Common Drug Review

Clinical Review Report

November 2014

Drug	golimumab (Simponi) (subcutaneous injection)
Indication	Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, or have medical contraindications for, conventional therapies including corticosteroids, aminosalicylates, azathioprine or 6-mercaptopurine
Listing request	As per indication
Manufacturer	Janssen Inc.

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions.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

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ABBREVIATIONS

AE	adverse event
ASA	aminosalicylic acid
AZA	azathioprine
BUD	budesonide
CDR	Common Drug Review
CHF	congestive heart failure
CI	confidence interval
CS	corticosteroid
DB	double blind
EQ-5D	EuroQol 5-Dimension Health-Related Quality of Life Questionnaire
GI	gastrointestinal
GO	golimumab
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICUR	incremental cost-utility ratio
IV	intravenous
MH	mucosal healing
MP	mercaptopurine
NR	not reported
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	Short-Form (36) Health Survey
SLE	systemic lupus erythematosus
TB	tuberculosis
TNF	tumour necrosis factor
UC	ulcerative colitis
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) that leads to severe gastrointestinal symptoms, including diarrhea, pain, and bloody stools. The inflammation can eventually lead to significant mucosal damage and to life-threatening complications such as bowel perforation and sepsis. Patients with UC are also at higher risk of malignancy, most notably colon cancer. UC is a relatively common disease in Canada, with a prevalence of 104,000 patients and an incidence of 4,500 per year.

There are a number of management options for UC, including aminosalicylic acid, immunomodulators, corticosteroids, and most recently, tumour necrosis factor (TNF) inhibitors. TNF is a key inflammatory mediator; thus, these inhibitors, all monoclonal antibodies, are anti-inflammatory. The objective of this review is to perform a systematic review of the beneficial and harmful effects of golimumab (Simponi) through subcutaneous injection at recommended doses for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, or have medical contraindications for, conventional therapy.

Indication Under Review
Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, or have medical contraindications for, conventional therapies including corticosteroids, aminosalicylates, azathioprine or 6-mercaptopurine.
Listing Criteria Requested by Sponsor
As per indication

Results and Interpretation

Included Studies

Two placebo-controlled double-blind randomized controlled trials (RCTs) met the inclusion criteria for this systematic review. The Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous (PURSUIT-SC) was a two-part induction study that included a dose-finding phase (N = 169) in which patients were randomized to one of four doses of golimumab in order to establish the doses that would be used in the second part of the study. In part 2, the lowest dose from part 1 was removed from the study (lack of efficacy), 896 new patients were randomized to golimumab (GO) 200 mg to 100 mg (start 200 mg at week 0, then 100 mg at week 2), GO 400 mg–200 mg (start 400 mg at week 0, then 200 mg at week 2), or placebo for 6 weeks. PURSUIT-MAINTENANCE included patients who were responders in PURSUIT-SC (and in PURSUIT-IV which was not included in the review because of the route of administration; the study is summarized in Appendix 6). PURSUIT-MAINTENANCE enrolled 464 patients for continued treatment with GO 50 mg, GO 100 mg, or placebo for 52 weeks. The primary outcome of both PURSUIT-SC and PURSUIT-MAINTENANCE was clinical response to the end of treatment; clinical response was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Efficacy

More golimumab-treated patients exhibited a clinical response compared with placebo-treated patients in both PURSUIT-SC and PURSUIT-MAINTENANCE. These differences were statistically significant versus placebo at the GO 200 mg–100 mg (52% versus 30%, $P < 0.0001$) and GO 400 mg–200 mg (55% versus 30%, $P < 0.0001$) doses in PURSUIT-SC, and at the GO 50 mg (47% versus 31%, $P = 0.010$) and GO 100 mg (51% versus 31%, $P < 0.001$) doses in PURSUIT-MAINTENANCE.

