Common Drug Review
Clinical Review Report

July 2015

Drug	golimumab (Simponi) IV
Indication	To be used in combination with methotrexate (MTX) for the treatment of adult patients with moderately to severely active rheumatoid arthritis.
Listing request	Golimumab (Simponi IV), in combination with methotrexate (MTX), be listed for the treatment of adult patients with moderately to severely active rheumatoid arthritis following failure of MTX or other disease-modifying antirheumatic drugs (DMARDs).
Manufacturer	Janssen Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in rheumatoid arthritis 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.

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ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ANOVA	analysis of variance
BRM	biologic response modifier
CADTH	Canadian Agency for Drugs and Technology in Health
CCP	cyclic citrullinated peptide
CDR	CADTH Common Drug Review
CI	confidence interval
CMH	Cochran–Mantel–Haenszel (test)
CRA	Canadian Rheumatology Association
CRP	C-reactive protein
CSR	Clinical Study Report
DAS	Disease Activity Score
DIC	deviance information criterion
DMARD	disease-modifying antirheumatic drug
HAQ	Health Assessment Questionnaire
HAQ-DI	Disability Index of the Health Assessment Questionnaire
HRQoL	health-related quality of life
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
IVRS	interactive voice response system
ITT	intention-to-treat (population)
MCID	minimal clinically important difference
MCS	Mental Component Summary
NMA	network meta-analysis
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PCS	Physical Component Summary
RA	rheumatoid arthritis
RCT	randomized controlled trial
RF	rheumatoid factor
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form 36 Health Survey
SOC	system organ class

TB	tuberculosis
TNF	tumour necrosis factor
URTI	upper respiratory tract infection
VAS	visual analogue scale
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. Disease prevalence in Canada is about 1% (0.9% in 2010), and it is expected to increase to 1.3% by 2040.[1]

Treatment guidelines for RA emphasize the use of non-drug interventions, which include exercise therapy, electro-physical modalities, orthoses and assistive devices, and self-management interventions (including education), in addition to pharmacological therapy.[2,3] Non-pharmacological care affords symptomatic relief without altering the course of disease progression. The pharmacological therapy of RA aims to achieve remission and, if that is not possible, to minimize disease activity while controlling symptoms, halting joint damage, preventing disability, and improving quality of life.[2]

Traditional 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 the first-line DMARD treatment in patients with RA unless contraindicated or not tolerated.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids (in the lowest effective dose possible) can be added to the initial treatment with DMARD as a bridge therapy while waiting for DMARD to take effect, to manage flares, or for symptom control if no other options exist.

It is recommended that patients with an inadequate response to the target dose of at least two DMARDs in mono- or combination therapy after three months be considered for biologic therapies, including currently available subcutaneous (SC) golimumab that targets specific mechanisms of inflammation.[2] The objective of this report is to evaluate the beneficial and harmful effects of IV golimumab (Simponi IV) at recommended doses in combination with methotrexate for the treatment of adult patients with moderately to severely active RA.

Indication under review
Golimumab 2 mg/kg intravenous injection (Simponi IV), in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.
Listing criteria requested by sponsor
Golimumab (Simponi IV), in combination with methotrexate (MTX), be listed for the treatment of adult patients with moderately to severely active rheumatoid arthritis following failure of MTX or other disease-modifying antirheumatic drugs (DMARDs).

Results and Interpretation

Included Studies

The GO-FURTHER study, which was evaluated for this report, was a multi-centre, randomized, double-blind, placebo-controlled phase 3 study involving patients with moderately to severely active RA despite methotrexate therapy. After screening, 592 participants were randomized in a 2:1 ratio, stratified by baseline C-reactive protein (CRP) to receive either golimumab 2 mg/kg administered intravenously (IV) + methotrexate at Weeks 0 and 4, then every eight weeks thereafter, or placebo + methotrexate in a

similar pattern through Week 24. Placebo-treated patients were eligible to enter early escape at Week 16 if they achieved less than 10% improvement in both the tender and swollen joint counts. Upon early escape, they received golimumab infusions of 2 mg/kg at Weeks 16 and 20, then every eight weeks thereafter. Patients completing the 24-week, placebo-controlled phase could continue into the extension phase, which followed patients through to Week 112. In the extension phase, patients originally randomized to the placebo + methotrexate group could cross over to the golimumab + methotrexate group; patients originally randomized to the golimumab + methotrexate group or who crossed over from the placebo + methotrexate group to the golimumab + methotrexate group at Week 16 (i.e., early escape patients) could continue on golimumab during the extension phase.

Baseline demographic and clinical disease characteristics were generally well balanced across treatment groups. The median age of the patients was 52 years (ranging from 18 years to 83 years). The majority (81.6%) of participants was female, and Caucasians formed 80.4% of the total patient population. Overall, the median number of swollen and tender joints was 12 and 23, respectively, and the mean Disease Activity Score for 28 joints using the CRP value (DAS 28-CRP) was approximately 6.0. Baseline disease could be rated as moderate to severe RA based on all American College of Rheumatology (ACR) components, and were similar between the treatment groups.

Key limitations include the early escape design, in which patients in the placebo + methotrexate group had an option to cross over to the golimumab + methotrexate group at Week 16 (two weeks after the primary end point assessment) if they were not responding to placebo. Although the early escape design is widely used in studies of interventions for RA based on ethical considerations and is accepted by regulatory agencies, it may introduce bias in subsequent efficacy and safety assessments. The statistical analysis plan did not explicitly state that placebo patients who entered early escape were coded as non-responders for the Week 24 outcome assessments. ACR 20 and ACR 50 responses for the early escape population were not reported separately at Week 24. Therefore, the extent to which the early escape population influenced reported ACR 20 and ACR 50 outcomes at Week 24 is uncertain. As well, the median dose (15 mg per week) of background methotrexate at baseline was below the recommended optimal dose range of between 20 mg per week and 25 mg per week. This raises questions about whether patients had an adequate response to methotrexate therapy prior to initiating study treatments. It is not clear what might have been the effect of increased methotrexate doses in some of these patients. The study required patients to be seropositive for rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (anti-CCP) to qualify for entry, which limits the generalizability of the findings because a substantial number of RA patients with moderately to severely active disease are likely to be seronegative in clinical practice. Furthermore, there were no head-to-head comparisons between IV golimumab and other biologic response modifiers (BRMs) including SC golimumab. The manufacturer submitted an indirect comparison of IV golimumab versus IV infliximab, IV abatacept, and SC golimumab; the comparison had numerous limitations including no clear explanation for the exclusion from the primary analysis of SC formulations of other BRMs used in RA, although these were included in a sensitivity analysis. Hence, there is limited comparative evidence clearly defining the place in therapy for IV golimumab, including where it fits relative to the SC formulation.

Efficacy

Because of the early escape design, efficacy data collected before patients entered early escape (i.e., Week 14) were emphasized in the review.

The primary end point for efficacy was the ACR 20 response at Week 14. A statistically significantly greater proportion (58.5%) of patients in the golimumab + methotrexate group achieved an ACR 20

response compared with 24.9% of patients in the placebo + methotrexate group ([redacted] *P* < 0.001). Good or moderate DAS 28-CRP responses at Week 14 were also statistically significantly greater (81.3%) among patients in the golimumab + methotrexate group compared with patients in the placebo + methotrexate group (40.1%, *P* < 0.001). Furthermore, median Disability Index of the Health Assessment Questionnaire (HAQ-DI) scores demonstrated a clinically and statistically significantly greater improvement (0.5000, minimal clinically important difference [MCID] 0.25) in patients in the golimumab + methotrexate group compared with patients in the placebo + methotrexate group (0.1250, *P* < 0.001). This was maintained through Week 24. Neither ACR 20 nor ACR 50 responses for the early escape population was separately reported at Week 24.

The ACR 50 response at Week 24 showed statistically significantly greater improvements in patients who received golimumab + methotrexate compared with patients who received placebo + methotrexate [34.9% versus 13.2%, respectively; [redacted]; *P* < 0.001]. Through Week 24, golimumab + methotrexate treatment resulted in statistically and clinically significantly greater improvement in the Mental Component Summary (MCS) scores and Physical Component Summary (PCS) scores of the SF-36 (version 2) relative to placebo + methotrexate treatment. Change from baseline at Week 24 in PCS scores was 8.28 ± 8.32 in the golimumab + methotrexate group and 3.82 ± 7.30 in the placebo + methotrexate group. The respective changes in the MCS scores from baseline were 6.94 ± 10.28 and 1.21 ± 10.07; *P* < 0.001 in all comparisons. The MCID for either the PCS or MCS of the SF-36 typically ranges from 2.5 points to 5 points.[4-6]

Harms

Comparable proportions of patients reported adverse events (AEs) in the golimumab + methotrexate and the placebo + methotrexate groups through Week 16 and Week 24. Before early escape at Week 16, the proportion of patients who experienced at least one AE in the golimumab + methotrexate group was 47.3% compared with 43.7% in the placebo + methotrexate group. The proportion of patients who experienced at least one AE at Week 24 in the golimumab + methotrexate group was 57.2% compared with 49.2% in the placebo + methotrexate group, using intention-to-treat (ITT) analysis. Among patients who entered early escape at Week 16, the proportion of patients who experienced AEs at Week 24 was 27.9%. The most commonly reported system organ class (SOC) of AEs at Week 24 was infections and infestations (7.3% in the golimumab + methotrexate group compared with 7.6 % in the placebo + methotrexate group).

[redacted] The proportion of patients with one or more serious adverse events (SAEs) through Week 24 was 4.8% in the golimumab + methotrexate group compared with 2.0% in the placebo + methotrexate group. The most frequently occurring SOC of SAEs were musculoskeletal and connective tissue disorders, infections and infestations, renal and urinary disorders, and gastrointestinal (GI) disorders. Apart from GI disorders, which occurred in 1.0% of the placebo + methotrexate group, the proportion of patients with an SAE was less than 1% in both study groups.

Twenty-two patients (4%) in total discontinued the study before Week 24. AEs were the most common reason for discontinuation. A total of 11 patients discontinued due to AEs (nine [2.3%] patients in the golimumab + methotrexate group and two [1.0%] patients in the placebo + methotrexate group).

Pharmacoeconomic Summary

Simponi IV (IV golimumab) is a tumour necrosis factor-alpha (TNF-alpha) inhibitor that is indicated, in combination with methotrexate, for the treatment of adult patients with moderately to severely active RA. IV golimumab is available as 50 mg vials for intravenous infusion as 2 mg/kg at Weeks 0 and 4, then every eight weeks thereafter. The manufacturer has submitted a price of $826.86 per vial. A subcutaneous (SC) form of golimumab is currently reimbursed by several public plans for patients with RA.

The manufacturer submitted a cost-minimization analysis in which only the drug costs of IV golimumab were compared with SC golimumab, IV infliximab, and IV abatacept, based on an average patient weight of 75 kg. Indirect health care costs, such as routine patient care, SAEs, hospitalization, and drug administration were assumed to be the same for the three drugs. The manufacturer's analysis had several limitations, the most significant of which was assuming an average weight of 75 kg for the analysis rather than using a range of plausible patient weights. Recalculations by the Canadian Agency for Drugs and Technology in Health (CADTH), accounting for wastage as well as including other relevant comparators, updated drug prices, and a range of patient body weights, suggested that when used in patients who weigh between 70 kg and 75 kg, the three-year treatment cost of IV golimumab ($41,982) is $4,489 to $13,122 (8% to 20%) less costly compared with SC golimumab, IV infliximab, IV abatacept, SC adalimumab, etanercept, or SC certolizumab pegol. However, IV golimumab is more costly than all other treatment options in patients who weigh between 75 kg and 90 kg, and is frequently the most costly treatment option in patients who weigh more than 90 kg.

Conclusions

At the end of 14 weeks in the GO-FURTHER study, golimumab 2 mg/kg + methotrexate administered IV demonstrated statistically significantly better efficacy than placebo + methotrexate in achieving the primary outcome; that is, the proportion of ACR 20 responders. This superior response in favour of the golimumab group was also observed at Week 24. Other key efficacy outcomes, namely ACR 50, DAS 28, HAQ-DI, and SF-36 scores were also statistically significantly better in the golimumab 2 mg/kg + methotrexate group compared with the placebo + methotrexate group at both Week 14 and Week 24. HAQ-DI score as well as the PCS and MCS scores of SF-36 achieved their respective MCIDs. IV golimumab was generally well tolerated, with an overall safety profile consistent with that of SC golimumab and other TNF-alpha blockers in comparable RA patient populations. Patients randomized to the golimumab + methotrexate group had a slightly greater incidence of AEs and SAEs than those randomized to the placebo + methotrexate group. There was no incidence of serious opportunistic infections in either group and there was one case of malignancy (breast cancer) in a golimumab-treated patient reported through Week 24. However, efficacy and safety outcomes assessed at 24 weeks are likely influenced by the early escape design of the study, potentially overestimating the effect of golimumab versus placebo. Without head-to-head trials, it is difficult to draw conclusions with respect to the relative efficacy and safety of IV golimumab versus other BRMs, including SC golimumab, in patients with moderately or severely active RA with an inadequate response to methotrexate.

TABLE 1: SUMMARY OF RESULTS

GO-FURTHER				
Outcome	**Week 14[a]**		**Week 24**	
	Placebo + MTX N = 197	**Golimumab 2 mg/kg + MTX N = 395**	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**
ACR 20 response, n (%)	49 (24.9)	231 (58.5)	62 (31.5)	248 (62.8)
P value	< 0.001		< 0.001	
OR (95% CI)	[redacted]		[redacted]	
ACR 50 response, n (%)	[redacted]	[redacted]	26 (13.2)	138 (34.9)
P value	[redacted]		< 0.001	
OR (95% CI)	4.5 (2.6 to 7.8)		3.5 (2.2 to 5.6)	
Baseline DAS 28-CRP score,[b] mean ± SD	5.9 ± 0.93	6.0 ± 0.82	5.9 ± 0.93	6.0 ± 0.82
Change from baseline in DAS 28 score, (mean ± SD)	[redacted]	[redacted]	[redacted]	[redacted]
P value	NR		NR	
Baseline HAQ-DI (0-3), mean ± SD	1.57 ± 0.62	1.56 ± 0.67	1.56 ± 0.65	1.57 ± 0.62
Change in HAQ-DI from baseline, (mean ± SD)	0.19 ± 0.56	0.50 ± 0.58	0.21 ± 0.55	0.53 ± 0.64
P value	< 0.001		< 0.001	
Baseline SF-36 – PCS, mean ± SD	30.86 ± 7.31	30.83 ± 6.78	30.86 ± 7.31	30.83 ± 6.78
Change from baseline PCS, mean ± SD	NR	NR	3.82 ± 7.30	8.28 ± 8.32
P value	NR		< 0.001	
Baseline SF-36 – MCS, mean ± SD	38.51 ± 11.60	37.14 ± 11.11	38.51 ± 11.60	37.14 ± 11.11
Change from baseline MCS, mean ± SD	NR	NR	1.21 ± 10.07	6.94 ± 10.28
P value	NR		< 0.001	
Withdrawals, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Week 16		**Week 24**	
AEs,[a] n (%)	86 (43.7)	187 (47.3)	97 (49.2)	226 (57.2)
SAEs, n (%)	[redacted]	[redacted]	4 (2.0)	19 (4.8)

GO-FURTHER							
Outcome	**Week 14[a]**			**Week 24**			
	Placebo + MTX N = 197		**Golimumab 2 mg/kg + MTX N = 395**	**Placebo + MTX N = 197**		**Golimumab 2 mg/kg + MTX N = 395**	
WDAEs, n (%)	[redacted]		[redacted]	[redacted]		[redacted]	
Notable Harms(s), n (%)							
	Placebo + MTX N = 197	**EE[c] at Week 16 N = 68**	**Golimumab 2 mg/kg + MTX N = 395**	**Placebo + MTX N = 197**	**EE[c] at Week 16 N = 68**	**Golimumab 2 mg/kg + MTX N = 395**	**Combined[d] 2 mg/kg Golimumab N = 463**
-Injection site reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Hypersensitivity reactions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Infections (TB and hepatitis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Hepatotoxicity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Malignancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Hematologic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-Lymphocytes, (decreased)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]
-Golimumab antibodies positive patients, n (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; AE = adverse event; CI = confidence interval; CRP = C-reactive protein; DAS = Disease Activity Score; EE = early escape; HAQ-DI = Disability Index of the Health Assessment Questionnaire; MCS = Mental Component Summary; MTX = methotrexate; NNT = number needed to treat; NR = not reported; OR = odds ratio; PCS = Physical Component Summary; SAE = serious adverse event; SD = standard deviation; TB = tuberculosis; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Data for AEs including notable harms were reported from Week 16 prior to early escape. AE data for Week 14 were not reported.

[b] For DAS 28 score, only 28 joints are evaluated for both tenderness and swelling.

[c] Patients who early escaped at Week 16 started receiving golimumab at Week 16.

[d] The combined 2 mg/kg golimumab + MTX group comprised patients originally randomized to the golimumab + MTX group plus patients who early escaped from the placebo + MTX group at Week 16 to receive 2 mg/kg golimumab + MTX at Weeks 16 and 20, then every eight weeks thereafter until the end of the study.

Source: GO-FURTHER Clinical Study Report.[7]

There were no incidences of serious opportunistic infections, and there was one case of malignancy (breast cancer) in a golimumab-treated patient reported through Week 24. However, efficacy and safety outcomes assessed at Week 24 are likely influenced by the early escape design of the study, potentially overestimating the effect of golimumab versus placebo. Without head-to-head trials, it is difficult to draw conclusions with respect to the relative efficacy and safety of IV golimumab versus other BRMs, including SC golimumab, in patients with moderately or severely active RA with inadequate response to methotrexate.

