.[22]

Source: SUMMACTA long-term extension Clinical Study Report.[25]

Conclusion

Results from the open-label extension phase of SUMMACTA[25] suggest that TCZ-SC and TCZ-IV demonstrated similar efficacy, as measured by ACR response as well as change in HAQ-DI and DAS28 scores, which was maintained through week 49. These response rates did not change significantly with a switch in treatment for the open-label phase. Increased AE and SAE rates were observed in the IV-to-SC switch group compared with the group that remained on IV; however, the difference in SAE rates between groups was not statistically significant and may have been a reflection of the smaller size of the treatment-switch groups.

BREVACTA (Study NA25220) LONG-TERM EXTENSION STUDY[26]

Objectives

To summarize the clinical efficacy and harms of SC administration of tocilizumab 162 mg every two weeks through 72 weeks in patients with rheumatoid arthritis (RA) reported during the open-label extension period of the pivotal study NA25220, also known as BREVACTA.[26]

Findings

BREVACTA began with a 24-week phase 3 double-blind, placebo-controlled RCT of TCZ-SC delivered by pre-filled syringe (PFS) in patients with active RA and inadequate response to one or more DMARDs. This was followed by a 72-week open-label extension phase in which remaining patients who had not received escape therapy were re-randomized 1:1 within their initial groups to receive TCZ-SC 162 mg once every two weeks, delivered by PFS or an autoinjector (AI). Patients who had received escape therapy before week 24 continued on TCZ-PFS until week 96.

A total of 453 patients, 334 (76.4%) from the original TCZ group and 119 (54.3%) from the original placebo group, were re-randomized for the open-label extension. As in the 24-week double-blind study period, patients continued to receive at least one permitted non-biologic DMARD throughout the open-label period. At the clinical cut-off date of May 28, 2012, 11 patients had withdrawn from the study and seven patients had initiated escape therapy during the open-label study period. The disposition of patients for the BREVACTA open-label extension phase is summarized in Table 23.

TABLE 23: PATIENT DISPOSITION FOR THE BREVACTA LONG-TERM EXTENSION STUDY

	BREVACTA LTE			
	TCZ-PFS 162 mg q.2w. → TCZ-PFS (n = 167)	**Placebo SC q.2w. → TCZ-PFS (n = 60)**	**TCZ-PFS 162 mg q.2w. → TCZ-AI (n = 167)**	**Placebo SC q.2w.→ TCZ-AI (n = 59)**
Re-randomized ITT set[a] (%)[b]	167 (38.2)	60 (27.4)	167 (38.2)	59 (27.0)
Safety population	437[c]	61[d]	168[e]	59
Completed to clinical cut-off (%)	164 (98.2)	58 (96.7)	161 (96.4)	59 (100)
Withdrew from study (%)	3 (1.8)	2 (3.3)	6 (3.6)	0
AE (%)	1 (0.6)	1 (1.7)	3 (1.8)	0
Death (%)	0	0	1 (0.6)	0
Patient withdrawal (%)	0	1 (1.7)	2 (1.2)	0
Protocol violation (%)	2 (1.2)	0	0	0

AE = adverse event; AI = autoinjector; ITT = intention-to-treat; LTE = long-term extension; PFS = pre-filled syringe; q.2w. = every two weeks; SC = subcutaneous; TCZ = tocilizumab.
[a] Includes all patients who completed week 24, were re-randomized at week 24, and received at least one dose of re-randomized study treatment.
[b] Percentage of original cohort.
[c] Includes all patients who were treated with TCZ 162 mg SC by PFS for their first dose, including during the 24-week double-blind period.
[d] One patient received placebo and then received TCZ-PFS but had no re-randomization date.
[e] One patient received TCZ-PFS and then received AI but had no re-randomization date.
Source: BREVACTA long-term extension Clinical Study Report.[26]

Duration of study treatment was variable, depending on group assignment for the double-blind phase, as the duration of study treatment calculations include exposure from baseline of the 24-week double-blind phase until clinical cut-off of the open-label extension phase. Details of treatment exposure are summarized in Table 24.

TABLE 24: DURATION OF BREVACTA OPEN-LABEL EXTENSION STUDY TREATMENT

Extent of exposure, years	BREVACTA LTE			
	TCZ-PFS 162 mg q.2w. → TCZ-PFS (n = 167)	**Placebo SC q.2w. → TCZ-PFS (n = 60)**	**TCZ-PFS 162 mg q.2w. → TCZ-AI (n = 167)**	**Placebo SC q.2w. → TCZ-AI (n = 59)**
Mean (SD)	0.68 (0.14)	0.25 (0.15)	0.68 (0.15)	0.26 (0.14)
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range (min–max)	[redacted]	[redacted]	[redacted]	[redacted]

AI = autoinjector; LTE = long-term extension; PFS = pre-filled syringe; q.2w. = every two weeks; SC = subcutaneous; SD = standard deviation; TCZ = tocilizumab.
Source: BREVACTA long-term extension Clinical Study Report.[26]

Efficacy

The intention-to-treat population was used for all efficacy analyses. Efficacy results for a limited number of patients were available until week 60; however, summary data for the majority of patients were presented for weeks 24, 32, and 36, and are presented in Table 25. ACR20/50/70 and DAS28 response rates were generally similar between TCZ-PFS and TCZ-AI groups at each time point, and responses were maintained beyond 24 weeks. Patients re-randomized from placebo to TCZ demonstrated an increase in ACR20/50/70 and DAS28 response rates, which began to approach the ACR response rates in TCZ groups by week 32, although these values remained lower in the placebo-to-TCZ-AI group than in all other groups. Variability between groups was occasionally seen as the sample size in the groups decreased. The proportion of patients with reductions in HAQ-DI scores greater than 0.3 were greatest in the TCZ-PFS alone group at each time point, compared with all other groups. These results suggest that the efficacy of TCZ observed during the double-blind phase was maintained throughout the open-label extension study, and that patients who switched from placebo to TCZ demonstrated disease improvement.