Clinical remission was defined as a Mayo score ≤ 2 points, with no individual subscore > 1. A higher proportion of golimumab-treated patients versus placebo-treated patients achieved clinical remission in each of the studies. The differences versus placebo were statistically significant at the GO 200 mg–100 mg (19% versus 6%, $P < 0.0001$) and GO 400 mg–200 mg (18% versus 6%, $P < 0.0001$) doses in PURSUIT-SC, and the GO 100 mg (29% versus 15%, $P = 0.003$) dose in PURSUIT-MAINTENANCE; the GO 50 mg dose was not statistically significantly different versus placebo (24% versus 15%, $P = 0.091$).

Quality of life was assessed using three different instruments in each study, and results were mixed depending on the instrument and study. In PURSUIT-SC, quality of life results were statistically significantly better for both GO 200 mg–100 mg doses and GO 400 mg–200 mg doses versus placebo for all of the main quality of life instruments (Short-Form [36] Health Survey [SF-36]-Physical and Mental Component Summary Scores; EuroQol 5-Dimension Quality of Life Questionnaire [EQ-5D]; and Inflammatory Bowel Disease Questionnaire [IBDQ]). [redacted]

Very few patients underwent colectomy in PURSUIT-MAINTENANCE, and this outcome was not specifically reported in PURSUIT-SC.

Harms

The incidence of adverse events was 73% in each of the GO 50 mg and GO 100 mg groups and 66% in the placebo group in PURSUIT-MAINTENANCE. The incidence of adverse events was similar between GO 200-100 mg (38%), GO 400-200 mg (39%), and placebo (38%) groups in PURSUIT-SC. The most common adverse events in both studies were nasopharyngitis and headache. UC was the most common adverse event in PURSUIT-MAINTENANCE. The incidence of infection was similar between groups in PURSUIT-SC (12% in each group), but was higher in each of the golimumab-treated groups (39% in each) versus the placebo group (28%) in PURSUIT-MAINTENANCE. Malignancies were rare, with no differences in incidence among groups.

Serious adverse events were experienced by 3% of golimumab-treated patients in each group and 6% of placebo-treated patients in PURSUIT-SC. In PURSUIT-MAINTENANCE, 8% of patients in GO 50 and in placebo groups experienced a serious adverse event, and 14% of patients in GO 100. Few patients withdrew due to an adverse event in PURSUIT-SC, with similar rates between groups; while in PURSUIT-MAINTENANCE 8% of golimumab-treated patients in each group withdrew due to an adverse event versus 11% of placebo-treated patients.

Pharmacoeconomic Summary

The manufacturer submitted a cost-utility analysis comparing golimumab with conventional therapy, infliximab, and adalimumab. The target population is those with moderately to severely active UC following inadequate response to conventional treatments, followed over a 10-year time horizon. The efficacy of treatments for inducing response or remission was taken from an indirect treatment comparison conducted by the manufacturer. The manufacturer reports that, when compared with conventional therapy, golimumab 50 mg and 100 mg are associated with an incremental cost-utility ratio (ICUR) per quality-adjusted life-year of $41,591 and $42,271, respectively. Infliximab and adalimumab are associated with an ICUR of $65,982 and $68,722, respectively, compared with conventional therapy.

The CADTH Common Drug Review (CDR) identified the following limitations of the manufacturer's economic evaluation:

- issues with the inclusion of results from the manufacturer's indirect treatment comparison for treatment effects of golimumab only while comparators' treatment effects were obtained directly from RCT data
- transformations conducted for input data not transparent
- underlying relationship between probability of outcome at induction and sustained outcomes at one year
- extended time horizon of 10 years.

Given the issues identified, full examination of the manufacturer's model and reanalyses using alternative clinical inputs were not possible. CDR reanalyses varying the time horizon of the manufacturer's economic model found that the ICUR for golimumab compared with conventional therapy could lie in a range of $52,000 to $104,000 per quality-adjusted life-year, based on a time horizon of 2.5 to 1.25 years to align with available RCT data.

The manufacturer also submitted a cost-minimization analysis comparing golimumab to infliximab and adalimumab in UC patients, based on the assumption of equivalent efficacy and harms, from the results of an indirect comparison. Golimumab was cost saving compared with adalimumab and infliximab, except when compared with infliximab for patients who weigh less than 60 kg. The cost-minimization analysis was considered as a secondary analysis, as biologic therapies are not listed by the majority of public drug plans for UC.