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.[8] According to a report by the Arthritis Alliance of Canada, RA is the most common inflammatory joint disease 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 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.[1]

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.[2,3] 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.[3] 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.[3]

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 joint damage, preventing disability, and improving quality of life.[2] Beginning treatment early and aggressively with traditional synthetic, disease-modifying antirheumatic drugs (DMARDs) have been shown to alter the clinical course of RA and slow or halt radiographic progression.[2]

Methotrexate is the preferred DMARD with respect to efficacy and safety and is usually the first-line DMARD in patients with RA unless contraindicated or not tolerated. Therapy with methotrexate is individualized, with doses rapidly titrated to a usual maximum dose of 25 mg per week for intramuscular or intravenous use, or 20 mg per week for oral use.[2] The Canadian Rheumatology Association (CRA) recommends parenteral administration of methotrexate in patients with an inadequate response or intolerance to oral methotrexate.[2] The initial treatment strategy with DMARDs can include nonsteroidal anti-inflammatory drugs (NSAIDs) and/or glucocorticoids (in the lowest effective dose possible) 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 prior to accessing a biologic response modifier (BRM), and many also require failure of an adequate trial of combination DMARD therapy.[2] Methotrexate is the preferred anchor drug in combination therapy with conventional DMARDs, unless contraindicated.[2] The CRA defines inadequate response to a DMARD as moderate to high disease activity despite treatment with at least two DMARDs (including methotrexate unless contraindicated) in mono- or combination therapy after three months at target doses.

Most BRMs currently approved for use in Canada belong to the tumour necrosis factor inhibitors (anti-TNF) class; these include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. Other approved BRMs are abatacept (T cell costimulatory inhibitor), rituximab (B lymphocyte-depleting drug), tocilizumab (interleukin 6 [IL-6] antagonist), and anakinra (IL-1 antagonist).[2] Although co-administration of methotrexate with BRMs is recommended for improved efficacy, adalimumab, certolizumab pegol, etanercept, abatacept, and tocilizumab each have an indication for use as monotherapy.[2,9-12] This is an important distinction as not all patients will tolerate methotrexate. In recently diagnosed patients who have not been previously treated with methotrexate, abatacept is to be used in combination with methotrexate.[10]

According to the CRA recommendations,[2] patients who have failed treatment with one or two anti-TNF drugs due to lack of efficacy or toxicity could be switched to another anti-TNF drug or to another BRM with a different mechanism of action. Both abatacept and tocilizumab are recommended for the treatment of patients with RA after an inadequate response to DMARD or to anti-TNF therapy.[2] Rituximab, in combination with methotrexate, is indicated in RA patients who have had an inadequate response or intolerance to one or more anti-TNF therapies. In situations of inadequate response to an anti-TNF used as monotherapy, adding methotrexate or other DMARD is recommended.[2]

1.3 Drug

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF, which prevents the binding of TNF to its receptors.[13] Golimumab is already available for the treatment of RA as an autoinjector/pre-filled syringe for subcutaneous (SC) injection to be administered at a Health Canada recommended dose of 50 mg once a month, on the same dates each month. SC golimumab, in combination with methotrexate, is indicated to reduce signs and symptoms and improve physical function in adult patients with moderately to severely active RA, and to inhibit the progression of structural damage in adult patients with moderately to severely active RA who have not previously been treated with methotrexate. The Health Canada product monograph for SC golimumab also notes that clinical response is usually achieved within 14 to 16 weeks of treatment, and that continued therapy should be carefully reconsidered in a patient not responding within this time period.[13] SC golimumab is also indicated for the treatment of psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis.[13]

Indication under review
Golimumab 2 mg/kg intravenous injection (Simponi IV), in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.
Listing criteria requested by sponsor
Golimumab (Simponi IV), in combination with methotrexate (MTX), be listed for the treatment of adult patients with moderately to severely active rheumatoid arthritis following failure of MTX or other disease-modifying antirheumatic drugs (DMARDs)

TABLE 2: KEY CHARACTERISTICS OF GOLIMUMAB AND OTHER BIOLOGIC RESPONSE MODIFIERS

	Golimumab	Other Anti-TNF drugs	Abatacept	Rituximab	Tocilizumab
Mechanism of Action	Binds human TNF and inhibits the binding of TNF to its receptors	Inhibits binding of TNF to TNF receptors	Selective T lymphocytes co-stimulation modulator inhibits downstream production of cytokines or other inflammatory mediators	Monoclonal antibody (chimeric) that binds specifically to transmembrane antigen CD20 to mediate B-cell lysis	Binds membrane-bound IL-6 receptors to inhibit signalling through these receptors
Indication[a]	**IV** In combination with MTX, golimumab is indicated for the treatment of adult patients with moderately to severely active RA. **SC** In combination with MTX, golimumab is indicated in adult patients with moderately to severely active RA for: • Reducing signs and symptoms and improving physical function; and • Inhibiting the progression of structural damage in patients who had not previously been treated with MTX.	Indicated for reducing signs and symptoms, improving physical function, and inhibiting the progression of structural damage in adult patients with moderately to severely active RA.	Indicated in the treatment of RA for: • reducing signs and symptoms • inducing clinical responses • long-term use to inhibit the progression of structural damage, and to improve physical function in adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs or to TNF antagonists, or to both.	In combination with MTX to reduce signs and symptoms in adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more TNF inhibitor therapies.	Indicated for reducing signs and symptoms in adult patients with moderately to severely active RA who had an inadequate response to one or more DMARDs and/or TNF antagonists.

	Golimumab	Other Anti-TNF drugs	Abatacept	Rituximab	Tocilizumab
Route of Administration	IV and SC	IV and SC	IV and SC	IV	IV
Recommended Dose	• IV, 2 mg/kg body weight Weeks 0 and 4, then every eight weeks thereafter. • SC, 50 mg once a month, on the same date each month.		Initial IV loading doses are: • 500 mg in patients weighing < 60 kg body weight • 750 mg in patients weighing 60 kg to 100 kg • 1 g in patients weighing > 100 kg Loading dose is followed by once-weekly SC injections at the fixed dose of 125 mg (regardless of weight)	Starting dose of 1,000 mg IV, followed two weeks later by the second 1,000 mg IV.	Starting dose of 4 mg per kg of body weight with an increase to 8 mg per kg of body weight, based on response.
Serious Side Effects/Safety Issues	• Infections, injection site reactions • Allergic reactions • Malignancies	• Infections, injection site reactions • Allergic reactions • Malignancies	• Serious infections • Malignancies • Allergic reactions	Serious and fatal • Allergic reactions and TLS • Hepatitis • Infections • Infusion reactions • Skin reactions • Cardiovascular events	• Serious infections • Allergic reactions
Other			Abatacept should not be taken with other biologic medications for RA.	No to be given with live viral vaccines.	

BRM = biologic response modifier; DMARD = disease-modifying antirheumatic drug; IV = intravenous; MTX = methotrexate; RA = rheumatoid arthritis; SC = subcutaneous; TLS = tumour lysis syndrome; TNF = tumour necrosis factor.

[a] Health Canada indication.

Sources: Source: GO-FURTHER Clinical Study Report;[7] Health Canada product monographs.[11,12,14]

2. OBJECTIVES AND METHODS

2.1 Objectives

To evaluate the beneficial and harmful effects of IV golimumab (Simponi IV) at recommended doses in combination with methotrexate for the treatment of adult patients with moderately to severely active RA.

2.2 Methods

Studies selected for inclusion in the systematic review included the pivotal studies provided in the manufacturer's submission to the CADTH Common Drug Review (CDR) as well as those meeting the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults (18 years or older) diagnosed with moderately or severely active RA and who are inadequately responsive to MTX Subgroups of interest: • Patient's age • Body weight at baseline • Seropositivity or seronegativity for RF or anti-CCP • MTX dose at baseline • Inadequate response to prior treatment
Intervention	Golimumab at recommended dose in combination with MTX
Comparators	BRMs at approved doses for RA including SC and IV formulations Placebo
Outcomes	**Key efficacy outcomes:** Clinical response (proportion of patients with an ACR 20 response and ACR 50 response) DAS 28 response Improvements in HRQoL determined with validated measures (e.g., Change in HAQ-DI and SF-36 from baseline) **Harms outcomes:** Mortality AEs, SAEs, WDAEs AEs of interest include, but are not limited to: • Injection site reactions and hypersensitivity reactions • Infections (particularly TB and hepatitis) • Malignancy • Hepatotoxicity • Hematologic (including anti-drug antibody production)
Study Design	Published and unpublished DB RCTs

ACR = American College of Rheumatology; AE = adverse event; BRM = biologic response modifier; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DAS = Disease Activity Score, DB = double-blind; DMARD = disease-modifying antirheumatic drugs; HAQ-DI = Disability Index of the Health Assessment Questionnaire; MTX = methotrexate; HRQoL = health-related quality of life; IV = intravenous; RA = rheumatoid arthritis; RCT = randomized controlled trial; RF = rheumatoid factor; SAE = serious adverse event; SC = subcutaneous; TB = tuberculosis; WDAE = withdrawal due to adverse event.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Simponi (golimumab) AND rheumatoid arthritis. No methodological filters were applied. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language.
The initial search was completed on January 28, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on June 18, 2014. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters):

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

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. The included study is presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 3 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

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

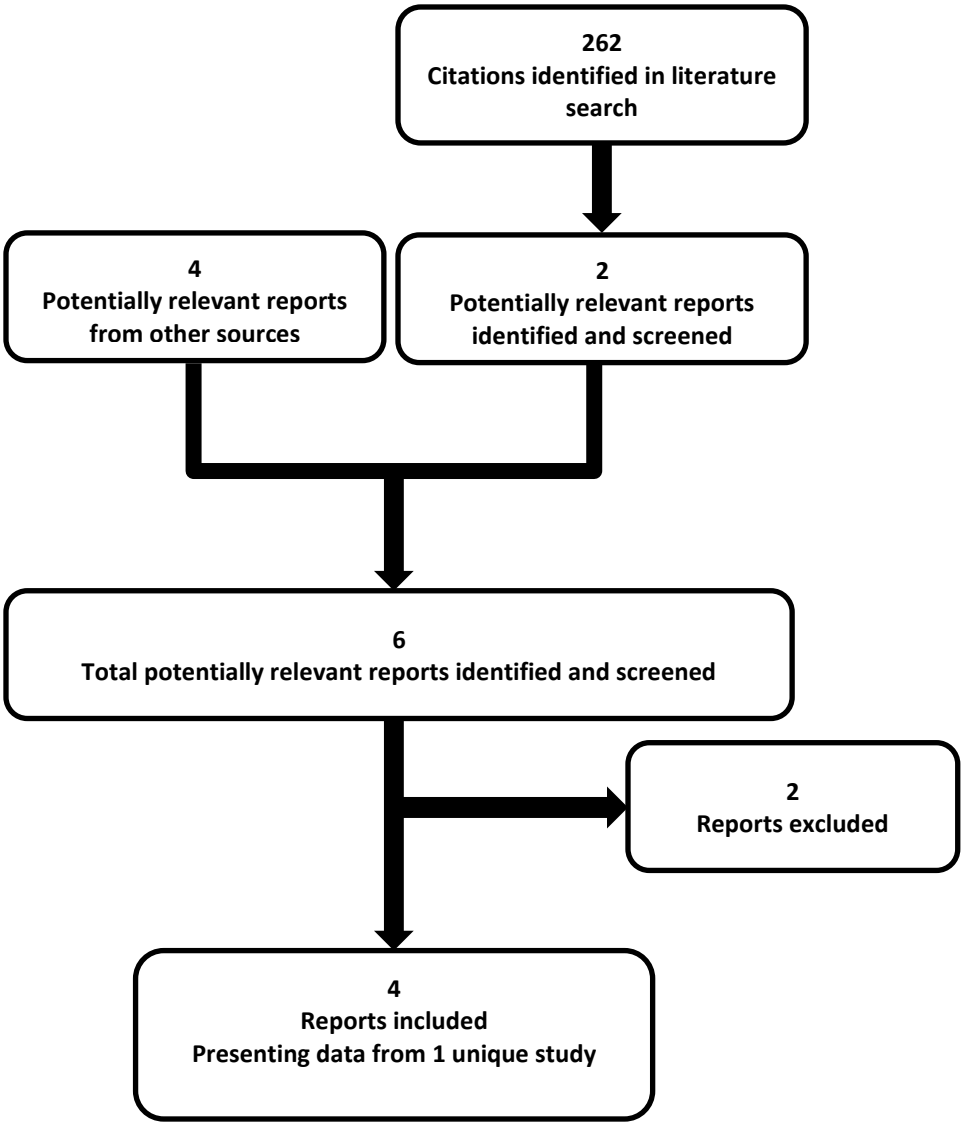


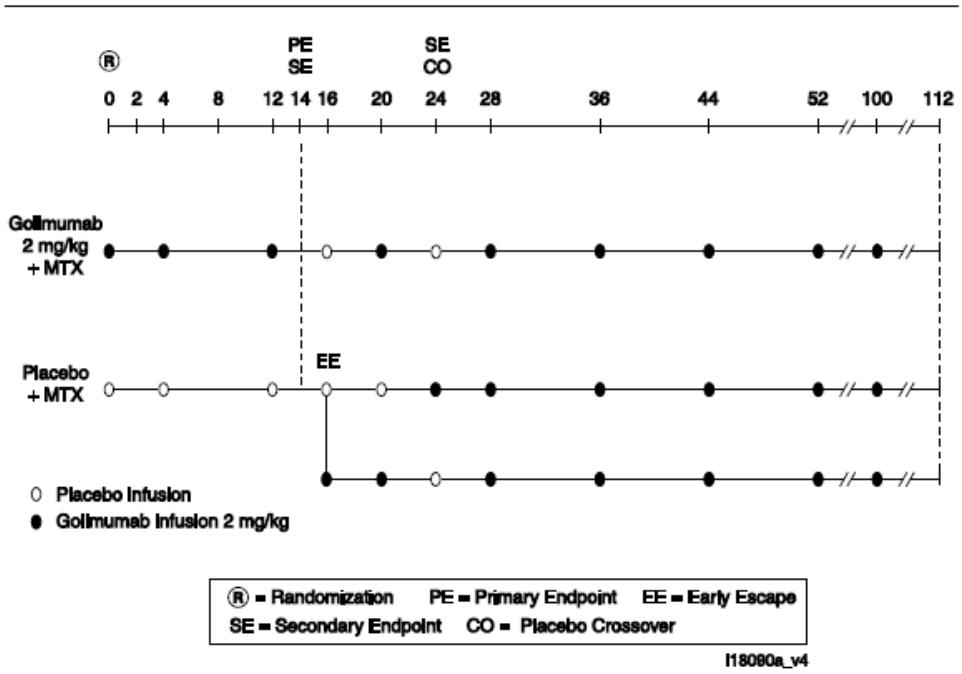
TABLE 4: DETAILS OF INCLUDED STUDIES

	GO-FURTHER 24-Week	
DESIGNS AND POPULATIONS	**Study design**	Phase 3, placebo-controlled, DB RCT
	Locations	92 sites in United States, Hungary, Lithuania, Poland, Russia, Ukraine, Argentina, Colombia, Mexico, Australia, Korea, Malaysia, and New Zealand.
	Randomized[a] (N)	592
	Inclusion Criteria	Adults (aged ≥ 18 years) diagnosed with RA (according to the revised 1987 ARA criteria; Arnett et al., 1988[15]) at least 3 months prior to screening. Moderately to severely active RA, defined as ≥ 6 tender joints and ≥ 6 swollen joints at screening and at baseline, despite concurrent therapy on a stable MTX dose of ≥ 15 mg/week and ≤ 25 mg/week for at least 4 weeks prior to screening. CRP ≥ 1.0 mg/dL at screening, and anti-CCP antibody-positive or RF-positive at screening. No history of latent or active TB, and/or other medical conditions prior to screening deemed as reason for exclusion.
	Exclusion Criteria	Other inflammatory diseases. Prior treatment with DMARDs (other than MTX), systemic immunosuppressives, or parenteral corticosteroids during the 4 weeks prior to first administration of study treatment. Have ever received rituximab or efalizumab, abatacept, natalizumab, or other drugs that target alpha-4-integrin, cytotoxic or alkylating drugs, or have received anakinra during the 4 weeks prior to first administration of study drug. Are pregnant, nursing, or planning a pregnancy or planning to father a child within 6 months after receiving the last administration of study drug. Have a current medical condition and/or a history of medication use or a medical condition that makes it unsuitable to include them in the study.
DRUGS	**Intervention[b]**	2 mg/kg golimumab administered as IV over 30 ± 10 minutes plus background MTX.
	Comparator[b]	Placebo administered as IV over 30 minutes ± 10 minutes, plus background MTX.[b]
DURATION	**Phase:**	
	Run-in	6 weeks
	Double-blind	24 weeks Early escape criteria at 16 weeks (< 10% improvement in both swollen and tender joint counts)
	Follow-up	88 weeks • Extension to 76 weeks • Safety follow-up of 12 weeks
OUTCOMES	**Primary End Point**	ACR 20 response at Week 14, defined as: • An improvement of ≥ 20% from baseline in both the swollen joint count (66 joints) and tender joint count (68 joints), and • An improvement of ≥ 20% from baseline in ≥ 3 of the following 5 assessments: ▪ Patient's assessment of pain (VAS) ▪ Patient's global assessment of disease activity (VAS) ▪ Physician's global assessment of disease activity (VAS) ▪ Patient's assessment of physical function as measured by HAQ-DI ▪ CRP
	Other End Points	DAS 28 response using CRP at Week 14. Change in baseline from HAQ-DI at Week 14. ACR 50 response at Week 24.

GO-FURTHER 24-Week		
NOTES	**Publications**	Weinblatt et al.[16]

ARA = American Rheumatism Association; ACR = American College of Rheumatology; BRM = biologic response modifiers; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DAS = Disease Activity Score; DB = double-blind; DMARD = disease-modifying antirheumatic drugs; HAQ-DI = Disability Index of the Health Assessment Questionnaire; MTX = methotrexate; RA = rheumatoid arthritis; RF = rheumatoid factor; RCT = randomized controlled trial; VAS = visual analogue scale.
Note: Three additional reports were included.[7,17,18]
[a] Randomization was stratified based upon a screening CRP of < 1.5 mg/dL or ≥ 1.5 mg/dL.
[b] Patients in the placebo + MTX group who met early escape criteria as described in Section 3.2.1 started receiving golimumab at Week 16.