TABLE 25: OVERVIEW OF BREVACTA OPEN-LABEL EXTENSION PHASE EFFICACY RESULTS UP TO WEEK 49 (INTENTION-TO-TREAT POPULATION)

Time Point	BREVACTA LTE			
	TCZ-PFS 162 mg q.2w. → TCZ-PFS (n = 167)	Placebo SC q.2w. → TCZ-PFS (n = 60)	TCZ-PFS 162 mg q.2w. → TCZ-AI (n = 167)	Placebo SC q.2w.→ TCZ-AI (n = 59)
ACR 20 response rate, n (%)				
Week 24	132/167 (79.0)	38/60 (63.3)	129/167 (77.2)	29/59 (49.2)
Week 32	84/114 (73.7)	30/42 (71.4)	83/114 (72.8)	27/42 (64.3)
Week 36	60/74 (81.1)	20/28 (71.4)	52/77 (67.5)	22/28 (78.6)
ACR 50 response rate, n (%)				
Week 24	90/167 (53.9)	14/60 (23.3)	82/167 (49.1)	12/59 (20.3)
Week 32	64/114 (56.1)	20/42 (47.6)	57/114 (50.0)	16/42 (38.1)
Week 36	38/74 (51.4)	16/28 (57.1)	37/77 (48.1)	11/28 (39.3)
ACR 70 response rate, n (%)				
Week 24	43/167 (25.7)	5/60 (8.3)	41/167 (24.6)	6/59 (10.2)
Week 32	35/114 (30.7)	12/42 (28.6)	33/114 (28.9)	9/42 (21.4)
Week 36	29/74 (39.2)	8/28 (28.6)	22/77 (28.6)	5/28 (17.9)
DAS LDAS (< 3.2), n (%)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
% DAS responders (good EULAR response), n (%)				
Week 24	[redacted]	[redacted]	[redacted]	[redacted]
Week 32	[redacted]	[redacted]	[redacted]	[redacted]
Week 36	[redacted]	[redacted]	[redacted]	[redacted]
Decrease in HAQ-DI ≥ 0.30, n (%)				
Week 24	105/166 (63.3)	[redacted]	90/167 (53.9)	[redacted]
Week 32	73/107 (68.2)	[redacted]	59/108 (54.6)	[redacted]
Week 36	48/69 (69.6)	[redacted]	38/72 (52.8)	[redacted]

ACR = American College of Rheumatology; AI = autoinjector; DAS = Disease Activity Score; HAQ-DI = Health Assessment Questionnaire–Disability Index; LDAS = low disease activity state; LTE = long-term extension; PFS = pre-filled syringe; q.2w. = every two weeks; SC = subcutaneous; TCZ = tocilizumab.
Source: BREVACTA long-term extension Clinical Study Report.[26]

Harms

The safety population (included all patients who received at least one dose of study drug and had at least one post-dose safety assessment) was used for the AE analyses. Total patient-years of drug exposure were calculated for the safety population to determine AE rates per 100 patient-years in each group. The TCZ-PFS group included patients exposed to TCZ-PFS in the double-blind period and during the open-label extension period, including those who were on placebo and re-randomized to TCZ-PFS at week 24. AE data presented for the three other groups (TCZ-PFS to AI, placebo to TCZ-PFS, placebo to TCZ-AI) only include events occurring during the open-label extension phase. Summaries of AEs and notable harms are presented in Table 26 and Table 27.

Four deaths were reported throughout the study until the clinical cut-off date. Three deaths were reported in the TCZ-PFS group during the double-blind period (due to sepsis) and one in the TCZ-PFS-to-AI group during the open-label period (due to angina pectoris). The rates of AEs were similar among the TCZ-PFS and both placebo-to-TCZ groups, yet somewhat higher in the TCZ-PFS-to-AI group. Likewise, the rate of SAEs was higher in the TCZ-PFS-to-AI group than in the TCZ-PFS group. This was attributed to a slightly higher rate of AEs across body systems in the TCZ-PFS-to-AI switch group rather than one particular AE, and conclusions are limited by the lower overall patient-year exposure in the TCZ-PFS-to-AI switch group compared with the TCZ-PFS group. No SAEs were reported in either of the placebo-to-TCZ groups. The safety profile of escape therapy (TCZ-SC every week) was similar to that of TCZ-SC delivered every two weeks, with the exception of an increased rate of injection-site reactions for escape therapy. However, this was expected because of the increased frequency of injections with the escape therapy dosing regimen, and none of these events were categorized as SAEs or led to withdrawal from the study. TCZ-SC was generally well tolerated by patients, and its safety profile was consistent with results from the double-blind study period.

TABLE 26: SUMMARY OF ADVERSE EVENTS IN THE BREVACTA OPEN-LABEL EXTENSION STUDY (SAFETY POPULATION)

	Open-Label Extension Study Groups				Escape Therapy[a]	
	TCZ-PFS 162 mg q.2w. (n = 437)[b]	**Placebo SC q.2w. → TCZ-PFS (n = 60)**	**TCZ-PFS 162 mg q.2w. → TCZ-AI (n = 167)**	**Placebo SC q.2w. → TCZ-AI (n = 59)**	**TCZ-PFS 162 mg q.2w. → TCZ-PFS 162 mg q.w. (n = 72)**	**Placebo SC q.2w. → TCZ-PFS 162 mg q.w. (n = 90)**
Total PY	222.1	13.8	37.2	13.8	33.3	39.4
AEs	947	56	201	51	[redacted]	[redacted]
AEs per 100 PY (95% CI)	426.4 (399.7 to 454.4)	405.3 (306.1 to 526.3)	540.3 (468.2 to 620.4)	370.9 (276.1 to 487.6)	[redacted]	[redacted]
SAEs	29	0	6	0	7	5
SAEs per 100 PY (95% CI)	13.1 (8.7 to 18.8)	0	16.1 (5.9 to 35.1)	0	21.0 (8.5 to 43.4)	12.7 (4.1 to 29.6)
WDAEs	10	1	3	0	[redacted]	[redacted]
WDAEs per 100 PY (95% CI)	4.5 (2.2 to 8.3)	7.2 (0.2 to 40.3)	8.1 (1.7 to 23.6)	0	[redacted]	[redacted]
Deaths	3	0	1	0	[redacted]	[redacted]
Deaths per 100 PY (95% CI)	1.4 (0.3 to 4.0)	0	2.7 (0.1 to 15.0)	0	[redacted]	[redacted]

AE = adverse event; AI = autoinjector; CI = confidence interval; PFS = pre-filled syringe; PY = patient-years; q.w. = every week; q.2w. = every two weeks; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab; WDAE = withdrawal due to adverse event.