Simponi (golimumab) is available in 50 mg/0.5 mL and 100 mg/1.0 mL pre-filled syringes or auto injectors for the treatment of UC at a flat price of $1,490.41 per syringe.

Conclusions

Two double-blind RCTs comparing golimumab with placebo, one using an induction regimen (PURSUIT-SC) and the other using maintenance (PURSUIT-MAINTENANCE), were included in this review. Results for the primary outcome, clinical response, were consistently statistically significantly in favour of golimumab versus placebo in each study. Remission was statistically significantly achieved only at the higher golimumab dose in the maintenance study, yet both this and the lower golimumab dose were approved by Health Canada. These results suggest that, although a clinical response is attainable at the lower golimumab dose, remission might not be. The mixed data on quality of life call into question whether golimumab improves patients' mental outlook or their global health. Disease-specific aspects of quality of life do appear to be improved with therapy, but, again, only at the higher golimumab dose.

The included studies had too small a sample and were too short in duration to adequately assess key outcomes such as need for colectomy, as well as infrequent harms such as malignancy, serious opportunistic infections, and serious immune reactions. No differences were detected between golimumab and placebo for any of these outcomes. The lack of a direct comparison with other TNF inhibitors is a limitation of this review.

TABLE 1: SUMMARY OF RESULTS

Outcome	PURSUIT-SC			PURSUIT-MAINTENANCE		
	GO 200 mg–100 mg	GO 400 mg–200 mg	Placebo	GO 50 mg	GO 100 mg	Placebo
Clinical response						
n/N (%)	133/257 (52)	142/258 (55)	76/256 (30)	72/153 (47)	78/154 (51)	49/156 (31)
RR (95% CI)	1.74 (1.40 to 2.18)	1.85 (1.49 to 2.31)		1.50 (1.13 to 2.00)	1.61 (1.22 to 2.13)	
NNT (95% CI)	5 (3 to 7)	4 (3 to 6)		6 (4 to 20)	5 (3 to 13)	
P value	*P* < 0.0001	*P* < 0.0001		*P* = 0.010	*P* < 0.001	
Clinical remission						
n/N (%)	48/257 (19)	46/258 (18)	16/256 (6)	36/153 (24)	44/154 (29)	24/156 (15)
RR (95% CI)	2.99 (1.74 to 5.12)	2.85 (1.66 to 4.90)		1.53 (0.96 to 2.44)	1.86 (1.19 to 2.90)	
NNT (95% CI)	8 (6 to 14)	8 (6 to 17)		NA	8 (5 to 25)	
P value	*P* < 0.0001	*P* < 0.0001		*P* = 0.091	*P* = 0.003	
QoL: IBDQ						
Mean (SD) at baseline	[redacted]					
Mean (SD) change from baseline	[redacted]					
P value	[redacted]					
QoL: SF-36						
PCS: Mean (SD) at baseline	[redacted]					
Mean (SD) change from baseline	4.5 (7.1)	3.8 (7.6)	2.5 (7.2)	[redacted]		
P value	[redacted]					
MCS: Mean (SD) at baseline	[redacted]					
Mean (SD) change from baseline	4.7 (10.7)	5.1 (10.3)	1.6 (8.8)	[redacted]		
P value	[redacted]					
QoL: EQ-5D						
Mean (SD) at baseline	[redacted]					
Mean (SD) change	[redacted]					

Outcome	PURSUIT-SC			PURSUIT-MAINTENANCE		
	GO 200 mg–100 mg	GO 400 mg–200 mg	Placebo	GO 50 mg	GO 100 mg	Placebo
from baseline						[redacted]
P value	[redacted]	[redacted]		[redacted]	[redacted]	
Colectomy, partial or full						
n/N (%)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P value				[redacted]	[redacted]	
Withdrawals						
Total, n/N (%)	7/331 (2)	9/332 (3)	13/330 (4)	18/154 (12)	21/154 (14)	18/156 (12)
SAEs						
n/N (%)	9/331 (3)	11/332 (3)	20/330 (6)	13/154 (8)	22/154 (14)	12/156 (8)
WDAEs						
n/N (%)	1/331 (<1)	1/332 (<1)	3/330 (1)	12/154 (8)	12/154 (8)	17/156 (11)
Infection						
n/N (%)	39/331 (12)	41/332 (12)	40/330 (12)	60/154 (39)	60/154 (39)	44/156 (28)