FIGURE 2: STUDY SCHEMA FROM WEEK 0 THROUGH WEEK 112



Source: GO-FURTHER Clinical Study Report.[7]

3.2 Included Studies

3.2.1 Description of Studies

GO-FURTHER was a multi-centre, randomized, double-blind, placebo-controlled phase 3 study conducted to evaluate the clinical efficacy and safety of IV administration of golimumab with methotrexate compared with methotrexate alone in patients 18 years of age or older with moderately to severely active RA despite methotrexate therapy for at least three months prior to screening. It was a two-arm study in which 592 patients were randomized through an interactive voice response system (IVRS) in a 2:1 ratio to receive IV golimumab 2 mg/kg (Group I) at Weeks 0 and 4 and every eight weeks thereafter, or placebo (0.9% saline solution) IV infusion (Group II) in a similar pattern through Week 24. (Figure 2 illustrates the study design.) Randomization was stratified by CRP level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL) and investigational site. All participants were maintained on their stable dose of methotrexate at doses of between 15 mg per week and 25 mg per week throughout the study.

Placebo-treated patients were eligible to enter early escape at Week 16 if they demonstrated less than 10% improvement in both tender and swollen joint counts. Patients who entered early escape from the placebo + methotrexate group received golimumab infusions of 2 mg/kg at Weeks 16 and 20 as part of the placebo-controlled phase, then every eight weeks thereafter as part of the extension and safety phases (APPENDIX 5: SUMMARY OF EXTENSION STUDIES). Patients in the placebo + methotrexate group who did not early escape at Week 16 crossed over to golimumab 2 mg/kg at the end of the placebo-controlled phase (i.e., Week 24) and received golimumab 2 mg/kg at Weeks 24 and 28, then every eight weeks thereafter as part of the extension and safety phases (APPENDIX 5). Patients in the golimumab + methotrexate group also received a placebo infusion at Weeks 16 and 24 to maintain the blind (see Figure 2). The golimumab dose for patients in the golimumab + methotrexate group was maintained at 2 mg/kg even if they had less than 10% improvement in both tender and swollen joint counts. The placebo-controlled phase of the study was 24 weeks. There was a 76-week extension phase and an additional 12-week safety follow-up period. The main focus of this evaluation is on the 24-week placebo-controlled phase. The extension phase is summarized in APPENDIX 5.

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients were included in the study if they were 18 years or older and diagnosed with moderately to severely active RA (defined as six or more tender joints and six or more swollen joints) for at least three months prior to screening and at baseline, despite concurrent therapy on a stable methotrexate dose of ≥ 15 mg per week and ≤ 25 mg per week. Included patients also had to have a serum CRP greater than or equal to 1.0 mg/dL and be anti-CCP antibody-positive or RF-positive. In addition, participants must have had no history of latent or active TB and/or other medical conditions prior to screening deemed as reason for exclusion. Patients were excluded from the study if they had other inflammatory diseases, or had received prior treatment with DMARDs (other than methotrexate), systemic immunosuppressives, or parenteral corticosteroids during the four weeks prior to the first administration of study treatment. In addition, patients who had received treatment with other BRMs, pregnant or nursing patients, or those planning to become parents within the next six months were also excluded (see details in Table 4: Details of Included Studies).

b) Baseline characteristics

Baseline demographic and clinical disease characteristics were generally well balanced across treatment groups. Patient demographics showed no significant differences in age, gender distribution, race, weight, height, and body mass index between the two groups (Table 5). The median age was 52 years (ranging from 18 years to 83 years). The majority (81.6%) of participants was female, and Caucasians formed 80.4% of the total patient population. Among randomized patients, the mean duration of disease was 6.9 ± 7.08 years, with a median of 4.6 years for the golimumab + methotrexate group and 4.8 years in the placebo + methotrexate group. Key disease indicators like swollen and tender joints, HAQ-DI, DAS 28-CRP, and SF-36 scores were similar in the two groups (Table 5). Overall, the median number of swollen and tender joints was 12 and 23, respectively. Based on all ACR components, baseline disease could be rated as moderate to severe RA.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

GO-FURTHER			
Characteristics	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**	**Total N = 592**
Age in Years, Mean ± SD	51.4 ± 11.26	51.9 ± 12.55	51.8 ± 12.13
Median Age (range)	52.0 (19 to 78)	53.0 (18 to 83)	52.0 (18 to 83)
Female Gender, n (%)	157 (79.7)	326 (82.5)	483 (81.6)
Asian, n (%)	[redacted]	[redacted]	[redacted]
Black, n (%)	[redacted]	[redacted]	[redacted]
Caucasian, n (%)	[redacted]	[redacted]	475 (80.4)
Other, n (%)	[redacted]	[redacted]	[redacted]
Weight (kg), Mean ± SD	[redacted]	[redacted]	[redacted]
Disease Characteristics			
RA Duration (Yrs), Mean ± SD	7.0 ± 7.24	6.9 ± 7.00	6.9 ± 7.08
Median (IQR)	4.8 (1.9 to 9.6)	4.6 (1.8 to 9.6)	4.7 (1.9 to 9.6)
Number of SJ (0-66), Mean ± SD	14.8 ± 8.54	15.0 ± 8.23	14.9 ± 8.33
Number of TJ (0-68), Mean ± SD	25.9 ± 14.13	26.4 ± 13.93	26.3 ± 13.99
CRP (mg/dL), Mean ± SD	2.23 ± 1.88	2.85 ± 2.86	2.64 ± 2.59
Median (IQR)	1.72 (0.899 to 3.020)	2.02 (0.998 to 3.430)	1.94 (0.943 to 3.285)
HAQ-DI (0-3) Mean ± SD	1.57 ± 0.62	1.56 ± 0.67	1.56 ± 0.65
DAS 28 (CRP) Score[a] Mean ± SD	5.9 ± 0.93	6.0 ± 0.82	5.9 ± 0.86
Summary SF-36 Version			
Physical Component Summary, Mean ± SD	30.86 ± 7.31	30.83 ± 6.78	30.84 ± 6.95
Mental Component Summary, Mean ± SD	38.51 (38.20)	37.14 (36.50)	37.59 (36.90)
RF-Positive Patients, n (%)	[redacted]	[redacted]	[redacted]
Anti-CCP–Positive Patients, n (%)	[redacted]	[redacted]	[redacted]
Selected Baseline Medications for RA			
Patients Taking MTX, n (%)	197 (100)	395 (100)	592 (100)
Maximum MTX Dose (mg/week)	[redacted]	[redacted]	[redacted]
Median Dose (IQR) (mg/week)	[redacted]	[redacted]	[redacted]
Patients Taking Oral Corticosteroids, n (%)	134 (68.0)	251 (63.5)	385 (65)
Patients Taking NSAIDs, n (%)	156 (79.2)	323 (81.8)	479 (80.9)
Patients who took DMARDs other than MTX, n (%)	92 (46.7)	206 (52.2)	298 (50.3)

CCP = cyclic citrullinated peptide antibody; CRP = C-reactive protein; DAS = Disease Activity Score; DMARD = disease-modifying antirheumatic drug; HAQ-DI = Health Assessment Questionnaire Disability Index; IQR = interquartile range; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SF-36 = Short Form 36 Health Survey; SJ = swollen joints; TJ = tender joints.

[a] For DAS 28 score, only 28 joints are evaluated for both tenderness and swelling.

Source: GO-FURTHER Clinical Study Report.[7]

3.2.3 Interventions

Patients in the golimumab + methotrexate group received 2 mg/kg of golimumab by intravenous infusion at Weeks 0 and 4, then every eight weeks thereafter. Patients in the placebo + methotrexate group received a placebo (normal saline) IV infusion following a similar schedule. All infusions were given over 30 ± 10 minutes. All patients were maintained on their stable dose of methotrexate (between 15 mg per week to 25 mg per week) throughout the study. Patients in the placebo + methotrexate group who demonstrated a less than 10% improvement in both tender and swollen joint counts at Week 16 were eligible for early escape to receive golimumab infusion of 2 mg/kg at Weeks 16 and 20, then every eight weeks thereafter until the end of the study. To maintain the blind, patients in the golimumab + methotrexate group also received a placebo infusion at Week 16 and Week 24 (Figure 2). The placebo-controlled phase lasted 24 weeks, at which point all patients in the placebo + methotrexate treatment group were crossed over to receive golimumab + methotrexate for the extension phase, which lasted 76 weeks.

Patients on a stable dose of NSAIDs or other analgesics for RA, or those on oral corticosteroids equivalent to 10 mg or less of prednisone per day for at least two weeks prior to first administration of study drug, were allowed to maintain their therapy on these drugs. However, parenteral corticosteroid use was not allowed. It was recommended that all patients received 1 mg oral folic acid daily for at least five days a week or 5 mg oral folinic acid weekly until the 112-week safety database lock.

3.2.4 Outcomes

The primary end point for efficacy was the ACR 20 response at Week 14. An ACR 20 responder is a patient who achieved an improvement of 20% or more from baseline in both the swollen joint count (66 joints) and the tender joint count (68 joints), and a 20% improvement in at least three of the remaining five parameters. ACR 20 is a composite measure of seven elements comprising swollen joint count (66 joints), tender joint count (68 joints), patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, and patient's assessment of physical function as measured by HAQ-DI, and CRP. All efficacy analyses were based on the intention-to-treat (ITT) principle; thus patients were analyzed according to the treatment for which they were randomized, regardless of the treatment they actually received.

The major secondary end points were the proportions of patients with moderate or good DAS 28-CRP at Week 14, change from baseline in HAQ-DI at Week 14, and ACR 50 response at Week 24. ACR 50 response at Week 24 is defined as the proportion of patients with improvement of 50% or more from baseline in both the swollen joint count (66 joints) and the tender joint count (68 joints), and a 50% improvement in at least three of the remaining five parameters. The DAS 28-CRP is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), CRP, and a global assessment of disease activity (see APPENDIX 4: VALIDITY OF OUTCOME MEASURES). Interpretation of improvements in DAS 28-CRP score as moderate or good depends on baseline score; however, a change of 0.6 or less is a "no response score" in all cases. The DAS 28-CRP remission criterion is defined as DAS 28-CRP value of < 2.6 at a visit.

The HAQ-DI is composed of eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common activities. Each of these categories has at least two component questions, requiring patients to record the amount of difficulty they had in performing various activities, and to indicate whether they used any aids or devices or if they needed help from another person to perform any of these activities. The highest score recorded by the patient for any component question determined the score for that category. The disability index was not computed if the patient did not

have scores for at least six categories. The average score (ranging from 0 for no disability to 3 for completely disabled) of all eight categories represents the overall HAQ-DI. It is a validated tool with a minimal clinically important difference (MCID) of 0.22; however, differences as small as 0.10 have been suggested as being clinically important.[19]

The SF-36 was one of the instruments used to measure health-related quality of life (HRQoL). It comprises 36 questions and yields an eight-scale profile of functional health and well-being scores as well as psychometrically based PCS and MCS scores. The eight multi-item scales of SF-36 instrument include limitations in physical functioning due to health problems, limitations in usual role activities due to physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities due to personal or emotional problems, limitations in social functioning due to physical or mental health problems, vitality (energy and fatigue), and general health perception. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, thereby allowing a comparison of the relative burden of different diseases and the relative benefit of different treatments. The MCID for either the PCS or MCS is reported to range between 2.5 and 5.[4-6]

All safety analyses were performed using the population of all patients who received at least one administration of the study drug. Analyses were performed using the treatment that the patient actually received. At Week 24, AEs and SAEs among patients who entered early escape from the placebo + methotrexate group to receive golimumab 2 mg/kg + methotrexate at Week 16 were reported separately in addition to the ITT groups. Also reported at Week 24 were AEs and SAEs for the combined golimumab 2 mg/kg + methotrexate group, which comprised patients who were originally assigned to that treatment group plus those who early escaped from the placebo + methotrexate group at Week 16. There were no incidences of SAE reported among patients in the early escape subgroup, and no specific pattern of association between SAEs and golimumab was identified. The discussion of AEs at Week 24 entails differences in follow-up and exposure to study drug administration between the treatment groups. Since 68 patients switched from the placebo + methotrexate group to the golimumab + methotrexate group at Week 16, 129 patients received only placebo + methotrexate and 395 patients received only golimumab + methotrexate. The average duration of follow-up was almost 21 weeks for the patients who only received placebo + methotrexate and almost 24 weeks for the patients who only received golimumab + methotrexate.

3.2.5 Statistical Analysis

In the GO-FURTHER study, the primary hypothesis was that golimumab 2 mg/kg infusions + methotrexate has superior efficacy to placebo infusions + methotrexate in treating RA patients with moderately to severely active disease. A sequential procedure was used to control multiplicity among end points. The primary end point was analyzed first. 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. Binary categorical data (e.g., the proportion of patients with an ACR 20 response) were analyzed using the chi-square test or the Cochran–Mantel–Haenszel (CMH) test when stratification was employed. Continuous data were analyzed using an analysis of variance (ANOVA) test on van der Waerden normal scores. Nominal *P* values were provided. All statistical testing was 2-sided (alpha = 0.05), and the CMH test was stratified by CRP level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL).[7]

For the primary end point, a total of 564 patients (376 in the golimumab + methotrexate group and 188 in the placebo + methotrexate group) was needed to ensure greater than 99% power to detect significant differences in the proportion of responders between treatment groups at Week 14, assuming a 52% ACR 20 response for the golimumab + methotrexate group and a 27% response for the placebo + methotrexate group at a two-sided significance level of 0.05 using the chi-square test.[7] Analyses of data for efficacy at both Week 14 and Week 24 used the ITT population (with patients analyzed according to the treatment to which they were originally randomized to receive, regardless of the treatment they actually received). Therefore, patients who early escaped from the placebo + methotrexate group at Week 16 to receive 2 mg/kg golimumab + methotrexate were counted as part of the placebo + methotrexate group for efficacy analysis at Week 24. In the safety analyses, data from patients who early escaped from the placebo + methotrexate group at Week 16 to receive 2 mg/kg golimumab + methotrexate were analyzed and reported separately, although safety data for the ITT population of the two groups were also reported. The statistical analysis plan did not explicitly state that patients who entered early escape were coded as non-responders for the Week 24 outcome assessments.

With respect to changes from baseline end points, if the value at baseline was missing, the median change from the baseline value of all patients in the same stratum was assigned. This method was also applied to per cent change from baseline end points. If the value at a specified time point other than baseline was missing, the missing value was replaced by the last non-missing observation (including baseline).[7]

a) Analysis Populations

All efficacy analyses were based on the ITT principle, with patients analyzed according to the treatment they were originally randomized to receive regardless of the treatment they actually received both at Week 14 and Week 24. According to the Clinical Study Report (CSR),[7] all safety analyses were performed using the population of all patients who received at least one administration of the study drug. Analyses were performed using the treatment that the patient actually received. Therefore, patients who early escaped from the placebo + methotrexate group at Week 16 to receive 2 mg/kg golimumab + methotrexate were counted as part of the placebo + methotrexate group for efficacy analysis at Week 24. In the safety analyses, data from patients who early escaped from the placebo + methotrexate group at Week 16 to receive 2 mg/kg golimumab + methotrexate were analyzed and reported separately, although safety data for the ITT population of the two groups were also reported. However, AEs for patients in the placebo + methotrexate who did not early escape (n = 129) were not reported separately at Week 24.

3.3 Patient Disposition

There was no clear difference between the proportions of patients who discontinued the study drug through Weeks 14 and 24 (Table 6: Patient Disposition). At Week 14, 3.8% of patients in the golimumab + methotrexate group discontinued the study drug, compared with 2.5% in the placebo + methotrexate group; 4.1% in the golimumab + methotrexate group discontinued at Week 24 compared with 3.0% in the placebo + methotrexate group. AEs were the most common reasons for discontinuation.

TABLE 6: PATIENT DISPOSITION

GO-FURTHER							
	Week 14			Week 24			
	Placebo + MTX		Golimumab 2 mg/kg + MTX	Placebo + MTX		Golimumab 2 mg/kg + MTX	
Screened, N							
Randomized, N (%)	197 (33.28)		395 (66.72)	197 (33.28)		395 (66.72)	
Discontinued, Total N (%)	5 (2.5)		15 (3.8)	6 (3.0)		16 (4.1)	
Reason for Discontinuation							
-Death, n (%)	[redacted]		[redacted]	1 (0.5)		0 (0.0)	
-Lost to Follow-up, n (%)	[redacted]		[redacted]	0 (0.0)		1 (0.3)	
-Withdrawal of Consent, n (%)	[redacted]		[redacted]	2 (1.0)		4 (1.0)	
-WDAEs, n (%)	[redacted]		[redacted]	2 (1.0)		9 (2.3)	
-Lack of Efficacy, n (%)	[redacted]		[redacted]	1 (0.5)		1 (0.3)	
-Protocol Violation, n (%)	[redacted]		[redacted]	0 (0.0)		1 (0.3)	
Analysis Populations	**Placebo + MTX**	**EE[a] to 2 mg/kg Golimumab + MTX**	**Golimumab 2 mg/kg + MTX**	**Placebo + MTX**	**EE[a] to 2 mg/kg Golimumab + MTX**	**Golimumab 2 mg/kg + MTX**	**Combined Golimumab 2 mg/kg + MTX[b]**
ITT, N	197	0	395	197	-	395	-
Safety Analyses	129	68	395	197	68	395	463

AE = adverse event; EE = early escape; ITT = intention-to-treat; MTX = methotrexate; WDAE = withdrawal due to adverse event.
[a] Sixty-eight (68) patients from the placebo + MTX group early escaped at Week 16 to receive golimumab 2 mg/kg + MTX.
[b] The combined golimumab 2 mg/kg + MTX group comprised patients originally randomized to the golimumab + MTX group plus patients who early escaped from the placebo + MTX group at Week 16 to receive 2 mg/kg golimumab + MTX for the remainder of the study for the rest of the double-blind phase (24 weeks).
Source: GO-FURTHER Clinical Study Report.[7]

3.4 Exposure to Study Treatments

[redacted]

Through Week 24, 463 patients received at least one infusion of golimumab (Table 7). These included the 68 patients in the placebo + methotrexate group who met early escape criteria at Week 16 and then began receiving golimumab 2 mg/kg + methotrexate, and all the 395 patients originally randomized to receive golimumab 2 mg/kg + methotrexate. [redacted]

[redacted]

[redacted] (Table 7).