[a] Includes data from the start of escape therapy during the double-blind period until the clinical cut-off. Due to low numbers of patients starting escape therapy after week 24 (n = 7), these AE data were not presented in the Clinical Study Report.

[b] The TCZ-PFS only group included all patients who were treated with TCZ 162 mg SC by PFS for their first dose, including during the 24-week double-blind period, up to the date of the data cut-off for patients re-randomized to TCZ-PFS.

Source: BREVACTA long-term extension Clinical Study Report.[26]

TABLE 27: ADVERSE EVENTS OF SPECIAL INTEREST PER 100 PATIENT-YEARS (95% CI) IN THE BREVACTA OPEN-LABEL EXTENSION STUDY (SAFETY POPULATION)

AESIs per 100 PY (95% CI)	Open-Label Extension Study Groups				Escape Therapy[a]	
	TCZ-PFS 162 mg q.2w. (n = 437)[b]	Placebo SC q.2w. → TCZ-PFS (n = 60)	TCZ-PFS 162 mg q.2w. → TCZ-AI (n = 167)	Placebo SC q.2w. → TCZ-AI (n = 59)	TCZ-PFS 162 mg q.2w. → TCZ-PFS 162 mg q.w. (n = 72)	Placebo SC q.2w. → TCZ-PFS 162 mg q.w. (n = 90)
Total PY	222.1	13.8	37.2	13.8	33.3	39.4
Infections and infestations	98.2 (85.6 to 112.1)	144.7 (88.4 to 223.5)	142.5 (106.7 to 186.4)	43.6 (16.0 to 95.0)	108.2 (75.8 to 149.8)	114.2 (83.3 to 152.8)
Infections and infestations (SAEs)	5.4 (2.8 to 9.4)	0	2.7 (0.1 to 15.0)	0	9.0 (1.9 to 26.4)	7.6 (1.6 to 22.3)
Malignancies	1.4 (0.3 to 4.0)	0	0	14.5 (1.8 to 52.5)	0	2.5 (0.1 to 14.1)
Malignancies (SAEs)	0.9 (0.1 to 3.3)	0	0	0	NR	NR
Anaphylaxis events	0	0	0	0	0	0
Hypersensitivity reactions	12.2 (8.0 to 17.7)	14.5 (1.8 to 52.3)	8.1 (1.7 to 23.6)	7.3 (0.2 to 40.5)	12.0 (3.3 to 30.8)	15.2 (5.6 to 33.1)
Hypersensitivity reactions (SAEs)	0	0	0	0	0	0
Injection-site reactions	29.3 (22.6 to 37.3)	7.2 (0.2 to 40.3)	40.3 (22.6 to 66.5)	7.3 (0.2 to 40.5)	45.1 (25.2 to 74.4)	17.8 (7.1 to 36.6)
Hepatic events (SAEs)	0	0	0	0	NR	NR
Stroke (SAEs)	0.5 (0.01 to 2.5)	0	0	0	0	0
Myocardial infarction (SAEs)	0.5 (0.01 to 2.5)	0	0	0	0	2.5 (0.1 to 14.1)
Gastrointestinal perforations (SAEs)	0	0	0	0	0	0
Bleeding events (SAEs)	0.5 (0.01 to 2.5)	0	0	0	0	0
Demyelinating disorders (SAEs)	0	0	0	0	NR	NR

AESIs = adverse events of special interest; AI = autoinjector; CI = confidence interval; NR = not reported; PFS = pre-filled syringe; PY = patient-years; q.2w. = every two weeks; SAE = serious adverse event; SC = subcutaneous; TCZ = tocilizumab.

[a] Includes data from the start of escape therapy during the double-blind period until the clinical cut-off. Due to low numbers of patients starting escape therapy after week 24 (n = 7), these AE data were not presented in the Clinical Study Report. Normal dosing of TCZ was every two weeks; escape therapy was delivered every week.

[b] The TCZ-PFS only group included all patients who were treated with TCZ 162 mg SC by PFS for their first dose, including during the 24-week double-blind period, up to the date of the data cut-off for patients re-randomized to TCZ-PFS.

Source: BREVACTA long-term extension Clinical Study Report.[26]

Conclusion

Results from the open-label extension phase of BREVACTA[26] suggest that the efficacy of TCZ-SC demonstrated during the double-blind study period was extended through week 36, and that this was not notably affected by method of delivery (PFS versus AI). The safety profile of TCZ during the extension study was also consistent with the results from the double-blind period. No new clinically meaningful safety signals were identified during the open-label extension phase, other than an increased rate of injection-site reactions in patients who received escape therapy, which had a higher dosing frequency.

APPENDIX 7: SUMMARY AND APPRAISAL OF NETWORK META-ANALYSES

Issues considered in this section were provided as supporting information. The information has not been systematically reviewed.

Objective

To conduct a systematic search of the literature for indirect comparisons for rheumatoid arthritis (RA) treatments published since 2009, and to summarize and critically appraise the methods and results of the included studies. Network meta-analysis (NMA) studies were included if they reported efficacy outcomes of interest (American College of Rheumatology [ACR] 20/50/70) or safety outcomes comparing tocilizumab with other biologic disease-modifying antirheumatic drugs (bDMARDs) for RA patients. A summary of the included NMAs is presented in Table 28.