CI = confidence interval; EQ-5D = EuroQol 5-Dimension Quality of Life Questionnaire; GO = golimumab; MCS = mental component summary score; NA = not applicable; NR = not reported; NNT = number needed to treat; PCS = physical component summary score; QoL = quality of life; RR = relative risk; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) and is most commonly associated with chronic inflammation of the colon, leading to diarrhea, pain, and bloody stools. Patients also experience extra-intestinal signs/symptoms, such as fatigue and weight loss. If left untreated, inflammation progresses leading to mucosal damage and potentially fatal complications such as perforation and sepsis. Chronic inflammation is a recognized risk factor for malignancy, and patients with UC are at increased risk of developing colon cancer.[1]

According to the Crohn's and Colitis Foundation of Canada, there are approximately 233,000 Canadians living with IBD and 104,000 with UC.[1] More than 10,200 new cases of IBD are diagnosed every year (5,700 with Crohn disease and 4,500 with UC), an incidence of 0.7%, and 20% to 30% of people with IBD are diagnosed before the age of 20. Canada has one of the highest incidences and prevalences of IBD in the world. There are 5,900 children in Canada with IBD.[1]

1.2 Standards of Therapy

Several drug classes are employed in treatment of UC, including aminosalicylic acid, immunosuppressants (azathioprine, cyclosporine), corticosteroids, and TNF inhibitors, which are all monoclonal antibodies. Probiotics are also increasingly being recognized as useful drugs in UC management. Non-pharmacological measures include dietary and lifestyle changes, and surgery, which is the ultimate outcome in a number of patients. Most of the pharmacological drugs have significant toxicities that can have either short- or long-term consequences. The TNF inhibitors are also known for their significant expense.

1.3 Drug

Golimumab is a fully human monoclonal antibody to TNF. TNF is a key inflammatory mediator that has been implicated in a variety of inflammatory disorders, including rheumatoid arthritis and IBD. Golimumab is administered as a subcutaneous injection. For induction, golimumab is administered 200 mg at week 0, then 100 mg at week 2, followed by maintenance of 50 mg every four weeks. A maintenance dose of 100 mg every four weeks may also be considered. Golimumab is also indicated for rheumatoid arthritis, in combination with methotrexate for patients with moderately to severely active disease who had not been previously treated with methotrexate. It is also indicated for patients with moderate to severe psoriatic arthritis and with active ankylosing spondylitis.[2]

Indication Under Review
Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, or have medical contraindications for, conventional therapies including corticosteroids, aminosalicylates, azathioprine, or 6-mercaptopurine.
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TABLE 2: KEY CHARACTERISTICS OF GOLIMUMAB, INFLIXIMAB, AND ADALIMUMAB

	Golimumab	Infliximab	Adalimumab
Mechanism of action	Monoclonal antibody (chimeric) to TNF	Monoclonal antibody (human) to TNF	Monoclonal antibody (human) to TNF
Indication[a]	Patients with moderate to severe UC and medical contraindications for or inadequate response to conventional therapies	Adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy	Approved only for Crohn disease[b]
Route of administration	SC	IV	Not applicable
Recommended dose	200 mg initially administered by SC injection at week 0, followed by 100 mg at week 2 and then 50 mg every 4 weeks thereafter. The maintenance dose of 100 mg every 4 weeks can be considered at the discretion of the treating physician.	5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by 5 mg/kg every 8 weeks. In some adult patients, consideration may be given to adjusting the dose up to 10 mg/kg to sustain clinical response and remission.	Not applicable
Serious side effects/safety issues	Infections, particularly opportunistic ones such as TB Malignancy, particularly lymphoma	Infections, particularly TB Malignancy Allergic reactions	Malignancy, particularly lymphoma Infections, particularly opportunistic ones such as TB

IV = intravenous; SC = subcutaneous; TB = tuberculosis; TNF = tumour necrosis factor; UC = ulcerative colitis.
[a] Health Canada indication.
[b] At the time the CDR review of golimumab was performed, adalimumab did not have a Health Canada Notice of Compliance for UC. Adalimumab, however, did receive Health Canada approval during the period this review was being prepared for public posting.
Sources: Golimumab product monograph;[2] Infliximab product monograph;[3] Adalimumab product monograph.[3]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of golimumab (Simponi) through subcutaneous injection at recommended doses for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, or have medical contraindications for, conventional therapy.