TABLE 7: CUMULATIVE DOSE OF GOLIMUMAB AND METHOTREXATE RECEIVED THROUGH WEEK 24

GO-FURTHER				
	Placebo + MTX[a] N = 197	Early Escape to Golimumab 2 mg/kg + MTX N = 68	Golimumab 2 mg/kg + MTX N = 395	Combined Golimumab 2 mg/kg + MTX[b] N = 463
Dose of Golimumab Received				
Cumulative Dose (mg), Mean ± SD	NA	[redacted]	[redacted]	[redacted]
Median (IQR)	NA	[redacted]	[redacted]	[redacted]
Cumulative Dose per kg (mg/kg), Mean ± SD	NA	[redacted]	[redacted]	[redacted]
Median (IQR)	NA	[redacted]	[redacted]	[redacted]
Dose of MTX Received	**N = 127**	**N = 68**	**N = 393**	**N = 461**
Cumulative Dose (mg), Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]	[redacted]	[redacted]

IQR = interquartile range; MTX = methotrexate; NA = not applicable; SD = standard deviation.
[a] Patients who early escaped at Week 16 started receiving golimumab at Week 16.
[b] The combined golimumab 2 mg/kg + MTX group comprised patients originally randomized to the golimumab + MTX group plus patients who early escaped from the placebo + MTX group at Week 16 to receive 2 mg/kg golimumab + MTX for the remainder of the study.
Source: GO-FURTHER Clinical Study Report.[7]

3.5 Critical Appraisal

3.5.1 Internal Validity

GO-FURTHER was a placebo-controlled, double-blind, phase 3 study in which patients were randomly assigned by using an adaptive randomization through IVRS to receive an IV infusion of golimumab 2 mg/kg or placebo (in a 2:1 ratio). Randomization was stratified by CRP level at screening (< 1.5 mg/dL or ≥ 1.5 mg/dL) and investigational site. Baseline characteristics were adequately balanced between the two groups and, according to the clinical expert who provided input on the conduct of this review and the interpretation of findings, are representative of the target patient population in Canada. For the primary end point, the investigators determined that a total of 564 patients (376 in the golimumab + methotrexate group and 188 in the placebo + methotrexate group) were needed to ensure greater than 99% power to detect significant differences in the proportion of responders between treatment groups at Week 14, assuming a 52% ACR 20 response for the golimumab + methotrexate group and a 27% response for the placebo + methotrexate group at a two-sided significance level of 0.05 using the chi-square test. Therefore, with the actual number of participants being 395 in the golimumab + methotrexate group and 197 in the placebo + methotrexate group, the study was powered adequately to detect differences between the treatment groups. Independent joint assessors were not used for joint assessments at screening, although each study centre had an independent joint assessor who performed all joint assessments in a blinded manner from baseline (Week 0) until the end of the study.

The design of the study allowed patients in the placebo + methotrexate group who demonstrated less than 10% improvement in both tender and swollen joint counts at Week 16 (after evaluation of the primary end point at Week 14) to cross over (early escape) to receive golimumab 2 mg/kg at Week 16 in a DB manner (Figure 2). More than one-third (n = 68, 34.5%) of placebo patients went on to early escape at Week 16. Of interest, 17 (4.3%) of patients in the golimumab + methotrexate group also met the early escape criteria at Week 16, but these individuals continued on treatment as per the study's investigational plan. If placebo + methotrexate patients who met early escape criteria were considered non-responders and their Week 16 observations carried forward for subsequent evaluations (i.e., ITT analysis), this could bias the 24-week assessment and overestimate the effect of golimumab. Conditions such as RA are characterized by flares; hence, it is possible that not all patients who met the early escape criteria were necessarily true non-responders to therapy. Meeting early escape may have been a result of the disease flaring and these patients may have improved if maintained on their randomized treatment. Safety analyses were performed using the treatment that the patient actually received instead of the ITT population. Per-protocol analyses can mask the time-dependent nature of certain harms. For example, if golimumab is associated with early harms, then the per-protocol analysis would capture this, as the early escapers had had eight weeks of therapy before the 24-week end point. However, if the harms are delayed or if the harms are cumulatively dose dependent, then the per-protocol analysis of counting the placebo early escapers in the combined golimumab + methotrexate group could bias the harms downward in favour of golimumab. This is a potential issue given the addition of 68 people to the denominator of the golimumab + methotrexate group, because the cumulative dose of golimumab for the early escape patients was much lower than the dose for the golimumab + methotrexate group. [redacted] Hence, the early escape design could potentially impact the interpretation of the findings of the GO-FURTHER study.

[redacted] While concern for tolerability and AEs may support lower doses, no reason is given for the seeming suboptimal methotrexate doses used in the trial, giving rise to questions about whether patients had an adequate response to methotrexate therapy. According to the clinical expert involved in the review, because the benefits of methotrexate are usually seen by 12 to 24 weeks of use, if the methotrexate doses had not been optimized three months before screening, the reported efficacy outcomes could have been considerably higher in the placebo + methotrexate group than they otherwise would have been.

GO-FURTHER defined clinical remission as a DAS 28-CRP score of < 2.6. There are reports of other studies that used the DAS 28 based on the erythrocyte sedimentation rate [ESR] value (DAS 28-ESR) score of < 2.6 as a measure of remission. The two scales are well correlated and both are validated measures for assessing disease activity in RA.[20-24] However, studies have shown that the DAS 28-CRP score is usually lower than the DAS 28-ESR score, with differences ranging from –0.2 to –0.8.[21-25] Therefore, using the same cut-off of < 2.6 to define remission on the DAS 28-CRP scale could significantly overestimate the improvement in disease activity and underestimate disease activity compared with DAS 28-ESR.

3.5.2 External Validity

Most of the patients were enrolled in Eastern Europe (60.0%) followed by Latin America (26.5%), Asia-Pacific (9.6%), and North America (3.9%; all from the US).[7] According to the clinical expert involved in the review, the management of RA varies across countries and regions and can impact procedures, including joint counting methods, leading to different conclusions about a patient's status and treatment outcomes. Hence, generalizability of the study findings is uncertain because of the absence of study sites in Canada. This may have been somewhat mitigated, as an ANOVA showed no statistically significant effect of study site on outcomes; no subanalysis testing was conducted of the sensitivity of overall outcomes to data from the US study sites.

The study required patients to be seropositive for RF and/or anti-CCP to qualify for entry.[7] According to the clinical expert involved in the review, a substantial proportion (approximately 30%) of patients seen in clinical practice are seronegative. Hence, the generalizability of the study may be limited; however, this limitation may be mitigated somewhat because the seropositivity requirement for inclusion likely increases the specificity of disease at entry.

One of the claims of the manufacturer of IV golimumab is that patients who receive IV BRM therapy for RA tend to have more severe disease, more comorbidities, less social support, and be less capable of self-injection than those who use SC formulations. However, there was no evidence that the patients who participated in GO-FURTHER met those descriptions, and there was no comparison to demonstrate advantages of IV golimumab over SC golimumab. Therefore, it is uncertain whether the findings of this study will apply to such RA patient population subgroups. According to the clinical expert involved in the review, a dichotomous patient population as described by the manufacturer is uncommon in practice, and family members can be taught to administer SC drugs, if needed.

GO-FURTHER used placebo as a comparator to the active drug in patients who are reported to have failed therapy with methotrexate. This is an important limitation, as placebo would not be a usual treatment choice in clinical practice for such patients. Another TNF inhibitor or SC golimumab already approved for RA treatment would be a more suitable comparator. However, despite this limitation, using placebo as comparator is common in clinical trials of drugs for RA, although there has been a study involving a head-to-head comparison of abatacept to SC adalimumab.[26] Furthermore, IV abatacept has been compared directly with SC abatacept.

GO-FURTHER was not intended to evaluate efficacy and safety in patients who have failed therapy with a combination of conventional DMARDs, [redacted](Table 7). Thus, it cannot be determined how the study findings compare with a combination of conventional DMARDs at optimal doses, which is another option for patients with an inadequate response to methotrexate. The placebo-controlled phase was only 24 weeks, with a 76-week, single-arm extension using only golimumab. Therefore, comparative efficacy data from GO-FURTHER are limited.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). Results presented from the GO-FURTHER study focus on the ITT analyses; that is, analyses of patients according to the treatment for which they were randomized regardless of the treatment they actually received.

3.6.1 Clinical Response (proportion of patients with an ACR 20 or ACR 50)

A statistically significantly higher proportion of patients in the golimumab + methotrexate treatment group achieved an ACR 20 response (58.5%) at Week 14 compared with the placebo + methotrexate group (24.9%) ([redacted] $P < 0.001$) (Table 8). The proportion of patients who achieved ACR 50 at Week 14 was also greater in the golimumab + methotrexate treatment group compared with the placebo + methotrexate treated group (29.9% versus 8.6%; [redacted] < 0.001). At Week 24, the proportion of patients who achieved ACR 20 was 62.8% in the golimumab + methotrexate treatment group compared with 31.5% in the placebo + methotrexate group ([redacted] $P < 0.001$). Similarly, a significantly greater proportion of patients in the golimumab + methotrexate treatment group achieved ACR 50 response at Week 24 compared with the placebo + methotrexate group (34.9% versus 13.2%, $P < 0.001$, Table 8). ACR 20 and ACR 50 responses for the early escape population were not reported separately at Week 24.

TABLE 8: KEY EFFICACY OUTCOMES

GO-FURTHER				
Outcome	**Week 14**		**Week 24**	
	Placebo + MTX N = 197	**Golimumab 2 mg/kg + MTX N = 395**	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**
ACR 20 Response, n (%)	49 (24.9)	231 (58.5)	62 (31.5)	248 (62.8)
P value	-	< 0.001	-	< 0.001
OR (95% CI)	-	[redacted]	-	[redacted]
ACR 50 Response, n (%)	17 (8.6)	118 (29.9)	26 (13.2)	138 (34.9)
P value	-	< 0.001	-	< 0.001
OR (95% CI)	-	[redacted]	-	[redacted]
Change from Baseline in DAS 28 Score, (mean ± SD)	–0.69 ± 1.35	–1.96 ± 1.23	–0.74 ± 1.43	–2.04 ± 1.38
P value		NR		NR
DAS 28 (CRP) Responders (Moderate or Good), n (%)	79 (40.1)	321 (81.3)	88 (44.7)	320 (81.0)
P value	-	< 0.001	-	< 0.001
Improvement in HAQ-DI from baseline, (mean ± SD)	0.19 ± 0.56	0.50 ± 0.58	0.21 ± 0.55	0.53 ± 0.64
Median (IQR)	0.13 (–0.13 to 0.50)	0.50 (0.13 to 0.88)	[redacted]	[redacted]
P value	-	< 0.001	-	< 0.001
Patients Achieving MCID (≥ 0.25) in HAQ	85 (43.1%)	270 (68.4%)	89 (45.2%)	266 (67.3%)
P value	-	< 0.001	-	< 0.001
Change in SF-36 from Baseline PCS, Mean ± SD	NR	NR	3.82 ± 7.30	8.28 ± 8.32
Median (IQR)	NR	NR	3.30 (-1.60, 7.80)	7.40 (2.50, 13.00)
P value				< 0.001
Change in SF-36 from Baseline MCS, Mean ± SD	NR	NR	1.21 ± 10.07	6.94 ± 10.28
Median (IQR)	NR	NR	1.10 (-3.60, 7.30)	6.40 (0.00, 13.40)
P value		NR		< 0.001

ACR = American College of Rheumatology; CI = confidence interval; CRP = C-reactive protein; DAS = Disease Activity Score, HAQ-DI = Disability Index of the Health Assessment Questionnaire; IQR = interquartile range; MCS = Mental Component Summary; MTX = methotrexate; NR = not reported; OR = odds ratio; PCS = Physical Component Summary; SD = standard deviation; SF-36 = Short Form 36 Health Survey.
Source: GO-FURTHER Clinical Study Report.[7]

Table 9 [redacted]

[redacted]

[redacted]

[redacted] Table 9. [redacted]

TABLE 9: ACR 20 RESPONSE RATE AT WEEK 14 BY SUBGROUPS

	GO-FURTHER			
	Placebo + MTX	Golimumab + MTX	OR (95% CI)	*P* Value
Patients' Age (years)				
< 45, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 45 to < 65, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Patients' Weight (kg)				
≤ 59.6, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
> 59.6 to ≤ 69.6, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
> 69.6 to ≤ 81.15, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 81.15, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP and RF Status				
Anti-CCP–Positive, n, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Anti-CCP–Negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
RF Positive, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
RF Negative, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Prior DMARD Use Other Than MTX				
Used Oral Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
Used no Oral Corticosteroids	[redacted]	[redacted]	[redacted]	[redacted]
No DMARD Used	[redacted]	[redacted]	[redacted]	[redacted]
DMARD Used (1 or 2)	[redacted]	[redacted]	[redacted]	[redacted]
DMARD Used (3+)	[redacted]	[redacted]	[redacted]	[redacted]
Used NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
Used no NSAIDs	[redacted]	[redacted]	[redacted]	[redacted]
Exposure to MTX (mg/kg/week)				
< 17.5, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 17.5 to 20, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]
≥ 20, n, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]

ACR = American College of Rheumatology; CCP = cyclic citrullinated peptide; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; NSAID = Nonsteroidal anti-inflammatory drug; OR = odds ratio; RF = rheumatoid factor.
Source: GO-FURTHER Clinical Study Report.[7]

Table 10 [redacted]. The overall study outcome shows that patients in the golimumab + methotrexate treatment group achieved ACR 20 and ACR 50 responses of 62.8% and 34.9%, respectively (see Table 8), which are higher than the respective scores achieved in the anti-drug antibody positive subgroup. However, response rates were still higher in the anti-golimumab antibody positive subpopulation compared with patients in the placebo + methotrexate group.

TABLE 10: ACR 20 AND ACR 50 RESPONDERS AT WEEK 24, BY ANTIBODY TO GOLIMUMAB STATUS

	GO-FURTHER			
	Placebo + MTX N = 129	Placebo + MTX EE to 2 mg/kg Golimumab + MTX N = 68	2 mg/kg Golimumab + MTX N = 365	Combined[a] 2 mg/kg Golimumab + MTX N = 463
Patients with Appropriate Samples,[b] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Antibodies Positive,[c, d] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ACR 20 Response, n (%)	NA	NA	[redacted]	[redacted]
ACR 50 Response, n (%)	NA	NA	[redacted]	[redacted]
Antibodies Negative,[c,e] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
ACR 20 Response, n (%)	[redacted]	NA	[redacted]	[redacted]
ACR 50 Response, n (%)	[redacted]	NA	[redacted]	[redacted]

ACR = American College of Rheumatology; EE = early escape, MTX = methotrexate; NA = not applicable.
[a] The combined 2 mg/kg golimumab + MTX group comprised patients originally randomized to the golimumab + MTX group plus patients who early escaped from placebo + MTX group at Week 16 to receive 2 mg/kg golimumab + MTX for the remainder of the study.
[b] Patients with appropriate samples had one or more samples obtained after their first study drug administration.
[c] Denominator comprises patients with appropriate samples.
[d] Includes all patients who had at least one positive sample at any time.
[e] Excludes patients who were positive at any time and includes patients whose samples may contain golimumab.

Source: GO-FURTHER Clinical Study Report.[7]

3.6.2 DAS 28 Response Using CRP

The proportion of patients who achieved a good or moderate DAS 28-CRP response at Week 14 was greater in the golimumab + methotrexate treatment group (81.3%) compared with the placebo + methotrexate treatment group (40.1%; $P < 0.001$ [Table 8]). Although a screening CRP level greater than or equal to 1.0 mg/dL was required for inclusion in the study, some patients had CRP levels below the 1.0 mg/dL level at baseline (Week 0). To differentiate these patients, analyses for selected end points, including DAS 28, were also done by baseline CRP levels (less than 1.0 mg/dL and greater than or equal to 1.0 mg/dL). [redacted]. At Week 24, a greater proportion of patients in the golimumab + methotrexate treatment group achieved good or moderate DAS 28-CRP response compared with the placebo + methotrexate treatment group (81.0% versus 44.7%, $P < 0.001$).

Patients in the golimumab + methotrexate treatment group also had greater DAS 28-CRP remission (defined as a DAS 28 value of less than 2.6 at a visit) compared with the placebo + methotrexate

treatment group at Week 14 (15.4% versus 4.6%, *P* < 0.001) and at Week 24 (17.7% versus 5.1%, *P* < 0.001).

3.6.3 Improvements in Health-Related Quality of Life

a) Change in HAQ-DI from baseline

The median improvement in HAQ-DI score from baseline at Week 14 was statistically, clinically, and significantly greater in the golimumab + methotrexate group than in the placebo + methotrexate group (0.5000 compared with 0.1250, respectively, *P* < 0.001 [Table 8]). [redacted]. At Week 14, the proportion of patients with clinically meaningful improvement in HAQ-DI (≥ 0. 25) from baseline was greater in the golimumab + methotrexate treatment group than in the placebo + methotrexate group (68.4% compared with 43.1%, *P* < 0.001).

Improvement in HAQ-DI from baseline to Week 24 was achieved by a statistically and clinically significantly greater proportion of patients in the golimumab + methotrexate treatment group compared with the placebo + methotrexate group (median value of 0.5000 compared with 0.1250, *P* < 0.001. The mean improvements between the two groups were 0.5292 ± 0.63743 versus 0.2054 ± 0.54769, respectively. The proportion of patients with a clinically meaningful improvement in HAD-DI response at Week 24 was 67.3% in the golimumab + methotrexate group compared with 45.2% in the placebo + methotrexate group (*P* < 0.001).

b) Change in SF-36 from baseline

As indicated by the mean ± SD changes from baseline at Weeks 12, 16, and 24, patients in the golimumab + methotrexate group achieved greater SF-36 PCS change scores (5.92 ± [redacted], and 8.28 ± [redacted], respectively) compared with their counterparts in the placebo + methotrexate group (3.19 ± [redacted] and 3.82 ± [redacted], respectively) (Table 8). The median change from baseline in SF-36 PCS scores was statistically and clinically significantly greater in the golimumab + methotrexate group than in the placebo + methotrexate group at Weeks 12, 16, and 24 (*P* < 0.001) for all time points.