Turkstra et al. 2011[5]

A systematic review was carried out by the investigators of the NMA to identify all randomized controlled trials (RCTs) investigating short-term efficacy of nine bDMARDs for the treatment of established moderate to severe RA. The following bDMARDs were included: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Two independent reviewers assessed the data to establish whether relevant outcomes were sufficiently and appropriately reported. The following inclusion criteria were used: double-blind RCTs presenting data on ACR20/50/70 at approximately 24 weeks; active established RA (six or more swollen joints, mean/median disease duration of three years or greater); and comparison of the listed bDMARDs with control treatments such as placebo or a DMARD. Studies were excluded if they were set in non-Western countries, used an open-label design, had a duration of less than 24 weeks, or if the recommended dose was not used. A total of 27 relevant RCTS (n = 11,049) were included in the analyses. The total number of RCTs retrieved by treatment can be found in Table 29. Bayesian meta-analytical techniques were employed for the NMA using the WinBUGS software with a random-effects model. Treatment effect estimates were provided for each bDMARD against placebo as well as each bDMARD compared with each other. Study level covariates such as C-reactive protein, duration of disease, baseline Health Assessment Questionnaire score, swollen joint count and tender joint count were assessed. Only covariates that were statistically significant were retained in the models. Results were presented with summary statistics for odds ratios (ORs).

TABLE 28: SUMMARY OF NETWORK META-ANALYSES FOR RHEUMATOID ARTHRITIS TREATMENTS PUBLISHED SINCE 2009

Study	Population	Intervention/ Comparators	Outcomes	Conclusions	Strengths	Limitations
Turkstra et al. 2011[5]	Patients with established moderate to severe RA (n = 11,049) from 27 RCTs	TCZ versus abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab	• ACR20 • ACR50 • ACR70 at 24 weeks	• Certolizumab was statistically superior to TCZ for the ACR20 and ACR50 outcomes at 24 weeks. • Anakinra was statistically inferior to TCZ for the ACR50 outcomes at 24 weeks. • Remaining comparisons with TCZ did not reach statistical significance.	• Appropriate methods were used for the MTC analyses. • All included studies were double-blind RCTs. • Results were generalizable to the Canadian population.	• Heterogeneity in study designs. • Only ACR outcomes at 24 weeks were included. • High dropout rate in the placebo groups of the certolizumab studies, which may have affected the relative efficacy. • Only short-term efficacy is assessed. • Safety outcomes were not assessed. • Methodological quality of the included studies was not described.
Bergman et al. 2010[6]	Patients with RA who have inadequate response to DMARDs (n = 10,419) from 18 RCTs	TCZ versus abatacept, rituximab, etanercept, infliximab, and adalimumab	• ACR20 • ACR50 • ACR70 at 24 to 30 weeks	• There were no differences between TCZ and other bDMARDs for ACR20 and ACR50 responses, with no results reaching statistical significance. • TCZ was statistically greater than TNF alpha inhibitors and abatacept for ACR70. • Remaining comparisons with TCZ did not reach statistical significance.	• Appropriate methods were used for the MTC analyses. • All included studies were double-blind RCTs. • Similar baseline characteristics across studies. • Similar placebo response rates between different DMARD studies. • Both fixed- and random-effects model results presented.	• Only short-term efficacy is assessed. • Safety outcomes were not assessed. • Specific exclusion criteria were not provided. • Methodological quality of the included studies was not described. • It is uncertain whether results are generalizable to the Canadian population.

Study	Population	Intervention/ Comparators	Outcomes	Conclusions	Strengths	Limitations
Desai et al. 2012[66]	Patients with RA meeting ACR criteria (n = 20,490 from 41 RCTs)[a]	TCZ versus abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab	• Overall withdrawals • Withdrawals resulting from lack of efficacy • WDAEs	• Certolizumab and etanercept had statistically significant reduced odds of overall withdrawal than TCZ. • TCZ had statistically significant reduced odds for withdrawals resulting from lack of efficacy compared with anakinra. • Rituximab and etanercept had statistically significant reduced odds of WDAE than TCZ. • Remaining comparisons with TCZ did not reach statistical significance.	• Appropriate methods were used for the MTC analyses. • Analyses included newer bDMARDs such as golimumab, certolizumab, and tocilizumab. • All included studies were double-blind RCTs. • Internal validity of the included studies was assessed.	• Most studies (N = 31) were of short duration (< 1 year). • It is uncertain whether results are generalizable to the Canadian population. • Efficacy was not assessed. • Heterogeneity in study designs, durations, and populations. •

ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; DMARD = disease-modifying antirheumatic drug; MTC = mixed-treatment comparison; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; TNF = tumour necrosis factor; WDAE = withdrawals due to adverse event.

TABLE 29: NUMBER OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN TURKSTRA ET AL. 2011[5] BY TREATMENT

Treatment	Included RCTs
Tocilizumab	4
Abatacept	2
Adalimumab	4
Anakinra	1
Certolizumab	3
Etanercept	4
Golimumab	3
Infliximab	2
Rituximab	3
Abatacept and infliximab	1

RCT = randomized controlled trial.

TABLE 30: RELATIVE EFFICACY OF BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS COMPARED WITH TOCILIZUMAB AT 24 WEEKS IN TURKSTRA ET AL. 2011[5]

bDMARD versus TCZ	ACR20	ACR50	ACR70
	OR (95% CrI)		
ABT	0.80 (0.42 to 1.70)	0.67 (0.35 to 1.43)	0.36 (0.15 to 1.09)
ADA	0.56 (0.31 to 1.16)	0.50 (0.27 to 1.04)	0.39 (0.16 to 1.23)
ANK	0.36 (0.16 to 1.05)	0.26 (0.11 to 0.80)[a]	0.18 (0.05 to 1.13)
CER	3.64 (1.75 to 8.45)[a]	3.08 (1.45 to 7.73)[a]	2.62 (0.96 to 13.19)
ETN	1.22 (0.67 to 2.59)	1.18 (0.63 to 2.68)	0.78 (0.35 to 2.86)
GOL	0.45 (0.17 to 1.76)	0.68 (0.24 to 3.26)	0.68 (0.17 to 8.30)
INF	0.60 (0.33 to 1.28)	0.59 (0.32 to 1.29)	0.42 (0.18 to 1.37)
RIT	0.77 (0.38 to 1.81)	0.42 (0.29 to 1.53)	0.42 (0.14 to 1.86)

ABT = abatacept; ACR = American College of Rheumatology; ADA = adalimumab; ANK = anakinra; bDMARD = biologic disease-modifying antirheumatic drug; CER = certolizumab; CrI = credible interval; ETN = etanercept; GOL = golimumab; INF = infliximab; OR = odds ratio; RIT = rituximab; TCZ = tocilizumab.
[a] Statistically significant.