2.2 Methods

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

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient population	Adults (≥ 18 years of age) diagnosed with UC who have had an inadequate response to, or have medical contraindications for, one or more conventional therapies.[a] Subgroups: • Severity of UC (moderate/severe) • Prior steroid use
Intervention	Golimumab at the approved dose as monotherapy or in combination with conventional therapies.[a]
Comparators	Conventional drugs[a] Adalimumab Infliximab Placebo

Outcomes	**Key efficacy outcomes:**
	• Clinical response (Mayo score reduction of > 30%)
	• Clinical remission (Mayo score < 2 with no individual subscore > 1)
	• HRQoL
	• Need for colectomy
	Other efficacy outcomes:
	• Mucosal healingb
	• Corticosteroid-free clinical remission
	• Markers of disease activity (e.g., fecal calprotectin, CRP, hemoglobin)
	• Generation of autoantibodies
	Harms outcomes:
	• Mortality
	• SAEs
	• WDAEs
	• AEs including but not limited to:
	  ○ injection-site reactions
	  ○ hypersensitivity reactions
	  ○ malignancy
	  ○ infections (particularly TB and hepatitis)
	  ○ hepatotoxicity
	  ○ hematologic AEs.

Study Design	Published and unpublished double-blind RCTs

AE = adverse event; CRP = C-reactive protein; DB = double-blind; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse events; SC = subcutaneously; TB = tuberculosis; UC = ulcerative colitis; WDAE = withdrawal due to adverse event.

[a] Conventional treatment: any combination of salicylates, probiotics, corticosteroids (includes steroid dependent disease – inability to taper steroids without relapse of symptoms), and immunosuppressants such as azathioprine, 6-mercaptopurine, and cyclosporine.

[b] Determined by endoscopic or histologic investigation.

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 inflammatory bowel disease.

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. See Appendix 2: LITERATURE SEARCH STRATEGY for the detailed search strategies.

The initial search was completed on August 28, 2013. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on January 15, 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)
- Internet Search

Google and other Internet search engines were used to search for additional web-based materials. 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. See Appendix 2: LITERATURE SEARCH STRATEGY for more information on the grey literature search strategy.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 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