Patients in the golimumab + methotrexate group also achieved greater improvements from baseline at Weeks 12, 16, and 24 in the SF-36 MCS scores, with mean ± SD scores of 4.91 ± [redacted] and 6.94 ± [redacted], respectively, compared with 1.46 ± [redacted] and 1.21 ± [redacted], respectively, for the placebo + methotrexate group (Table 8). The median change from baseline in SF-36 MCS scores was statistically and clinically significantly greater in the golimumab + methotrexate group than in the placebo + methotrexate group at Weeks 12, 16, and 24 (*P* < 0.001) for all time points.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol).

3.7.1 Mortality

There was one death through Week 24, which occurred in a patient in the placebo + methotrexate group with a history of hypertension and moderate obesity (weight 112.3 kg). The death was presumed (without autopsy or follow-up information) to be due to a stroke secondary to a hypertensive crisis.

3.7.2 Adverse Events

The study investigators performed safety analyses using the treatment that the patient actually received; however, the CDR review also focuses on the ITT population. The proportion of patients who experienced at least one AE was greater in the golimumab + methotrexate group (47.3%) than in the

placebo + methotrexate group (43.7%) through Week 16, prior to early escape. Infections and infestations were the AEs with the highest incidence (24.3%) through Week 16 in the golimumab + methotrexate group compared with 20.8% in the placebo + methotrexate group. The incidence of AEs was generally similar between the two treatment groups, with the exception of skin and SC tissue disorders in which the incidence for the golimumab + methotrexate group was greater than the placebo + methotrexate group (6.6% and 3.6%, respectively). Upper respiratory tract infection (URTI) was the only AE for which the proportion of affected patients was greater than 5% in both groups (5.1% in the golimumab + methotrexate group and 5.6% in the placebo + methotrexate group).

Through Week 24, a slightly greater proportion (57.2%) of patients in the golimumab + methotrexate group experienced at least one AE compared with 49.2% of patients originally randomized to receive placebo + methotrexate (i.e., including those who early escaped). Safety data at Week 24 were not reported for patients who received placebo + methotrexate only (n = 129). Among the patients who early escaped to receive golimumab + methotrexate at Week 16, the incidence of AEs at Week 24 was 27.9%.

TABLE 11: HARMS

GO-FURTHER							
	Week 16[a]			Week 24			
Adverse Events (AEs), n (%)	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**	**EE[b] to at Week 16 N = 68**	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**	**EE to at Week 16 N = 68**	**Combined[c] 2 mg/kg Golimumab N = 463**
Patients with > 0 AEs	86 (43.7)	187 (47.3)	1 (1.5)	97 (49.2)	226 (57.2)	19 (27.9)	245 (52.9)
Most common AEs							
Infections and Infestations	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
URTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAEs							
Patients with > 0 SAEs	[redacted]	[redacted]	[redacted]	4 (2.0)	19 (4.8)	0	19 (4.1)
Most common SAEs							
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	3 (0.8)	0	3 (0.6)
Musculoskeletal and connective Tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs							
WDAEs	[redacted][d]	[redacted][d]	[redacted]	2 (1.0)	9 (2.3)	0	9 (1.9)
Most Common Reasons							
Infections and Infestations	NR	NR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms							
Injection site Reactions	0	0	0	0	0	0	0
Hypersensitivity Reactions				1 (0.3)	0	0	1 (0.2)

GO-FURTHER							
	Week 16[a]			Week 24			
Adverse Events (AEs), n (%)	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**	**EE[b] to at Week 16 N = 68**	**Placebo + MTX N = 197**	**Golimumab 2 mg/kg + MTX N = 395**	**EE to at Week 16 N = 68**	**Combined[c] 2 mg/kg Golimumab N = 463**
Infections (TB or Hepatitis)	0	0	0	0	0	0	0
Hepatotoxicity	0	0	0	0	0	0	0
Malignancy	0	0	0	0	1 (0.3)	0	1 (0.2
				[redacted]	[redacted]	[redacted]	[redacted]
Lymphocytes (decreased)	NR	NR		N = 196 13 (6.6)	N = 391 17 (4.3)	N = 66 1 (1.5)	N = 457 18 (3.9)
Golimumab antibodies positive patients[e]	NR	NR	NR	0	N = 373 13 (3.5)	N = 67 0	N = 440 13 (3.0)

AE = adverse event; EE = early escape, MTX = methotrexate, NR = not reported; SAE = serious adverse event; TB = tuberculosis; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Safety data were reported at Week 16 prior to early escape, except WDAEs which were reported at Week 14.

[b] Patients who early escaped at Week 16 started receiving golimumab at Week 16.

[c] The combined 2 mg/kg golimumab + MTX group comprised patients originally randomized to the golimumab + MTX group plus patients who early escaped from placebo + MTX group at Week 16 to receive 2 mg/kg golimumab + MTX for the remainder of the study.

[d] These data were reported at Week 14. However, in the interval between Week 14 and Week 24, no additional patients in the placebo + MTX group discontinued, but one additional patient in the golimumab + MTX group discontinued study drug due to AE.

[e] Patients who either had antibodies to golimumab at some time point following their first study drug administration or who had one or more samples obtained after their last study drug administration.

Source: GO-FURTHER Clinical Study Report.[7]

The incidence of AEs was generally similar between the two treatment groups. The highest incidence of AEs was infections and infestations, which occurred in [redacted] of patients randomized to the golimumab + methotrexate group compared with [redacted] randomized to the placebo + methotrexate group and [redacted] in the early escape subgroup. URTIs were the most frequently occurring AEs, with [redacted] the golimumab + methotrexate group compared with [redacted] in the placebo + methotrexate group and [redacted] in the early escape group. Table 11 provides more details, including data for patients who early escaped from the placebo + methotrexate group at Week 16 to receive golimumab + methotrexate, and data for the combined golimumab + methotrexate group.

3.7.3 Serious Adverse Events

The proportion of patients with at least one SAE reported prior to early escape at Week 16 was [redacted] in the golimumab + methotrexate group and [redacted] in the placebo + methotrexate group. Through Week 24, the proportion of patients with one or more SAEs was 4.8% among patients originally randomized to receive golimumab + methotrexate, compared with 2.0% in the placebo + methotrexate group (Table 11). There were no SAEs reported among patients in the early escape subgroup. Thus, the proportion (4.1%) of SAE in the combined golimumab + methotrexate group is slightly lower because the included early escape patients had no SAEs. No specific pattern of association between SAEs and golimumab was identified.

3.7.4 Withdrawals Due to Adverse Events

In the golimumab + methotrexate group, 2.8% discontinued treatment because of an AE through Week 16, compared with 0.5% of those in the placebo + methotrexate group (Table 11). The AE that led to discontinuation of study in the latter group was [redacted]. AEs leading to discontinuation of study in the golimumab + methotrexate group included [redacted].

3.7.5 Notable Harms

There were no incidences of injection-site or hypersensitivity reactions, tuberculosis (TB), hepatitis, serious opportunistic infections, or hepatotoxicity reported in this study. One patient in the golimumab + methotrexate group had a malignancy (breast cancer) through Week 24. There were no incidences of any notable harms in the patients who early escaped (Table 11).

4. DISCUSSION

4.1 Summary of Available Evidence

GO-FURTHER was a multi-centre, randomized, double-blind, placebo-controlled trial in which the clinical efficacy of IV administration of golimumab 2 mg/kg + methotrexate was compared with placebo + methotrexate in adult patients with active RA despite prior methotrexate therapy. The primary end point of the study was ACR 20 response at Week 14, which was achieved by a statistically significantly greater proportion of patients in the golimumab + methotrexate group (58.5%) compared with patients in the placebo + methotrexate group (24.9%, $P < 0.001$). There is no validated MCID for ACR scores.

The main SEs tested were DAS 28-CRT, HAQ-DI, and ACR 50 at Weeks 14 and 24. A significantly greater proportion of patients in the golimumab + methotrexate group achieved improvement in all indexes compared with those in the placebo + methotrexate group. In addition to the HAQ-DI measure, SF-36 (version 2) scores were also determined to assess patients' HRQoL. For both HAQ-DI and SF-36 scores, patients in the golimumab + methotrexate group demonstrated a clinically and statistically significantly greater improvement, achieving the respective MCIDs in all comparisons (Table 8) [redacted] (see Table 9 and Table 10) [redacted].

The manufacturer submitted a network meta-analysis (NMA) comparing the efficacy and safety of IV golimumab (Simponi IV) with IV infliximab, IV abatacept, and SC golimumab in patients with moderate to severe RA who had had an inadequate response to methotrexate (Appendix 7: Summary and Critical Appraisal of Manufacturer-Submitted Network Meta-Analysis). There was limited justification for excluding SC formulations of other BRMs used in the treatment of RA. Other limitations of the NMA include differences in baseline methotrexate doses between the studies (with doses ranging from 6 mg per week to 30 mg per week in the individual randomized controlled trials [RCTs]), and the lack of long-term comparative data for selected outcomes. Overall, the NMA showed no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, and SC golimumab in terms of measured outcomes (ACR 20, ACR 50, ACR 70, HAQ-DI, and DAS 28) at all relevant time points. There was no difference between IV golimumab and its comparators with respect to WDAEs. This is in consonance with both a Cochrane review[27] and a therapeutic review by CADTH of BRMs,[28] which also found no statistically significant differences between the drugs.

No members of the responding patient groups had had experience with Simponi IV, although they expect that this route of administration will have a similar clinical success rate to that of Simponi administered through SC injection; they noted that some patients may have difficulty self-injecting. The patient groups emphasized that having a range of treatment options increases the likelihood that patients will have better access to affordable and effective medications with fewer side effects.

Key limitations of the GO-FURTHER study included the early escape design, in which patients in the placebo group had an option to cross over to the golimumab + methotrexate group at Week 16 (two weeks after the primary end point assessment) if they were not responding to placebo. Although the early escape design is widely used in studies of interventions for RA based on ethical considerations and is accepted by regulatory agencies, it may introduce bias in subsequent efficacy and safety assessments. The statistical analysis plan did not explicitly state that patients who entered early escape were coded as non-responders for the Week 24 outcome assessments. ACR 20 and ACR 50 responses for the early escape population were not separately reported at Week 24. Therefore, it is uncertain the extent to which the early escape population influenced the reported ACR 20 and ACR 50 outcomes at Week 24.

As well, the median dose (15 mg per week) of background methotrexate at baseline was below the recommended optimal dose range of between 20 mg per week and 25 mg per week. This raises questions about whether patients had had an adequate response to methotrexate therapy prior to initiating study treatments. It is not clear what might have been the effect of increased methotrexate doses in some of these patients. The study required patients to be seropositive for RF and/or anti-CCP to qualify for entry, which limits the generalizability of the findings because a substantial number of RA patients with moderately to severely active disease are likely to be seronegative in clinical practice. Furthermore, there were no head-to-head comparisons between IV golimumab and other BRMs, including SC golimumab. The manufacturer submitted an indirect comparison of IV golimumab versus IV infliximab and abatacept as well as SC golimumab, which had numerous limitations including no clear explanation for the exclusion of SC formulations of other BRMs used in the treatment of RA. Hence, there is limited comparative evidence clearly defining the place in therapy for IV golimumab, including where it fits relative to the SC formulation.

4.2 Interpretation of Results

4.2.1 Efficacy

For this review, both the primary end point and the three main secondary end points in the GO-FURTHER study were considered as key efficacy outcomes. Golimumab 2 mg/kg + methotrexate demonstrated greater efficacy than placebo + methotrexate as determined by ACR 20 responders at Week 14 (study primary end point; 58.5% versus 24.9%; [redacted] $P < 0.001$). The proportion of patients achieving an ACR 20 response through Week 24 was also statistically significantly greater in the golimumab + methotrexate group than in the placebo + methotrexate group (62.8% versus 31.5%; [redacted] $P < 0.001$). Therefore, the evidence suggests that IV golimumab is statistically significantly more efficacious than placebo in treating patients with moderately to severely active RA when used in combination with methotrexate, through to 24 weeks. Both the GO-FORWARD study and GO-AFTER extension study, which compared golimumab 50 mg SC + methotrexate to placebo + methotrexate for RA in methotrexate-experienced patients, reported similar superior efficacy results in favour of golimumab at Week 14 (55.1% versus 33.1% and 35.3% versus 18.1%, respectively).[29,30]

[redacted]

Table 9, [redacted] It must be noted that the populations in these subgroups, which showed no statistically significant differences between the study groups, were relatively small, thereby making the detection of relevant differences difficult.

[redacted].

Statistically significantly greater improvements were observed in the MCS and PCS scores of the SF-36 among golimumab-treated patients compared with those in the placebo group at Weeks 12, 16, and 24.

In addition, patients in the golimumab + methotrexate group fared better than patients in the placebo + methotrexate group in DAS 28 scores (81.3% versus 40.1%), median HAQ-DI (0.5000 versus 0.1250), and ACR 50 response (34.9% versus 13.2%), with $P < 0.001$ in all comparisons. The latter is in agreement with a Cochrane review that reported that, compared with patients treated with placebo + methotrexate, patients treated with golimumab + methotrexate were 2.6 times more likely to reach ACR 50 (relative risk [RR], 2.57; 95% CI, 1.3 to 4.9; $P = 0.005$; number needed to treat (NNT) = 5, 95% CI, 2 to 20).[27] The reported outcomes for golimumab 2 mg/kg IV + methotrexate are in agreement with outcomes reported for the golimumab 50 mg SC + methotrexate, without substantial differences between them. However, there was no head-to-head comparison between IV golimumab and SC golimumab, making it uncertain as to which of the two formulations of golimumab is better for the study population. The manufacturer conducted a Bayesian NMA based on RCTs to compare IV golimumab with IV infliximab, abatacept, and SC golimumab. Overall, the NMA showed no statistical differences in efficacy between IV golimumab and its indirect comparators in terms of the specified ACRs, HAQ-DI, and DAS 28 outcomes at all time points of the evaluation (APPENDIX 6: SUMMARY OF COMPARATORS). Therefore, there is limited evidence suggesting any advantage of one formulation of golimumab over the other for the treatment of RA. Weeks 100 and 112 efficacy outcomes suggest that the ACR response achieved with golimumab 2 mg/kg administered IV + methotrexate at Week 24 were at least maintained through the extension phase of the GO-FURTHER study (APPENDIX 5: SUMMARY OF EXTENSION STUDIES). However, there was no evidence provided on the efficacy of IV golimumab in patients with inadequate response to other TNF-alpha antagonists or other BRMs.

4.2.2 Harms

All patients were monitored from baseline through Week 24 and assessed for vital signs, AEs, and infusion reactions. TB evaluations were performed, and samples were collected for routine laboratory analyses and determination of the presence of antinuclear antibodies.

Overall, treatment was well tolerated in both the golimumab + methotrexate group and the placebo + methotrexate group of the trial through Week 16 and Week 24, with the proportion of patients who reported an AE being comparable in the two groups at both time points (47.3% compared with 43.7%, and 52.9% compared with 49.2%, respectively). This is in consonance with findings from a Cochrane review of four RCTs that evaluated golimumab for the treatment of RA; the review reported that, compared with patients treated with placebo + methotrexate, patients treated with golimumab + methotrexate were no more likely to have an AE (RR 1.1; 95% CI, 0.9 to 1.2; $P = 0.44$) and were 0.5 times as likely to withdraw from their respective studies (95% CI, 0.3 to 0.8; $P = 0.005$).[27]

Infections and infestations (predominantly URTI, urinary tract infections [UTI], and nasopharyngitis) were the most commonly reported SOC of AEs in the placebo + methotrexate group and in the golimumab + methotrexate group. TNF-alpha plays a role in infection control by orderly recruiting the necessary cells (e.g., granulomas and macrophages) in the host defence mechanisms to sequester and destroy pathogens.[31] Therefore, disruption of this defence mechanism by anti-TNF drugs like golimumab makes patients susceptible to infections, including serious and life-threatening reactivation of latent TB and hepatitis B; clinically important active infections such as severe sepsis, TB, and opportunistic infections are listed in the product monograph as contraindications for the use of golimumab.[32] However, no cases of TB, hepatitis, or serious opportunistic infections were reported in this trial. Nevertheless, measures to screen and exclude high-risk patients from using golimumab should be taken as recommended.[32]

One treatment-related malignancy was reported through Week 24, involving a case of breast cancer in a golimumab-treated patient. Concern about malignancies in patients treated with TNF-alpha inhibitors like golimumab stems from the ability of TNF-alpha to lyse tumour cells, suggesting the possibility that inhibition of this cytokine might increase the risk of malignancy.[31] In fact, more patients receiving anti-TNF therapy have been reported to develop malignancies (including leukemia, lymphoma, and non-lymphoma malignancy) than the general population.[31]

The incidence of markedly abnormal hematology values was small and was balanced between the combined golimumab + methotrexate group and the placebo + methotrexate group. [redacted] Hematologic AEs including pancytopenia, leukopenia, neutropenia, and thrombocytopenia have been reported in patients receiving TNF blockers.

The overall incidence of antibodies to golimumab was low. Thirteen patients (3%) in the combined golimumab + methotrexate group (n = 440) who had one or more samples obtained after their first study drug administration were classified as positive for antibodies to golimumab through Week 24. A similar proportion (3.7%) of antibody-positive patients was reported for SC golimumab in the GO-AFTER study, while the study by Kay et al. reported a higher incidence (14.8 %).[30] [redacted] Serum golimumab concentrations were generally lower among antibody-positive patients than among antibody-negative patients. However, given the small number of patients who were antibody-positive, it was difficult to make a definitive conclusion about the correlation between antibody positivity and the efficacy of therapy.