The analyses were performed with the swollen joint count and disease duration as covariates, as both demonstrated statistical significance in the preliminary analyses. The between-treatment comparison revealed that certolizumab was statistically superior to tocilizumab for the ACR20 and ACR50 outcomes with ORs (95% credible interval [CrI]) of 3.64 (1.75 to 8.45) and 3.08 (1.45 to 7.73), respectively, at 24 weeks. Anakinra was statistically inferior to tocilizumab for the ACR50 outcomes, with an OR of 0.26 (0.11 to 0.80) at 24 weeks. The remaining comparisons did not reach statistical significance (Table 30). The investigators appeared to use appropriate methods for the mixed-treatment comparison (MTC) analyses. The analyses included a comprehensive list of bDMARDs, and all included studies were double-blind RCTs. The results are likely generalizable to the Canadian population, as studies consisting of non-Western populations were excluded. Results should be interpreted with caution, because there was heterogeneity in study designs with some studies; for example, the golimumab studies required a dose increase for patients with minimal response at 12 or 14 weeks. Furthermore, as noted by the investigators, the dropout rates in the placebo group of the certolizumab studies were high, which may have affected the relative efficacy. This NMA did not assess safety outcomes or long-term efficacy, as results were limited to 24 weeks. Lastly, although all included studies were double-blind and randomized, the methodological quality of the included studies is unclear, as the investigators did not perform an assessment.

Bergman et al. 2010[6]

A systematic review was carried out by the investigators of the NMA to identify all RCTs investigating short-term efficacy of tocilizumab, abatacept, rituximab, and TNF alpha inhibitors (etanercept, infliximab, and adalimumab) for patients with RA who have inadequate response to DMARDs. Two independent reviewers assessed the data to establish whether relevant outcomes were sufficiently and appropriately reported. The following inclusion criteria were used: double-blind RCTs presenting data on ACR20/50/70; treatment with tocilizumab, adalimumab, etanercept, infliximab, abatacept, or rituximab; patient population defined as DMARD inadequate responders or methotrexate inadequate responders; and study duration of at least 24 weeks. Specific exclusion criteria were not provided. A total of 18 relevant RCTS (n = 10,419) were included in the analyses. The total number of RCTs retrieved by treatment can be found in Table 31. Bayesian meta-analytical techniques were employed for the NMA using the WinBUGS software with both random- and fixed-effects model. The appropriateness of each model was determined by residual deviance calculations. Treatment effect estimates were provided for each bDMARD against placebo, as well as each bDMARD compared with each other. Results were presented with summary statistics for relative risk. The investigators rationalized grouping tumour necrosis factor (TNF) alpha inhibitors as a single category, assuming similar efficacy between agents based on findings from the scientific literature.

TABLE 31: NUMBER OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN BERGMAN ET AL. 2010[6] BY TREATMENT

Treatment	Included RCTs
Tocilizumab	3
Abatacept	2
Rituximab	2
TNF alpha inhibitors	11

RCT = randomized controlled trial; TNF = tumour necrosis factor.

TABLE 32: RELATIVE EFFICACY OF BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS COMPARED WITH TOCILIZUMAB AT 24 TO 36 WEEKS IN BERGMAN ET AL. 2010[6]

bDMARD versus TCZ	ACR20[a]	ACR50[a]	ACR70[b]
	RR (95% CrI)		
TNF alpha inhibitor	1.1 (0.8 to 1.3)	1.1 (0.7 to 1.6)	1.8 (1.2 to 2.6)[c]
ABT	1.1 (0.8 to 1.6)	1.1 (0.8 to 2.3)	2.0 (1.3 to 3.1)[c]
RIT	1.1 (0.8 to 1.7)	1.1 (0.7 to 2.5)	1.6 (0.7 to 3.3)

ABT = abatacept; ACR = American College of Rheumatology; bDMARD = biologic disease-modifying antirheumatic drug; CrI = credible interval; RR = relative risk; RIT = rituximab; TCZ = tocilizumab; TNF = tumour necrosis factor.
[a] Random-effects model used and considered more appropriate.
[b] Fixed-effects model used and considered more appropriate.
[c] Statistically significant.

The between-treatment comparison revealed no statistically significant differences between tocilizumab and the comparators for the ACR20 and ACR50 outcomes at 24 to 36 weeks using the random-effects model. With the fixed-effects model, ACR70 for tocilizumab was superior to TNF alpha inhibitors and abatacept with relative risks (95% CrI) of 1.8 (1.2 to 2.6) and 2.0 (1.3 to 3.1), respectively. Under the random-effects assumption (results not shown), tocilizumab compared with TNF alpha inhibitors and abatacept remained relevant, with the lower bound CrI being 1.0 for each. The remaining comparisons did not reach statistical significance (Table 32). The investigators appeared to use appropriate methods for the MTC analyses and included both fixed- and random-effects models. All included studies were double-blind

RCTs with similar baseline characteristics. The placebo response rates between different DMARD studies were similar. Results should be interpreted with caution, because the methodological quality of the included studies is unclear, as the investigators did not perform an assessment. There were differences in study design for two infliximab studies, which included a follow-up period of 30 weeks, while all other studies had a 24-week follow-up period. This NMA also did not assess safety outcomes or long-term efficacy, as results were limited to 24 to 30 weeks. It also remains unclear whether the results are generalizable to the Canadian population, since no details concerning the geographic location of the included studies were provided.