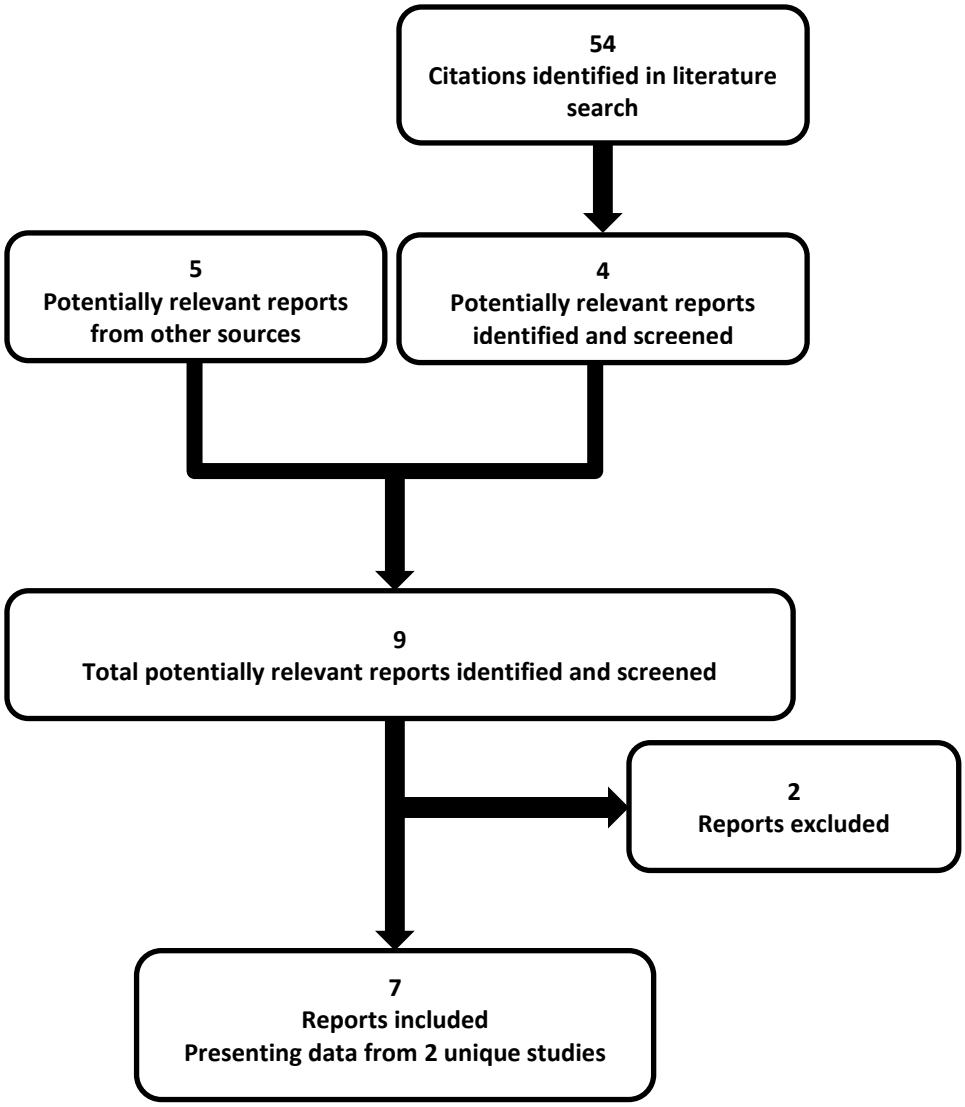

TABLE 4: DETAILS OF INCLUDED STUDIES

		PURSUIT-SC	PURSUIT-MAINTENANCE
DESIGNS & POPULATIONS	**Study design**	DB RCT	DB RCT
	Locations	217 sites North America Europe Asia Pacific South Africa	172 sites North America Europe Asia Pacific South Africa
	Randomized (N)	1,065 part 1: 169 Part 2: 896	464
	Inclusion criteria	18 years of age or older Moderately to severely active UC defined by a Mayo score of 6 to 12 inclusive at baseline (week 0), including an endoscopic subscore of ≥ 2. Biopsy consistent with the diagnosis of UC and ambulatory (i.e., not at imminent risk of colectomy). Demonstrated an inadequate response to, or have failed to tolerate, at least 1 of the following conventional therapies: oral 5-ASAs, oral corticosteroids, or AZA or 6-MP, or corticosteroid dependence (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC).	Received all study drug administrations and completed the week 6 Mayo score evaluation in 1 of the induction studies, PURSUIT-IV or PURSUIT-SC, and completed the week 0 visit for this maintenance study on the same day as the week 6 visit of the induction study (unless approval was received from the medical monitor to complete their week 0 visit within 7 days of the week 6 visit).
	Exclusion criteria	Imminent risk for colectomy UC limited to the rectum only or < 20 cm of the colon, a stoma, a fistula, an obstruction, or adenomatous colonic polyps that were not removed History of latent or active granulomatous infection (including TB), a predisposition to infections, or a history of or increased potential for malignancy Diagnosis or history of CHF, lymphoproliferative disease, SLE, or demyelinating disease Prior exposure to biologic TNF inhibitor drugs	Increased the dose of their concomitant UC medications since week 0 of induction studies, initiated a concomitant UC medication since week 0 of an induction study, or underwent a colectomy (partial or total) or ostomy (i.e., temporary colostomy, permanent colostomy, ileostomy, or other enterostomy) since week 0 of an induction study. Signs or symptoms of any of the following: a granulomatous infection (including TB), a nontuberculous mycobacterial infection or opportunistic infection; infection with HIV, hepatitis B, or hepatitis C; any malignancy or possible lymphoproliferative disease; CHF; SLE; or demyelinating disease. Patients who had a clinically significant infection since week 0 of an induction study or who had a clinically significant hypersensitivity reaction in an induction study were not eligible for enrolment into this maintenance study.