The manufacturer's indirect comparison, including data for discontinuations due to AEs, was available for 11 RCTs (APPENDIX 6: SUMMARY OF COMPARATORS). Follow-up durations varied between studies, ranging from 14 weeks to one year in length. There were no differences between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab for this outcome. No analysis was conducted for AEs or SAEs in the NMA; therefore, the comparative risks of SAEs such as infection and malignancy are unknown.

5. CONCLUSIONS

At the end of 14 weeks in the GO-FURTHER study, golimumab 2 mg/kg + methotrexate administered IV demonstrated statistically significantly better efficacy than placebo + methotrexate in achieving the primary outcome; that is, the proportion of ACR 20 responders. This superior response in favour of the golimumab group was also observed at Week 24. Other key efficacy outcomes, namely ACR 50, DAS 28, HAQ-DI, and SF-36 scores were also statistically significantly better in the golimumab 2 mg/kg + methotrexate group compared with the placebo + methotrexate group at both Week 14 and Week 24. HAQ-DI score as well as the PCS and MCS scores of SF-36 achieved their respective MCIDs. IV golimumab was generally well tolerated, with an overall safety profile consistent with that of SC golimumab and other TNF-alpha blockers in comparable RA patient populations. Patients randomized to the golimumab + methotrexate group had a slightly greater incidence of AEs and SAEs than those randomized to the placebo + methotrexate group. There was no incidence of serious opportunistic infections in either group and there was one case of malignancy (breast cancer) in a golimumab-treated patient reported through Week 24. However, efficacy and safety outcomes assessed at 24 weeks are likely influenced by the early escape design of the study, potentially overestimating the effect of golimumab versus placebo. Without head-to-head trials, it is difficult to draw conclusions with respect to the relative efficacy and safety of IV golimumab versus other BRMs, including SC golimumab, in patients with moderately or severely active RA with an inadequate response to methotrexate.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups representing people with rheumatoid arthritis (RA) provided input.

Arthritis Consumer Experts (ACE) is a national non-profit organization committed to informing, educating and empowering people with arthritis to help them control their disease and improve quality of life as well as providing evidence-based information and research decision-making training to people with arthritis to help them participate meaningfully in research organizations and government consultation. ACE is funded by unrestricted grants from public and private sectors and individual donations. It has received unrestricted grants from several pharmaceutical companies including Janssen Inc., AbbVie Corporation, Amgen Canada, Arthritis Research Centre of Canada, Bristol-Myers Squibb Canada, Canadian Institutes of Health Research, GlaxoSmithKline, Hoffman-La Roche Canada Ltd., Pfizer Canada, and Takeda Canada, Inc. but declares no conflicts of interest in the preparation of their submission.

The Arthritis Society is a national charity that provides information and programs for people with arthritis, funding for research projects investigating the causes of and potential treatments for arthritis, and funding to train rheumatologists. The Arthritis Society receives the vast majority of funding from individual donors. Over the past 12 months it has received funding from pharmaceutical manufacturers including: Abbvie, Amgen, Bayer, Bristol Myers Squibb, Celgene, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche and UCB. The Arthritis Society and Janssen Inc. are members of the Arthritis Alliance of Canada, and the President and CEO of The Arthritis Society is also the Chair of the Arthritis Alliance of Canada. No declaration regarding conflict of interest in the preparation of the submission was made.

2. Condition-Related and Current Therapy-Related Information

This information was collected through online surveys, one-to-one conversations and correspondence with patients and caregivers, and printed sources.

RA is a chronic, disabling autoimmune condition that greatly impacts every aspect of patients' lives. RA causes severe inflammation leading to joint destruction, and people with RA experience daily debilitating pain and fatigue. Sleep is often restless, disrupted due to pain, and insufficient to address the constant fatigue. Swollen and stiff joints restrict range of motion and dexterity, which can impact daily activities including personal hygiene, dressing, walking, shopping, meal preparation, housework, and child care. People with RA become unable to participate in the activities they enjoy, such as sports, travelling, and socializing 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 no longer wearing high heels or shirts with buttons, or changing how they exercise. They can suffer from depression, decreased libido, feelings of frustration and loss of independence, and they may have to withdraw from employment or educational opportunities.

Caregivers of those living with RA also face significant demands. They may need to administer medications by injection and thus may have concerns about correct administration and 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 the need for flexibility were also identified as significant challenges for caregivers when they need to care for patients incapacitated by adverse effects. Support groups for patients and their caregivers organized by health care facilities are an important resource for some people.

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 partially 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. This is especially a concern for young patients who will require treatment for the rest of their lives.

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, feeling short of breath, rapid heart rate, loss of appetite, dark urine, clay-coloured stools, and jaundice. Some patients may have difficulty self-injecting. Requiring frequent injections makes travel difficult as the medication needs to be kept chilled, bringing needles through security checkpoints is challenging, and coverage of a larger treatment supply may be restricted by drug plans, thus hindering extended trips. RA medications are very expensive, and thus 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 medications with fewer side effects.

3. Related Information About the Drug Being Reviewed

No members of the responding patient groups had experience with Simponi IV (intravenous), although they expect that this route of administration will have a similar clinical success rate to that of Simponi administered through SC. One patient commented that there are infection-related adverse effects associated with Simponi IV, and that the side effect profile of this treatment is similar to other biologics. Patients expect that Simponi IV, with its less frequent intravenous dosing, short infusion duration, and minimal infusion reactions, will provide another RA treatment option. With less frequent administration, patients anticipate fewer visits to the doctor or pharmacist, corresponding to fewer absences from work and therefore increased work productivity. Travel planning will be easier, and the IV administration may also alleviate the fear or discomfort some patients experience with self-injection. General expectations of new RA treatment options are improved quality of life for patients and alleviated stress for caregivers.

4. Additional Information

No additional information was reported.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	January 28, 2014
Alerts:	Weekly search updates until June 18, 2014
Study Types:	No search filters were applied
Limits:	No date or language limits were used

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(simponi* or golimumab* or cnto148 or cnto-148).mi,tn,ti,ab,ot,rn,hw,nm.
2	476181-74-5.rn,nm.
3	1 or 2
4	exp arthritis rheumatoid/
5	((chronic or rheumatic) adj2 (polyarthrit* or poly-arthrit*)).ti,ab.
6	(arthritis deformans or arthrosis deformans or Beauvais disease or rheumarthrit* or rheumatism or rheumatic or RA).ti,ab.
7	((still* or felty* or caplan* or sicca* or sjogren* or chauffard*) adj2 (syndrome* or disease*)).ti,ab.
8	((rheumatoid or inflammatory or rheumatic) adj2 (arthriti* or nodule*)).ti,ab.
9	4 or 5 or 6 or 7 or 8
10	3 and 9
11	10 use pmez
12	(simponi* or golimumab* or cnto148 or cnto-148).ti,ab.
13	*golimumab/
14	12 or 13
15	*rheumatoid arthritis/
16	((chronic or rheumatic) adj2 (polyarthrit* or poly-arthrit*)).ti,ab.
17	(arthritis deformans or arthrosis deformans or Beauvais disease or rheumarthrit* or rheumatism or rheumatic or RA).ti,ab.
18	((still* or felty* or caplan* or sicca* or sjogren* or chauffard*) adj2 (syndrome* or disease*)).ti,ab.
19	((rheumatoid or inflammatory or rheumatic) adj2 (arthriti* or nodule*)).ti,ab.
20	15 or 16 or 17 or 18 or 19
21	14 and 20
22	21 use oemezd
23	11 or 22
24	remove duplicates from 23

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:	January 2014
Keywords:	Simponi, golimumab, rheumatoid arthritis
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Kremer J, et al. Arthritis Rheum [Internet]. 2010 Apr [cited 2014 Feb 3];62(4):917-28.[33] Available from: http://onlinelibrary.wiley.com/doi/10.1002/art.27348/pdf	Inappropriate population and outcome
Onuora S. Nat Rev Rheumatol. 2012 Aug;8(8):439.[34]	Poster

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and the minimal clinically important differences (MCIDs) of the following outcome measures:

- American College of Rheumatology (ACR) 20 and ACR 50
- Disease Activity Score (DAS) 28 C-reactive protein (CRP)
- Disability Index of the Health Assessment Questionnaire (HAQ-DI)
- Short Form 36 Health Survey (SF-36)

Findings

ACR criteria, DAS 28-CRP, HAQ-DI, and SF-36 are briefly summarized in Table 12.

TABLE 12: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
ACR 20 ACR 50	ACR 20 and ACR 50 responses represent at least a 20% and 50% improvement, respectively in tender and swollen joint counts and three of the five additional criteria. Patient global assessment of disease activity; Physician global assessment of disease activity; Patient assessment of pain; HAQ; CRP or ESR.	Yes	Unspecified	van Riel PL[35] Cohen[36] Bansback[37] ACR criteria[38] Chung[39]
DAS 28-CRP	DAS 28 is an abbreviated version of the DAS, based on a 28-joint count that omits the feet and ankle joints.	Yes	Unspecified	Wells[20] Crowson[40]
HAQ-DI	The HAQ Disability Index (HAQ-DI) is the disability assessment component of the HAQ.	Yes	0.22	Bruce[19,41]
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 zero to 100, with an increase in score indicating improvement in health status.	Yes	2.5 to 5	Gallagher[42] Hays[4] Samsa[5] Strand[6]

ACR = American College of Rheumatology; CRP = C-reactive protein; DAS = Disease Activity Score; HAQ = Health Assessment Questionnaire; HAQ-DI = The HAQ Disability Index; MCID = minimal clinically important difference; MCS = Mental Component Summary; PCS = Physical Component Summary.

American College of Rheumatology Response Criteria

ACR criteria for assessing joint status was initially developed for patients with rheumatoid arthritis (RA).[35] The ACR joint count for RA assesses 68 joints for tenderness and 66 joints for swelling. ACR 20 or ACR 50 responses represent at least a 20% or 50% improvement in tender and swollen joint counts and in three of the five additional criteria.[36] The ACR 20 is most commonly used as the primary end point in RCTs evaluating biologics used in RA. The Food and Drug Administration considers ACR 20 a well-validated composite end point for assessing the signs and symptoms of RA.[43] ACR 50 is often cited as evidence of a more robust treatment effect. The limitation associated with ACR criteria is that it only

indicates the change from baseline; it does not reflect the final level of disease severity that the patient attains.[37,38] No MCID exists for ACR criteria.

Disease Activity Score

DAS is a measure of disease activity and includes the Ritchie Articular Index (0 to 78) that is performed on 53 joints, a 44-joint swollen joint count (0 to 44), CRP or ESR, and a general health item using a visual analogue scale (VAS) (0 to 100).[44] DAS 28 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 only had inflammation at the feet and ankles would be counted as being in remission.[45] The DAS components correlate well with each other and with the ACR criteria.[46-49] CRP has been used to calculate the DAS 28.[20,40] The formula used to calculate the DAS 28-CRP[17] is as follows:

DAS 28-CRP = 0.56 × SQRT (TEN28) + 0.28 × SQRT (SW28) + 0.36 × ln (CRP+1) + 0.014 × GH + 0.96, where SQRT = square root, TEN28 = tender joint 28, SW28 = swollen joint 28, ln [CRP+1] is the natural logarithm of [CRP value + 1, CRP unit: mg/L], and GH = general health measured by Patient's Global Assessment of Disease Activity on a VAS of 100 mm.

A DAS 28 score indicates an absolute level of disease activity, with a score of 5.1 or greater indicating a high disease activity state, while DAS 28 < 3.2 indicates a low disease activity state and DAS 28 < 2.6 indicates clinical remission (Table 17).[20,24,50] Overall, the DAS 28-CRP correlates well with DAS 28-ESR—both are validated measures for assessing disease activity in RA.[20-24] However, studies[21-23,23-25] have shown that the DAS 28-CRP score value is usually lower than the DAS 28-ESR score.[21-25] The difference (DAS 28-CRP minus DAS-ESR) ranges from –0.2[21] to –0.8.[25] Because the definitions of remission (< 2.6) are the same for both DAS 28-CRP and DAS-ESR, it was concluded that DAS 28-CRP underestimates disease activity and overestimates the improvement in disease activity and the remission rate compared with DAS 28-ESR. It was also suggested that DAS 28-CRP should be evaluated using different criteria from those used for DAS 28-ESR.[23] Furthermore, the European League Against Rheumatism (EULAR) recommended that the clinical implications of the DAS 28 score (such as good response, moderate response, or no response) should be determined based on the baseline DAS 28 scores[51] (see Table 13). Finally, no MCID exists for DAS 28 change scores.

TABLE 13: THE EULAR IMPROVEMENT RESPONSE CRITERIA (DAS 28)

Baseline DAS 28 Score	DAS 28 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 28 = Disease Activity Score 28 items; EULAR = European League Against Rheumatism.
Source: Matsui T.[23]

Health Assessment Questionnaire and HAQ Disability Index

The HAQ has been widely validated in patients with RA.[52,53] The full HAQ collects data on five generic, patient-centred health dimensions: to avoid disability, to be free of pain and discomfort, to avoid adverse treatment effects, to keep dollar costs of treatment low, and to postpone death.[19]

The 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 the patient's physical functional status:

dressing, arising, eating, walking, hygiene, reach, grip, and common activities.[19,41] For each of these categories, patients report the amount of difficulty they have in performing specific activities on a scale that ranges 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.[54,55] A number of investigators have suggested that the MCID is 0.22; however, differences as small as 0.10 have been suggested as being clinically important.[19]

Short-Form 36

The Short-Form 36 (SF-36) is a generic HAQ that has been used in clinical trials to study the impact of chronic disease on HRQoL. 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.[42] 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 typically ranges from 2.5 points to 5 points.[4-6]

Summary

The ACR criteria and DAS 28 CRP are commonly used and accepted measures of disease activity. The ACR 20 and ACR 50 indicate 20% and 50% improvement from baseline, respectively. ACR 20 is most commonly reported in clinical trials; however, ACR 50 is often cited as evidence of a more robust treatment effect. The DAS 28-CRP uses a 28-joint count that does not include the feet or ankles, which is a limitation of the scale. DAS 28 measures an absolute rather than relative level of disease activity and thus may be preferred to the ACR responder rates. The DAS 28 components correlate well with each other and with the ACR components. However, it has been reported that DAS 28-CRP underestimates disease activity and overestimates the improvement in disease activity and the remission rate compared with DAS 28-ESR. 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 scores range 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 as being clinically important. The SF-36 is a generic HAQ that has been used in clinical trials to study the impact of chronic disease on HRQoL. The suggested MCID for either the PCS or MCS of the SF-36 typically ranges from 2.5 points to 5 points.[4-6]

APPENDIX 5: SUMMARY OF EXTENSION STUDIES

Objectives

To summarize the clinical efficacy and harms of intravenous (IV) administration of golimumab 2 mg/kg + methotrexate through 112 weeks in patients with active rheumatoid arthritis (RA) despite prior methotrexate therapy, reported in the extension period of the included study (GO-FURTHER).[17]

Study Characteristics

At the end of the 24-week, placebo-controlled phase of GO-FURTHER, patients originally randomized to placebo could cross over to treatment with golimumab and continue into the extension phase out to Week 112. This was also true for placebo patients meeting the early escape criteria at Week 16 who crossed over to golimumab treatment at that time point of the placebo-controlled phase. Patients and investigators continued to be blinded through Week 112.[17] The overall duration of GO-FURTHER (placebo plus extension phases) was 112 weeks from randomization, which included 100 weeks of treatment plus an additional 12 weeks of follow-up for safety and health-related quality of life (HRQoL).[17] The disposition of patients through Week 112 is summarized in Table 14. [redacted]

The average duration of follow-up and average exposure are summarized in Table 16. Through Week 112, 481 (81.3%) of the 592 randomized patients completed study drug administrations and post-treatment follow-up; five (0.8%) patients completed study drug administrations but not post treatment follow-up; and 106 (17.9%) discontinued study drug administration before Week 100, mainly due to adverse events (AEs). Only 12 (2%) patients discontinued the trial due to lack of efficacy through Week 112.

TABLE 14: NUMBER OF PATIENTS WHO DISCONTINUED STUDY DRUG OR STUDY AND/OR POST-TREATMENT FOLLOW-UP THROUGH WEEK 112 (RANDOMIZED PATIENTS)

	Placebo + MTX[a]	GO 2 mg/kg + MTX	Total
Randomized Patients	[redacted]	[redacted]	592
Did not Discontinue Study Drug	[redacted]	[redacted]	486 (82.1%)
Discontinued Study Drug	[redacted]	[redacted]	106 (17.9%)
Reason for Discontinuing Study Drug			
Death	[redacted]	[redacted]	[redacted]
Lost to Follow-up	[redacted]	[redacted]	[redacted]
Withdrawal of Consent	[redacted]	[redacted]	[redacted]
Adverse Event	[redacted]	[redacted]	44 (7.4%)
Lack of Efficacy	[redacted]	[redacted]	12 (2.0%)
Protocol Violation	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Post-treatment Follow-up	[redacted]	[redacted]	[redacted]
Completed Post-treatment Follow-up	[redacted]	[redacted]	[redacted]
Did not Complete Post-treatment Follow-up	[redacted]	[redacted]	[redacted]
Did not Participate in Post-treatment Follow-up	[redacted]	[redacted]	[redacted]

GO = golimumab; MTX = methotrexate; SD = standard deviation.
[a] Patients who early escaped at Week 16 started receiving golimumab at Week 16. All patients started receiving golimumab at Week 24.
Source: GO-FURTHER Clinical Study Report.17

TABLE 15: SUMMARY OF CUMULATIVE DOSE OF GOLIMUMAB RECEIVED THROUGH WEEK 112 (TREATED PATIENTS)

	Placebo + MTX→GO + MTX at Week 16	Placebo + MTX→GO + MTX at Week 24	GO + MTX at Week 112	GO Combined at Week 112
Patients Treated, N	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Dose (mg)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Dose per kg (mg/kg)				
N	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]

Source: GO-FURTHER CSR.[17]
GO = golimumab; MTX = methotrexate; SD = standard deviation.