Desai et al. 2012[66]

A systematic review was carried out by the authors of the NMA to identify all RCTs investigating treatment discontinuation of nine bDMARDs for patients with RA meeting ACR criteria. The following bDMARDs were included: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Two independent reviewers assessed the data to establish whether relevant outcomes were sufficiently and appropriately reported. The methodological quality of included studies was assessed based on the UK National Health Service Centre for Reviews and Dissemination and on predefined criteria developed by the US Preventive Services Task Force (ratings: good, fair, and poor). The following inclusion criteria were used: double-blind RCTs presenting data on at least one of the discontinuation outcomes of interest (overall withdrawals, withdrawals resulting from lack of efficacy, or withdrawals resulting from adverse events [WDAEs]). The RCTs must have compared either a biologic with placebo, a biologic with biologic, or a biologic plus an oral DMARD with an oral DMARD. The minimum study duration was 12 weeks. Only US FDA–approved dosages were included to achieve better equivalency between drugs. Studies were excluded if they did not meet the eligibility criteria. A total of 40 relevant RCTS (n = 18,758) were included in the analyses for overall withdrawals, 33 RCTs (n = 13,808) were included for withdrawals due to lack of efficacy, and 41 RCTs (n = 20,490) were included for WDAEs. The total number of RCTs retrieved by outcome and treatment can be found in Table 33. Bayesian meta-analytical techniques were employed for the NMA using the WinBUGS software with a random-effects model. Treatment effect estimates were provided for each bDMARD against placebo as well as each bDMARD compared with each other. Results were presented with summary statistics for ORs. The random-effects logistic regression model was adjusted for correlations between groups within each study.

TABLE 33: NUMBER OF RANDOMIZED CONTROLLED TRIALS INCLUDED IN DESAI ET AL. 2012[66] BY TREATMENT AND OUTCOME

Treatment	Included RCTs		
	Reason for Withdrawal		
	Overall (N = 40)	Tolerability (WDAEs) (N = 41)	Lack of Efficacy (N = 33)
Tocilizumab	3	4	3
Abatacept	4	4	3
Adalimumab	7	8	5
Anakinra	4	5	3
Certolizumab	3	3	3
Etanercept	6	4	6
Golimumab	3	3	3
Infliximab	5	5	3
Rituximab	5	5	4

RCT = randomized controlled trial; WDAE = withdrawal due to adverse events.

TABLE 34: DISCONTINUATION OF BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS COMPARED WITH TOCILIZUMAB IN DESAI ET AL. 2012[66]

bDMARD versus TCZ	Reason for Withdrawal		
	Overall	Tolerability (WDAEs)	Lack of Efficacy
	OR (95% CrI)		
ABT	0.64 (0.29 to 1.73)	0.50 (0.27 to 1.00)	0.97 (0.42 to 3.05)
ADA	0.71 (0.33 to 1.82)	0.75 (0.43 to 1.49)	1.15 (0.53 to 3.27)
ANK	1.15 (0.5 to 3.43)	0.79 (0.45 to 1.66)	2.76 (1.14 to 9.62)[a]
CER	0.10 (0.04 to 0.31)[a]	1.27 (0.54 to 4.07)	0.44 (0.20 to 1.23)
ETN	0.33 (0.15 to 0.87)[a]	0.35 (0.19 to 0.72)[a]	0.81 (0.35 to 2.36)
GOL	0.62 (0.22 to 2.41)	0.54 (0.20 to 2.28)	0.84 (0.16 to 17.99)
INF	0.81 (0.37 to 2.21)	1.11 (0.60 to 2.24)	1.23 (0.53 to 3.80)
RIT	0.37 (0.17 to 1.03)	0.36 (0.17 to 0.92)[a]	0.95 (0.38 to 3.05)

ABT = abatacept; ACR = American College of Rheumatology; ADA = adalimumab; ANK = anakinra; bDMARD = biologic disease-modifying antirheumatic drug; CER = certolizumab; CrI = credible interval; ETN = etanercept; GOL = golimumab; INF = infliximab; OR = odds ratio; RIT = rituximab; TCZ = tocilizumab; WDAE = withdrawal due to adverse event.
[a] Statistically significant.

The between-treatment comparison revealed that certolizumab and etanercept had statistically significant reduced odds of overall withdrawal compared with tocilizumab, with an OR (95 CrI) of 0.10 (0.04 to 0.31) and 0.33 (0.15 to 0.87), respectively. Rituximab and etanercept had statistically significant reduced odds for WDAEs compared with tocilizumab, with an OR (95% CrI) of 0.36 (0.17 to 0.92) and 0.35 (0.19 to 0.72), respectively. Anakinra had statistically significant greater odds for withdrawals resulting from lack of efficacy compared with tocilizumab, with an OR (95% CrI) of 2.76 (1.14 to 9.62). The remaining comparisons did not reach statistical significance (Table 34). The investigators appeared to use appropriate methods for the MTC analyses. All included studies were double-blind RCTs, and only studies rated good or fair were retained for analysis. Results should be interpreted with caution, as there was heterogeneity in trial designs, durations, and populations. The durations of the included studies ranged from 12 to 104 weeks. The investigators also noted the challenges of pooling safety outcomes, as the included studies may have defined these outcomes differently. Most studies (N = 31) were of short duration (less than one year); thus, a sensitivity analysis was performed for short-duration (less than one year) and long-duration (more than year) studies. The results suggested trends in a similar direction to the original analyses, although some of the statically significant differences were no longer seen, given the smaller sample sizes and wider CrIs.

Conclusions

Based on the findings from two NMAs[5,6] that assessed efficacy, there were no differences between tocilizumab and most bDMARDs for ACR20/50/70 at 24 weeks, as most differences did not reach statistical significance. Tocilizumab was statistically inferior to certolizumab for ACR20 and ACR50, and statistically superior to anakinra for ACR50 at 24 weeks.[5] In a separate NMA,[6] tocilizumab was statistically superior to TNF alpha inhibitors and abatacept for the ACR70 outcome at 24 to 30 weeks. Based on the findings of another NMA, tocilizumab demonstrated a similar safety profile to most bDMARDs, as most comparisons did not reach statistical significance. Certolizumab and etanercept demonstrated statistically significant reduced odds of overall withdrawal, and rituximab and etanercept had statistically significant reduced odds of WDAEs when compared with tocilizumab. Tocilizumab had statistically significant reduced odds of withdrawals resulting from lack of efficacy when compared with anakinra.[66] All results should be interpreted with caution, given the numerous limitations, including heterogeneity in study designs, durations, and populations, as well the uncertainty of the methodological quality of the included studies in the efficacy analyses. There were no published indirect comparisons of subcutaneous tocilizumab versus other biologics in patients with RA.