TABLE 16: TREATMENT GROUPS, AVERAGE DURATION OF FOLLOW-UP, AND AVERAGE EXPOSURE THROUGH WEEK 112

	Placebo + MTX	Placebo + MTX →GO + MTX at Week 16	Placebo + MTX →GO + MTX at Week 24	GO + MTX	GO Combined
Patients Treated, N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Duration of Follow-up (Weeks)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean Exposure (Number of Administrations)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

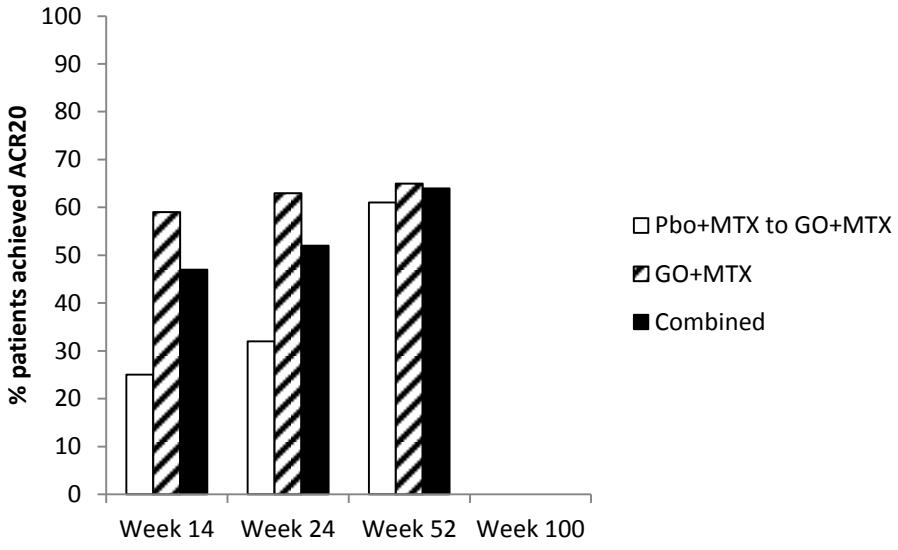
GO = golimumab; MTX = methotrexate.
Source: GO-FURTHER Clinical Study Report.[17]

Results

Efficacy

At Week 100, the proportions of patients achieving ACR 20 and ACR 50 responses were 68.1% and 43.8%, respectively. ACR 20 and ACR 50 response rates from Week 14 through Week 100 are presented in Figure 3 and Figure 4, respectively. Eighty-two per cent of patients achieved a moderate or good Disease Activity Score (DAS) 28 C-reactive protein (CRP) response. HRQoL measured with Short-Form 36 Health Survey (SF-36) was also improved at Week 112. The level of functional ability measured with Health Assessment Questionnaire (HAQ) was improved as well (Table 17).

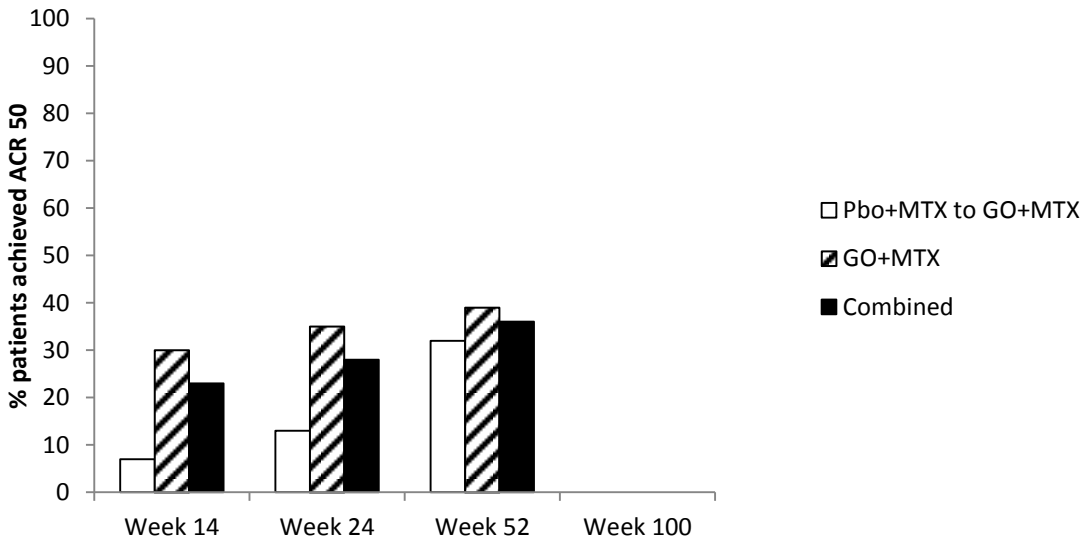
FIGURE 3: PERCENTAGE OF PATIENTS WHO ACHIEVED ACR 20 FROM WEEK 14 THROUGH WEEK 100



ACR = American College of Rheumatology; GO = golimumab; MTX = methotrexate; Pbo = placebo.

Note: Confidential data regarding the percentage of patients Achieving ACR 20 at Week 100 were removed from Figure 3 at the manufacturer's request.

FIGURE 4: PERCENTAGE OF PATIENTS WHO ACHIEVED ACR 50 FROM WEEK 14 THROUGH WEEK 100



ACR = American College of Rheumatology; GO = golimumab; MTX = methotrexate; Pbo = placebo.
Note: Confidential data regarding the percentage of patients Achieving ACR 50 at Week 100 were removed from Figure 4 at the manufacturer's request.

TABLE 17: SUMMARY OF THE CLINICAL RESPONSE AT WEEK 100 AND DAS 28, SF-36, AND HAQ AT WEEK 112

	Placebo + MTX → GO + MTX (n = 197)	GO + MTX (n = 395)
ACR 20 at Week 100	[redacted]	[redacted]
ACR 50 at Week 100	[redacted]	[redacted]
DAS 28 (CRP) Moderate or Good Responses at Week 100	[redacted]	[redacted]
HAQ Scores at Week 100		
Median Improvement	NR	0.5
Achieved ≥ 0.25 HAQ Improvement	NR	67.3%
SF-36 PCS Mean Scores Change from Baseline at Week 112	[redacted]	[redacted]
SF-36 MCS Scores Change from Baseline at Week 112	[redacted]	[redacted]

ACR = American College of Rheumatology; DAS = Disease Activity Score; GO = golimumab; HAQ = Health Assessment Questionnaire, MCS = Mental Component Summary; MTX = methotrexate; PCS = Physical Component Summary; SD = standard deviation; SF-36 = Short Form 36 Health Survey.
Source: GO-FURTHER Clinical Study Report.[17]

Harms

The main AEs, serious adverse events (SAEs), and mortality are summarized in Table 18**:** Six deaths were reported through Week 112. One death (cerebrovascular accident) was reported through Week 24 in a patient in the placebo + methotrexate group, and the second death (pneumonia and myocardial infarction) was reported through Week 52 in a patient in the golimumab 2 mg/kg + methotrexate group. The remaining four deaths occurred between Week 52 and Week 112. Three of the four deaths were

due to infections, and the cause of the other death was unknown. It was reported that the pattern of mortality does not appear significantly different from the mortality patterns reported for other similar biologic drugs. Overall, these findings at Week 112 are consistent with the safety profile reported through Week 52 and represent no new safety signals or increased pattern of events.

TABLE 18: SUMMARY OF ADVERSE EVENTS REPORTED IN THE GOLIMUMAB COMBINED GROUP THROUGH WEEK 112

	GO combined group (N = 584)
Deaths (N)	6
SAEs (≥ 1%) (%)	18.2%
SOC with the Highest Frequency of SAEs: Infections and Infestations	5.5%
Major Individual SAEs: %	
Pneumonia	[redacted]
UTI	[redacted]
Erysipelas	[redacted]
SOCs With an Incidence of AEs > 10%	
Infections and Infestations	[redacted]
Musculoskeletal and Connective Tissue Disorders	[redacted]
Gastrointestinal Disorders	[redacted]
Skin and Subcutaneous Tissue Disorders	[redacted]
Nervous System Disorders	[redacted]
Individual AEs (> 10%)	
URTI	[redacted]
Individual AEs (> 5%)	
Bronchitis	[redacted]
Nasopharyngitis	[redacted]
UTI	[redacted]
Pharyngitis	[redacted]
Alanine Aminotransferase Increased	[redacted]
Headache	[redacted]
Hypertension	[redacted]

AE = adverse event; SAE = serious adverse event; SOC = system organ class; URTI = upper respiratory tract infection; UTI = urinary tract infection.
Source: GO-FURTHER Clinical Study Report.[17]

Summary

Results from the extension phase of GO-FURTHER suggest that the ACR response achieved with golimumab 2 mg/kg administered IV + methotrexate at Week 24 were maintained at least through Week 100. The improvement of HRQoL was also observed at Week 112. However, the efficacy findings observed at Week 100 or Week 112 should be interpreted with caution because there was no pure placebo-controlled group from Week 24 through Week 112. Golimumab 2 mg/kg administered IV was generally well tolerated and demonstrated a safety profile that was consistent with the class of anti-TNF-alpha drugs.

APPENDIX 6: SUMMARY OF COMPARATORS

Summary and Critical Appraisal of Manufacturer-Submitted Network Meta-Analysis

Objective

To summarize the methods and results, and to conduct a critical appraisal of the manufacturer-submitted network meta-analysis (NMA) comparing the efficacy and safety of intravenous (IV) golimumab (Simponi IV) with other IV biologic response modifiers (BRMs), specifically IV infliximab and IV abatacept, as well as subcutaneous (SC) golimumab in patients with moderate to severe rheumatoid arthritis (RA) with inadequate response to methotrexate.

Summary of Network Meta-Analysis

Rationale

The manufacturer indicated that the systematic review and NMA were undertaken because the comparative efficacy and safety of the IV golimumab formulation versus other biologics, in particular IV biologics such as IV infliximab and IV abatacept, have yet to be established from identified randomized controlled trials (RCTs). Comparative data were needed in order to inform the economic analysis.

Methods

Eligibility Criteria

The inclusion criteria for trials' eligibility in the NMA consisted of the following:

Population	Adult patients ≥ 18 years that meet ACR criteria for moderate to severe RA, and who have had an inadequate response to MTX
Intervention	Primary objective: IV golimumab 2 mg/kg at Weeks 0 and 4, then every 8 weeks thereafter IV infliximab 3 mg/kg at Weeks 0, 2, and 6, then every 8 weeks thereafter IV abatacept 10 mg/kg at Weeks 0, 2, and 4, then every 4 weeks thereafter Secondary objective: IV golimumab 2 mg/kg at Weeks 0 and 4, then every 8 weeks thereafter SC golimumab 50 mg once monthly *All considered biologics are administered with concomitant MTX.*
Comparator	Background MTX therapy plus placebo
Outcomes	Primary outcomes: ACR 20, ACR 50, ACR 70 DAS 28 HAQ-DI Discontinuations due to AEs All outcomes are considered for the following time points: Week 2 Week 4 Weeks 12 to 16 Weeks 24 to 26
Study design	RCTs, including open-label RCTs

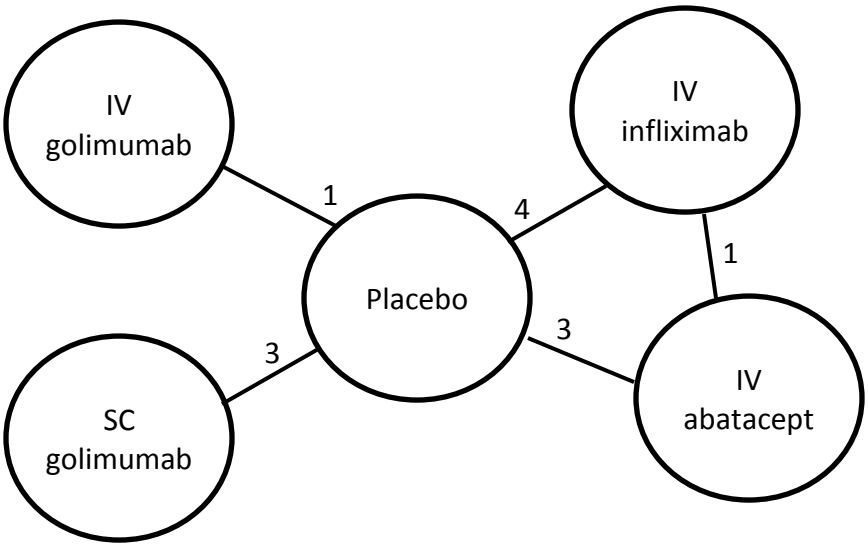
ACR = American College of Rheumatology; AE = adverse event; DAS 28 = Disease Activity Score in 28 joints; HAQ-DI = Disability Index of the Health Assessment Questionnaire; IV = intravenous; MTX = methotrexate; NR = not reported; RCT = randomized controlled trial; SC = subcutaneous.

Network Meta-Analysis

Bayesian NMA models were used to analyze the outcomes of interest in order to obtain relative efficacy outcomes at Weeks 2, 4, 6, 12 to 16, and 24 to 26. For safety outcomes, the follow-up duration ranged from 14 weeks to one year. For binary outcomes (e.g., ACR 20, ACR 50, ACR 70, and safety outcome), a conventional logistic regression model was used to produce odds ratios [ORs] with associated 95% credible intervals (CrIs). For each binary outcome, a random-effects model using a moderately informative heterogeneity variance prior was evaluated. Sensitivity analysis was performed using non-informative priors for the binary outcomes. The deviance information criterion (DIC) was calculated for all models to compare fits based on informative variance prior and non-informative variance prior. For continuous outcomes (e.g., Disease Activity Score [DAS] 28; Health Assessment Questionnaire Disability Index [HAQ-DI]), a linear regression, continuous variable model was used to produce mean differences with associated 95% CrIs. For each continuous outcome, a fixed-effect model with non-informative priors was evaluated. Due to the limitations of available data, no sensitivity analysis or model fit statistics were completed for continuous outcomes. WinBUGS version 1.4.3 statistical software was used for the analyses. A sensitivity analysis was also conducted that assessed the efficacy of IV golimumab to IV tocilizumab and other SC drugs.

Results

FIGURE 5: NETWORK OF INCLUDED RANDOMIZED CONTROLLED TRIALS



IV = intravenous; SC = subcutaneous.

Study and Patient Characteristics

Eleven RCTs were included in the meta-analysis. All studies were double-blind, parallel RCTs with a placebo comparator arm; one study also compared IV abatacept to IV infliximab. The majority of the trials were multi-centre trials. The studies evaluated the following interventions: IV golimumab 2 mg/kg at Weeks 0, 2 and 4, then every eight weeks thereafter (n = 1 study), IV infliximab 3 mg/kg at Weeks 0, 2, and 6, then every eight weeks thereafter (n = 4 studies), IV abatacept 10 mg/kg at Weeks 0, 2, and 4, then every four weeks thereafter (n = 3 studies), and SC golimumab 50 mg once monthly (n = 3 studies). All study drugs were given in combination with methotrexate.

Although the disease definition for active RA varied across the studies, the minimum trial duration of methotrexate therapy, the minimum dose of methotrexate, and the study inclusion criteria were broadly comparable. Outcome definitions were consistent across the studies, but some studies did not report the DAS 28 (n = 5 studies did not report) or HAQ-DI (n = 4 studies did not report) outcomes. Overall, the studies included patients from North America, Europe, Australia, New Zealand, Asia, and South America, with two studies conducted solely in Japan and one study conducted solely in China. The number of patients per study varied, with an average sample size of 306 patients (range from 96 to 654). Trial durations ranged from 14 weeks to one year.

The NMA report did not include a validity assessment of the individual trials. The authors described the quality of the studies as being adequate based on conclusions made from previously published indirect comparisons, including the CADTH therapeutic review on BRMs for RA.[28] However, three studies included in the NMA were not included in the CADTH therapeutic review and therefore were not critically appraised in the CADTH therapeutic review. Hence, at a minimum, the authors should have provided a critical appraisal for these three studies.

The enrolled patients were adults (≥ 18 years) with moderate to severe RA who had had an inadequate response to prior treatment with methotrexate. The RCT populations were predominantly female, ranging from 66% to 87%. The mean age was 52 years, ranging from 48 years to 57 years. Duration of disease at baseline ranged from 4.5 years to 9.7 years. At baseline, the number of swollen joints and tender joints varied across the studies, with ranges from 11 to 22 and from 13 to 32, respectively. When reported, baseline HAQ-DI ranged from 1.0 to 1.8. DAS 28 scores were reported either as DAS 28-ESR or DAS 28-CRP. DAS 28-ESR scores (n = 4 studies) ranged from 5.3 to 6.9, and DAS 28-CRP scores (n = 3 studies) ranged from 4.9 to 6.0. Most trials included only anti-tumour necrosis factor (TNF) treatment-naive patients, although two studies had a small number of patients with prior biologic use. All trials permitted patients to continue corticosteroid (dose equivalent to ≤ 10 mg/day of prednisone) and NSAID therapy if stable prior to study initiation. Methotrexate was continued at doses taken prior to the studies, with minimum doses ranging from ≥ 6 mg per week to 30 mg per week. Baseline methotrexate doses were not provided for the majority of studies; therefore, the adequacy of methotrexate therapy at baseline was unable to be assessed.

Results of the Meta-Analysis

TABLE 19: ACR RESULTS FOR IV GOLIMUMAB VERSUS ACTIVE COMPARATORS

	ACR 20 OR (95% CrI)	ACR 50 OR (95% CrI)	ACR 70 OR (95% CrI)
ACR at Week 2	**(n = 6 trials)**	**(n = 3 trials)**	
IV Golimumab vs. IV Abatacept	**3.34 (1.26 to 9.51)**	2.91 (0.57 to 21.1)	NR
IV Golimumab vs. IV Infliximab	1.06 (0.30 to 3.66)	NA	NR
IV Golimumab vs. SC Golimumab	1.46 (0.16 to 10.6)	NA	NR
Other Comparisons (Sensitivity Analysis)	Number of trials was not reported		
IV Golimumab vs. IV Tocilizumab (Actemra)	1.46 (0.52 to 3.89)	1.22 (0.22 to 6.56)	NR
IV Golimumab vs. SC Adalimumab	1.67 (0.59 to 5.49)	1.26 (0.26 to 6.88)	NR
IV Golimumab vs. SC Etanercept	1.76 (0.58 to 5.43)	0.90 (0.17 to 5.31)	NR
IV Golimumab vs. SC Certolizumab	1.32 (0.44 to 3.77)	1.12 (0.21 to 6.01)	NR

	ACR 20 OR (95% CrI)	ACR 50 OR (95% CrI)	ACR 70 OR (95% CrI)
Pegol			
ACR at Week 4	**(n = 9 trials)**	**(n = 7 trials)**	
IV Golimumab vs. IV Abatacept	**4.36 (1.19 to 12.7)**	**6.31 (1.37 to 29.6)**	NR
IV Golimumab vs. IV Infliximab	1.95 (0.54 to 6.24)	2.86 (0.57 to 14.8)	NR
IV Golimumab vs. SC Golimumab	2.08 (0.60 to 7.12)	1.09 (0.20 to 6.26)	NR
Other Comparisons (Sensitivity Analysis)	Number of trials was not reported		
IV Golimumab vs. IV Tocilizumab	1.32 (0.36 to 4.35)	1.99 (0.39 to 9.50)	NR
IV Golimumab vs. SC Adalimumab	2.28 (0.70 to 7.66)	4.48 (0.91 to 18.8)	NR
IV Golimumab vs. SC etanercept	2.74 (0.66 to 11.1)	2.63 (0.50 to 12.4)	NR
IV Golimumab vs. SC certolizumab pegol	1.39 (0.38 to 4.83)	1.39 (0.38 to 4.83)	NR
ACR at Weeks 12–16	**(n = 10 trials)**	**(n = 9 trials)**	**(n = 9 trials)**
IV Golimumab vs. IV Abatacept	2.07 (0.87 to 4.92)	2.21 (0.65 to 7.61)	2.64 (0.34 to 17.9)
IV Golimumab vs. IV Infliximab	1.96 (0.81 to 4.55)	2.15 (0.58 to 7.46)	2.01 (0.25 to 14.1)
IV Golimumab vs. SC Golimumab	1.87 (0.77 to 4.64)	1.05 (0.29 to 3.80)	1.04 (0.12 to 7.73)
Other Comparison (Sensitivity Analysis)	Number of trials was not reported		
IV Golimumab vs. IV Tocilizumab	2.88 (1.20 to 6.88)	2.92 (0.84 to 11.7)	2.36 (0.30 to 20.3)
IV Golimumab vs. SC Adalimumab	1.67 (0.69 to 3.93)	1.53 (0.46 to 5.30)	0.86 (0.11 to 6.13)
IV Golimumab vs. SC Etanercept	1.98 (0.73 to 4.67)	1.52 (0.30 to 4.96)	1.59 (0.16 to 10.6)
IV Golimumab vs. SC Certolizumab Pegol	0.70 (0.28 to 1.74)	0.95 (0.26 to 3.68)	0.67 (0.08 to 5.80)
ACR at Weeks 24–26	**(n = 9 trials)**	**(n = 9 trials)**	**(n = 9 trials)**
IV Golimumab vs. IV Abatacept	2.02 (0.74 to 5.60)	1.01 (0.33 to 3.51)	1.68 (0.54 to 5.78)
IV Golimumab vs. IV Infliximab	1.91 (0.69 to 5.20)	1.23 (0.38 to 4.06)	1.53 (0.49 to 5.42)
IV Golimumab vs. SC Golimumab	1.51 (0.53 to 4.40)	1.43 (0.43 to 5.22)	0.99 (0.27 to 4.61)
Other Comparison (Sensitivity Analysis)	Number of trials was not reported		
IV Golimumab vs. IV Tocilizumab	NR	NR	NR
IV Golimumab vs. SC Adalimumab	1.29 (0.43 to 3.61)	0.74 (0.21 to 2.51)	0.94 (0.27 to 3.55)
IV Golimumab vs. SC Etanercept	2.66 (0.75 to 7.50)	1.77 (0.39 to 5.58)	1.65 (0.47 to 6.28)
IV Golimumab vs. SC Certolizumab Pegol	2.34 (0.65 to 8.48)	1.45 (0.29 to 7.22)	NR

ACR = American College of Rheumatology criteria; CrI = credible interval; IV = intravenous; NR = not reported; OR = odds ratio; SC = subcutaneous.

ACR 20

Data for ACR 20 at Week 2, Week 4, Weeks 12–16, and Weeks 24–26 were available from six RCTs, nine RCTs, 10 RCTs, and nine RCTs, respectively. At Week 2 and Week 4, IV golimumab was more efficacious than IV abatacept (OR = 3.34; 95% CrI, 1.26 to 9.51 at Week 2, and OR = 4.36; 95% CrI, 1.19 to 12.7 at Week 4). There was no significant difference between IV golimumab versus IV infliximab, or between IV golimumab versus SC golimumab at Week 2 and Week 4. At Weeks 12–16 and Weeks 24–26, no differences were seen between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab.

ACR 50

Data for ACR 50 at Week 2, Week 4, Weeks 12–16, and Weeks 24–26 were available from three RCTs, seven RCTs, nine RCTs, and nine RCTs, respectively. At Week 2, no data were available for IV infliximab or SC golimumab, and there was no significant difference between IV golimumab and IV abatacept. At Week 4, IV golimumab was more efficacious than IV abatacept [OR = 6.31; 95% CrI, 1.37 to 26.9). At Weeks 12–16 and Weeks 24–26, no differences were seen between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab.

ACR 70

No data were available for ACR 70 at Week 2 and Week 4. At Weeks 12–16 and Week 24–26, data were available from nine RCTs for both time points. No comparisons were made with this outcome at Week 2 and Week 4, as data were unavailable. At Weeks 12–16 and Weeks 24–26, no differences were seen between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab.

DAS 28

TABLE 20: DAS 28 RESULTS FOR IV GOLIMUMAB VERSUS ACTIVE COMPARATORS

	DAS 28 at 12–16 Weeks MD (95% CrI)	DAS 28 at 24–26 Weeks MD (95% CrI)
IV Golimumab vs. IV Infliximab	NA	–0.15 (–0.45 to 0.16)
IV Golimumab vs. IV Abatacept	NA	0.10 (–0.39 to 0.60)
IV Golimumab vs. SC Golimumab	0.07 (–0.29, 0.45)	0.25 (–0.22 to 0.72)
IV Golimumab vs. IV Tocilizumab[a]	–0.13 (–0.41 to 0.15)	0.07 (–0.20 to 0.34)
IV Golimumab vs. SC Adalimumab[a]	NR	NR
IV Golimumab vs. SC Etanercept[a]	NR	NR
IV Golimumab vs. SC Certolizumab Pegol[a]	0.05 (–0.19 to 0.33)	0.61 (0.29 to 0.93)

CrI = credible interval; DAS 28 = Disease Activity Score in 28 joints; IV = intravenous; MD = mean difference; NA = not applicable; NR = not reported; SC = subcutaneous.
[a] Comparisons made as part of sensitivity analyses.

Data for DAS 28 at Weeks 12 to 16 and at Weeks 24 to 26 were available for three RCTs and four RCTs, respectively. At Weeks 12 to 16, no data were available for IV abatacept or IV infliximab, and no difference was seen between IV golimumab and SC golimumab. At Weeks 24 to 26, there were no differences between IV golimumab and its active comparators, namely IV infliximab, IV abatacept and SC golimumab. In addition, the findings of DAS 28 in the NMA should be interpreted with caution, since the clinical implications of the DAS 28 score (such as good response, moderate response, or no response) are supposed to be determined based on the baseline DAS 28 scores.[51]

HAQ-DI

HAQ-DI was measured only at Weeks 12–16. Data for this outcome were available for four RCTs. No HAQ-DI data were available for IV abatacept. There was no statistically significant difference between IV golimumab and IV infliximab (mean difference [MD] = 0.00; 95% CrI, –0.15 to 0.15) or between IV golimumab and SC golimumab (MD = –0.06; 95% CrI, –0.22 to 0.09). No statistically significant difference was found between IV golimumab and IV tocilizumab (MD = –0.01; 95% CrI, –0.14 to 0.12), between IV golimumab and SC adalimumab (MD = –0.03; 95% CrI, –0.18 to 0.12), or between IV golimumab and SC certolizumab pegol (MD = –0.02; 95% CrI, –0.13 to 0.17).

Discontinuations Due to Adverse Events

TABLE 21: DISCONTINUATIONS DUE TO ADVERSE EVENTS RESULTS FOR IV GOLIMUMAB VERSUS ACTIVE COMPARATORS

	Discontinuations Due to AEs OR (95% CrI)
IV Golimumab vs. IV Infliximab	0.73 (0.14 to 4.74)
IV Golimumab vs. IV Abatacept	1.61 (0.29 to 10.9)
IV Golimumab vs. SC Golimumab	1.25 (0.27 to 11.4)
IV Golimumab vs. IV Tocilizumab (Actemra)[a]	0.63 (0.12 to 3.81)
IV Golimumab vs. SC Adalimumab (Humira)[a]	1.17 (0.21 to 7.30)
IV Golimumab vs. SC Etanercept (Enbrel)[a]	1.60 (0.08 to 33.6)
IV Golimumab vs. SC Certolizumab Pegol (Cimzia)[a]	1.30 (0.21 to 7.59)

AE = adverse event; IV = intravenous; OR = odds ratio; SC = subcutaneous.
[a] Comparisons made as part of sensitivity analyses.

Data for discontinuations due to AE were available for 11 RCTs. Follow-up durations varied between studies, ranging from 14 weeks to one year in length. There were no differences between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab for this outcome.

Sensitivity Analyses

Results from the sensitivity analysis conducted with conventionally non-informative priors differed from the results using informed heterogeneity priors for ACR 20 at Week 2 and Week 4 and ACR 70 at Weeks 12 to 16. In the sensitivity analysis, IV golimumab was no longer more efficacious than IV abatacept for ACR 20 at Week 2 and Week 4. In addition, IV golimumab and IV abatacept were no longer more efficacious than placebo for ACR 70 at Weeks 12 to 16.

In the sensitivity analysis assessing the efficacy of IV golimumab to IV tocilizumab and other SC BRM drugs, the number of RCTs informing the trials for each outcome was unknown. Overall, 14 trials were included in the analysis. For ACR 20 and ACR 50, no differences were seen between IV golimumab and its active comparators at any time point, except that IV golimumab achieved a statistically significantly higher ACR 20 response compared with IV tocilizumab at Weeks 12 to 16. ACR 70 data were unavailable at Week 2 and Week 4; at Weeks 12 to 16 and Weeks 24 to 26, no difference was seen between IV golimumab and SC adalimumab and between IV golimumab and etanercept. At Weeks 24 to 26, no data were available for IV tocilizumab for all ACR outcomes and for SC certolizumab pegol for ACR 70. No data were available for etanercept with respect to the HAQ-DI outcome. Therefore, no comparisons with IV golimumab could be made for these outcomes. For HAQ-DI, no difference was seen between IV golimumab and IV tocilizumab, SC adalimumab, and SC certolizumab pegol. Data for DAS 28 were unavailable for SC adalimumab and etanercept at Weeks 12–16 and Weeks 24–26. No differences were seen between IV golimumab and IV tocilizumab for DAS 28 at any time point. For the same outcome, IV golimumab was no different than SC certolizumab pegol at Weeks 12–16, but was inferior to SC certolizumab pegol at Weeks 24–26. No differences were seen between IV golimumab and its active comparators for discontinuations due to AEs.

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer-submitted NMA was assessed according to recommendations provided by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on

Indirect Treatment Comparisons. Details and commentary for each of the relevant items identified by ISPOR are provided in Table 22.

Strengths

The NMA appears to satisfy many of the ISPOR criteria. The inclusion criteria for the NMA were clearly outlined. The patient population chosen for the analysis is consistent with patients in whom biologic therapy would be considered. A comprehensive search strategy was employed to identify and select relevant RCTs for the IV biologic interventions. Patient characteristics were reported for individual studies, and most characteristics were similar between the studies. The dosages of the individual comparators were consistent with those listed in the Canadian product monographs.

The NMA was conducted using appropriate and well-reported methodology (i.e., Bayesian NMA models created with WinBUGS 1.4.1). The outcome measures assessed in the NMA were appropriate. Model diagnostic statistics such as DIC were used to assess model fit.

Limitations

One limitation of the NMA was the insufficient justification provided for not including all available SC biologic comparators in the main analyses. The authors' rationale for this decision was that the population who utilize IV biologic drugs may be different from the population who utilizes SC biologic drugs, although some SC formulations were included in the NMA without explanation for why they, and not others, were selected. A sensitivity analysis was undertaken to assess the comparative efficacy and safety of IV golimumab versus IV tocilizumab and SC BRMs. However, it may have been more appropriate to include the SC drugs as comparators in the main analysis. Another limitation of the NMA were the differences in baseline methotrexate doses among the studies, with doses ranging from 6 mg per week to 30 mg per week in the individual RCTs. No sensitivity analysis was conducted to adjust for these differences because the manufacturer reported that a recent meta-regression by Kanters et al.[56] indicated that effect modification in RA studies due to differences in baseline methotrexate dose may be less important than previously thought. However, Kanters et al. noted that the methotrexate dose appears to influence ACR 50 (although possibly not ACR 20), but that their analysis had several key limitations (e.g., missing data on baseline methotrexate dose in the studies and bias due to unmeasured confounders such as indication bias).[56] The third limitation of the NMA was the lack of long-term data for the outcomes. In terms of the efficacy outcomes, ACR at Weeks 2 and 4 were analyzed; however, Week 14 was the earliest time point at which ACR 20 was analyzed as the primary end point in the individual RCTs. Moreover, results for the efficacy outcomes were only available until Weeks 24 to 26; therefore, the longer-term comparative efficacy of the included biologics remains unknown. Similarly, the long-term comparative safety of the included biologics also remains unknown. Only one RCT had data for up to one year, with all other RCTs having data for 30 weeks or fewer. No analysis was conducted for AEs or SAEs in the NMA; therefore, the comparative risks of SAEs such as infection and malignancy are unknown.

Although the results of the NMA did not show differences between golimumab and its active comparators, data were not available for analysis from all included studies at all the selected time points. Therefore, a small number of studies informed the results for several of the outcomes, especially at earlier time points, contributing to imprecise estimates of treatment effect as demonstrated by the wide CrIs.

In terms of methods, one limitation of the NMA was the lack of assessment for validity of the individual studies. Though the authors justified their decision by stating that "the vast majority of the published [indirect treatment comparisons] have already assessed the Cochrane type risk of bias associated with

the published trials, and concluded that trials in general are of adequate quality," this does not ensure that all trials included in this NMA have an adequately low risk of bias. Furthermore, sensitivity analyses were not conducted to examine whether individual trials could impact the NMA results. Another limitation of the methods for this study was the pooling of DAS 28 results, using both DAS 28-CRP and DAS 28-ESR results from the studies. Though measuring the same outcome, these two scores are calculated differently and therefore are not identical. As such, a measure of treatment effect other than MD may have been preferable.

Summary

Without head-to-head trial data for IV golimumab versus other IV biologic comparators, the manufacturer conducted a Bayesian NMA based on RCTs to compare IV golimumab with IV infliximab, abatacept, and SC golimumab. Overall, the NMA showed no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26. There were no differences between IV golimumab and its comparators with respect to WDAEs. NMA methodology was well detailed and appropriate. The NMA is limited by variable baseline methotrexate dose across the studies and the lack of long-term comparative data for selected outcomes.

TABLE 22: APPRAISAL OF NMA USING ISPOR CRITERIA

ISPOR Checklist Item	Details and Comments
Are the rationale for the study and the objectives stated clearly?	The rationale for conducting a NMA and its study objectives were clearly stated.
Does the Methods section include the following? Eligibility criteria Information sources Search strategy Study selection process Data extraction Validity of individual studies	Eligibility criteria for individual RCTs are clearly stated. Search strategy, study selection process, and data extraction are clearly stated for IV comparators. Search strategy, study selection process, and data extraction are not stated for the sensitivity analysis comparing IV golimumab with IV tocilizumab and SC biologics. All treatments were administered in DB fashion during periods in which data were extracted. Validity of the individual trials was not assessed.
Are the outcome measures described?	Specific outcomes were not clearly stated in the Methods section. Justification for the efficacy outcomes used was that they were primary outcomes conventionally employed in RA clinical trials and that they are indirect comparisons that are well established and understood. Discontinuations due to AEs were chosen as the safety outcome as it is a surrogate for treatment tolerability. SAEs were not included due to the heterogeneity of the definitions in the individual trials. No justification was provided for the time frames in which data for the outcomes were to be extracted for analysis.
Is there a description of methods for analysis/synthesis of evidence? Description of analyses methods/models Handling of potential bias/inconsistency Analysis framework	A description of the statistical model was provided for both the dichotomous and continuous outcomes. The DIC was used to compare the random-effects model and fixed-effects model for the dichotomous outcomes. The rationale for using an informative prior for dichotomous outcomes was provided. The rationale for using a fixed-effects model for continuous outcomes was provided.

ISPOR Checklist Item	Details and Comments
Are sensitivity analyses presented?	Sensitivity analysis was conducted using non-informative priors for dichotomous outcomes. Sensitivity analysis was also conducted to compare the efficacy of IV golimumab with the efficacy of IV tocilizumab and the other SC biologics.
Do the results include a summary of the studies included in the network of evidence? Individual study data? Network of studies?	A table with study/patient characteristics was provided. Tables were provided with results from the individual studies for each outcome. A figure showing the network of studies was provided.
Does the study describe an assessment of model fit?	Model fit statistics were provided for each dichotomous outcome. No model fit statistics were provided for the continuous outcomes.
Are the results of the evidence synthesis presented clearly?	Tables were provided with results from the NMA with ORs and 95% CrIs for each outcome.
Sensitivity/scenario analyses	Results of the sensitivity analysis were provided in the report.

AE = adverse event; CrI = credible interval; DB = double-blind; DIC = deviance information criterion; IV = intravenous; ISPOR = International Society of Pharmacoeconomics and Outcomes Research; NMA = network meta-analysis; OR = odds ratio; RCT = randomized controlled trial; SC = subcutaneous.

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