REFERENCES

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, III, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum [Internet]. 2010 Sep [cited 2014 Oct 14];62(9):2569-81. Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.27584/pdf
2. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012 Aug;39(8):1559-82.
3. [Pr]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; 2014 Oct 7.
4. Canadian Expert Drug Advisory Committee (CEDAC). CEDAC Final Recommendation: Tocilizumab. (Actemra – Hoffmann-La Roche Limited) Indication: Rheumatoid Arthritis [Internet]. Ottawa: Canadian Agency for Drugs and Technology in Health; 2010 Nov 19. 1-7 p. [cited 2014 Oct 14]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Actemra-Nov-19-2010.pdf
5. Turkstra E, Ng SK, Scuffham PA. A mixed treatment comparison of the short-term efficacy of biologic disease modifying anti-rheumatic drugs in established rheumatoid arthritis. Curr Med Res Opin. 2011 Oct;27(10):1885-97.
6. Bergman GJ, Hochberg MC, Boers M, Wintfeld N, Kielhorn A, Jansen JP. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum. 2010 Jun;39(6):425-41.
7. The impact of arthritis in Canada: today and over the next 30 years [Internet]. Toronto: Arthritis Alliance of Canada; 2011. [cited 2014 Oct 14]. Available from: http://www.arthritisalliance.ca/en/initiativesen/impact-of-arthritis
8. Vliet Vlieland TP. Non-drug care for RA--is the era of evidence-based practice approaching? Rheumatology (Oxford) [Internet]. 2007 Sep [cited 2014 Oct 14];46(9):1397-404. Available from: http://rheumatology.oxfordjournals.org/content/46/9/1397.full.pdf+html
9. Cividino AA. Use of biologic monotherapy for rheumatoid arthritis. CRA e-newsletter [Internet]. 2012 [cited 2014 Oct 14];(8). Available from: http://rheum.ca/images/documents/Issue_08_Biologic_Monotherapy_EN.pdf
10. [Pr]Orencia® (abatacept) Intravenous Infusion, 250 mg / 15 mL vial Solution for Subcutaneous Injection, 125 mg/ mL [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2013 Oct 7.
11. [Pr]Rituxan® (rituximab) 10 mg/mL intravenous infusion [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2014 May 29.
12. [Pr]Kineret® (anakinra) Solution for Injection in a Prefilled Syringe 100 mg per syringe (150 mg/mL) Subcutaneous Injection [product monograph]. Stockholm (Sweden): Swedish Orphan BioVitrum AB SE-11276; 2013 May 28.
13. [Pr]Simponi® (golimumab) Solution for Injection 50 mg/0.5 mL 100 mg/1.0 ml [product monograph]. Toronto (ON): Janssen Inc.; 2013 Sep 19.
14. [Pr]Humira® (adalimumab) 40 mg in 0.8 mL sterile solution (50 mg/mL) subcutaneous injection [product monograph]. St-Laurent (QC): AbbVie Corporation; 2014 Jan 17.

15. [Pr]Simponi® I.V.(golimumab) Solution for Infusion 50 mg/4.0 mL [product monograph]. Toronto (ON): Janssen Inc.; 2014 May 15.

16. [Pr]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; 2013 Sep 13.

17. [Pr]Cimzia® (certolizumab pegol) Solution for Injection in a Single-use Pre-filled Glass Syringe, 200 mg/mL [product monograph]. Oakville (ON): UCB Canada Inc.; 2014 Jan 15.

18. [Pr]Remicade® (infliximab) Powder for Solution, Sterile, Lyophilized, 100 mg/vial [product monograph]. Toronto (ON): Janssen Inc.; 2014 Sep 26.

19. Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). Ann Rheum Dis [Internet]. 2014 Jan [cited 2014 Sep 25];73(1):69-74. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888614

20. Ogata A, Tanimura K, Sugimoto T, Inoue H, Urata Y, Matsubara T, et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014 Mar;66(3):344-54.

21. Kivitz A, Olech E, Borofsky M, Zazueta BM, Navarro-Sarabia F, Radominski SC, et al. Subcutaneous Tocilizumab vs Placebo in Combination With Disease Modifying Antirheumatic Drugs in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken) [Internet]. 2014 Jun 18 [cited 2014 Sep 25]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/acr.22384/pdf

22. Clinical study report WA22762: a randomized, double-blind, parallel group study of the safety and effect on clinical outcome of tocilizumab SC versus tocilizumab IV, in combination with traditional disease-modifying anti-rheumatic drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Hoffmann-La Roche Limited; 2012 Oct.

23. Clinical Study Report: MRA229JP. Double-blind, parallel-group, comparative phase III study of MRA-SC in patients with rheumatoid arthritis (clinical study report based on blind period results) [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Hoffmann-La Roche Limited; 2012 Feb 28.

24. Clinical study report NA25220: a randomized, double-blind, parallel-group study of safety and the effect on clinical outcome of tocilizumab (TCZ) subcutaneous (SC) versus placebo sc in combination with traditional disease modifying anti-rheumatic drugs (DMARDs) in patients with moderate to severe active rheumatoid arthritis. Primary analysis at week 24 [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Hoffmann-La Roche Limited; 2012 Dec.

25. Clinical study report WA22762: a randomized, double-blind, parallel group study of the safety and effect on clinical outcome of tocilizumab sc versus tocilizumab iv, in combination with traditional disease-modifying anti-rheumatic drugs (DMARDs), in patients with moderate to severe active rheumatoid arthritis. Report of exploratory long-term analyses based on a clinical cutoff date of 16 January 2012. [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Hoffmann-La Roche Limited; 2012 Oct.

26. Clinical Study Report – NA25220 – A randomized, double-blind, parallel-group study of safety and the effect on clinical outcome of tocilizumab SC versus placebo SC in combination with traditional disease modifying anti-rheumatic drugs (DMARDs) in patients with moderate to severe active

rheumatoid arthritis – Results of the long-term extension (LTE) – Report No. 1050275. [**CONFIDENTIAL** internal manufacturer's report]. Mississauga (ON): Hoffmann-La Roche Limited; 2012 Dec 12.

27. CDR submission: [Pr]Actemra® (tocilizumab) 20 mg/mL concentrate solution for infusion 162 mg/ 0.9 mL solution for injection. Company: Hoffmann-La Roche Limited [**CONFIDENTIAL** manufacturer's submission]. Mississauga (ON): Hoffmann-La Roche Limited; 2014 Feb 28.
28. Health Canada reviewer's report: Actemra (tocilizumab) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2014 Jun 5.
29. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Actemra (tocilizumab) solution for subcutaneous injection. Company: Genentech, Inc. Application no.: 125472 Approval date: 10/21/2013. Rockville (MD): FDA; 2013 Sep 16 [cited 2014 Sep 5]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125472Orig1s000MedR.pdf.
30. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Actemra (tocilizumab) solution for subcutaneous injection. Company: Genentech, Inc. Application no.: 125472. Approval date: 10/21/2013. Rockville (MD): FDA; 2013 Oct 21 [cited 2014 Sep 5]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125472Orig1s000StatR.pdf.
31. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of Disease Activity Score (DAS)28- erythrocyte sedimentation rate and DAS28- C-reactive protein threshold values. Ann Rheum Dis [Internet]. 2007 Mar [cited 2014 Oct 14];66(3):407-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856019/pdf/407.pdf
32. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun;68(6):954-60.
33. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, et al. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken). 2012 May;64(5):640-7.
34. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003;1:20.
35. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003 Jan;30(1):167-78.
36. Cohen JD, Dougados M, Goupille P, Cantagrel A, Meyer O, Sibilia J, et al. Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis. J Rheumatol. 2006 Oct;33(10):1936-41.
37. Linde L, Sorensen J, Ostergaard M, Horslev-Petersen K, Hetland ML. Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D RAQoL, and HAQ in patients with rheumatoid arthritis. J Rheumatol. 2008 Aug;35(8):1528-37.
38. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001 Dec;38(6):633-8.
39. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med. 2001 Jul;33(5):350-7.

40. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. PharmacoEconomics. 1999 Feb;15(2):141-55.

41. Strand V, Singh JA. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: evidence from randomized controlled trials. Am J Manag Care. 2008 Apr;14(4):239-53.

42. Karsh J, Keystone EC, Haraoui B, Thorne JC, Pope JE, Bykerk VP, et al. Canadian recommendations for clinical trials of pharmacologic interventions in rheumatoid arthritis: inclusion criteria and study design. J Rheumatol. 2011 Oct;38(10):2095-104.

43. Pincus T, Sokka T. Should contemporary rheumatoid arthritis clinical trials be more like standard patient care and vice versa? Ann Rheum Dis [Internet]. 2004 Nov [cited 2014 Oct 14];63 Suppl 2:ii32-ii39. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766773

44. van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis [Internet]. 2000 Nov [cited 2014 Oct 14];59 Suppl 1:i28-i31. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766622

45. Bansback N, Ara R, Karnon J, Anis A. Economic evaluations in rheumatoid arthritis: a critical review of measures used to define health states. PharmacoEconomics. 2008;26(5):395-408.

46. American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum. 2007 Mar 15;57(2):193-202.

47. Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Ann Rheum Dis. 2006;65(12):1602-7.

48. Crowson CS, Rahman MU, Matteson EL. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. J Rheumatol. 2009 Aug;36(8):1606-10.

49. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.

50. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Guidance for industry: clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA) [Internet]. Rockville (MD): Food and Drug Administration; 1999. [cited 2014 Oct 14]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071579.pdf

51. Felson DT, Furst DE, Boers M. Rationale and strategies for reevaluating the ACR20. J Rheumatol. 2007 May;34(5):1184-7.

52. Fransen J, Antoni C, Mease PJ, Uter W, Kavanaugh A, Kalden JR, et al. Performance of response criteria for assessing peripheral arthritis in patients with psoriatic arthritis: analysis of data from randomized, controlled trials of two TNF inhibitors. Ann Rheum Dis [Internet]. 2006 Apr 27 [cited 2014 Oct 14];65(10):1373-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798317/pdf/1373.pdf

53. Landewe R, van der Heijde D. The validity of a rheumatoid arthritis medical records-based index of severity compared with the DAS28. Arthritis Res Ther. 2006;8(3):107.

54. van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990 Nov;49(11):916-20.

55. van der Heijde DM, van 't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB. Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis. 1992 Feb;51(2):177-81.

56. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44-8.

57. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. J Rheumatol. 1999 Mar;26(3):705-11.

58. Ranganath VK, Khanna D, Paulus HE. ACR remission criteria and response criteria. Clin Exp Rheumatol. 2006 Nov;24(6 Suppl 43):S14-S21.

59. Siemons L, Vonkeman HE, Ten Klooster PM, van Riel PL, van de Laar MA. Interchangeability of 28-joint disease activity scores using the erythrocyte sedimentation rate or the C-reactive protein as inflammatory marker. Clin Rheumatol. 2014;33(6):783-9.

60. Fernandez-Montero JV, Barreiro P, Soriano V. HIV protease inhibitors: recent clinical trials and recommendations on use. Expert Opin Pharmacother. 2009;10(10):1615-29.

61. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis [Internet]. 2007 Sep [cited 2014 Oct 14];66(9):1221-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1955164/pdf/1221.pdf

62. Tamhane A, Redden DT, McGwin G, Jr., Brown EE, Westfall AO, Reynolds RJ, et al. Comparison of the disease activity score using erythrocyte sedimentation rate and C-reactive protein in African Americans with rheumatoid arthritis. J Rheumatol. 2013 Nov;40(11):1812-22.

63. Disease activity score in 28 joints (DAS28) [Internet]. Philadelphia: The Institute for Continuing Healthcare Education; 2009. [cited 2014 Oct 14]. Available from: http://www.iche.edu/newsletter/DAS28.pdf

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

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

66. Desai RJ, Hansen RA, Rao JK, Wilkins TM, Harden EA, Yuen A, et al. Mixed treatment comparison of the treatment discontinuations of biologic disease-modifying antirheumatic drugs in adults with rheumatoid arthritis. Ann Pharmacother. 2012 Nov;46(11):1491-505.