		PURSUIT-SC	PURSUIT-MAINTENANCE
Drugs	**Intervention**	GO 100 mg SC at week 0 and 50 mg at week 2 GO 200 mg SC at week 0 and 100 mg at week 2 GO 400 mg SC at week 0 and 200 mg at week 2	GO 50 mg SC every 4 weeks GO 100 mg SC every 4 weeks Week 0 to week 52
	Comparator	Placebo	Placebo
Duration	**Phase:**		
	Run-in	NR	Patients enrolled from PURSUIT-SC/IV
	Double-blind	6 weeks	52 weeks
	Follow-up	91% of patients entered PURSUIT-MAINTENANCE 16 weeks follow-up otherwise	16 weeks Extension to 228 weeks for those who might benefit
Outcomes	**Primary endpoint**	Clinical response at week 6 (decrease from baseline in the Mayo score by ≥ 30% and 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 at week 6)	Clinical response through week 54 (decrease from week 0 of PURSUIT-IV or PURSUIT-SC in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1)
	Other end points	Clinical remission at week 6 Mucosal healing at week 6 Change from baseline in IBDQ scores at week 6 Change from baseline in Mayo score at week 6 Patients with normal or inactive mucosal disease Patients in clinical remission with normal or inactive mucosal disease IBDQ, SF-36, and EQ-5D	Proportions of patients in clinical remission at both week 30 and week 54 Proportions of patients with mucosal healing at both week 30 and week 54 Among patients who were in clinical remission at week 0 in this study, the proportions of patients in clinical remission at both week 30 and week 54 Among patients receiving concomitant corticosteroids at week 0, the proportions of patients at week 54 in clinical remission and not receiving concomitant corticosteroids
Notes	**Publications**	Sandborn et al., 2013[4]	Sandborn et al., 2013[5]

ASA = aminosalicylic acid; AZA = azathioprine; CHF = congestive heart failure; DB = double-blind; EQ-5D = EuroQol 5-Dimension Quality of Life Questionnaire; GO = golimumab; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; MP = mercaptopurine; NR = not reported; RCT = randomized controlled trial; SC = subcutaneous; SF-36 = Short-Form (36) Health Survey; SLE = systemic lupus erythematosus; TB = tuberculosis; TNF = tumour necrosis factor; UC = ulcerative colitis.
Note: Five additional reports were included.[6-10]

3.2 Included Studies

3.2.1 Description of Studies

Two multinational, manufacturer-sponsored double-blind RCTs met the inclusion criteria for this review. The Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous (PURSUIT-SC) was a two-part study; part 1 was a dose-finding study that randomized 169 patients to one of GO 100 mg–50 mg, GO 200 mg–100 mg, GO, 400 mg–200 mg, or placebo. A dose-selection committee

determined the induction dosing regimen for part 2 after an interim analysis of data from all patients who completed the week 6 visit or who had withdrawn in part 1. As a result of this dose selection, newly enrolled patients in part 2 (N = 896) were randomized to GO 200 mg–100 mg, GO 400 mg–200 mg, or placebo. PURSUIT-MAINTENANCE enrolled GO-treated patients from PURSUIT-SC or PURSUIT-IV who had completed a week 6 Mayo score evaluation in one of these studies and had shown a clinical response, a total of 464 patients. Patients in PURSUIT-MAINTENANCE were randomized to either GO 50 mg every four weeks, GO 100 mg every four weeks, or placebo; all were treated for 52 weeks. Patients in PURSUIT-SC who were in the placebo group or had not shown a clinical response were also eligible to enrol in PURSUIT-MAINTENANCE, but were in a separate, non-randomized group whose treatment allocation was based on their treatment allocation and response in PURSUIT-SC. This non-randomized cohort does not meet the inclusion criteria for this systematic review, and thus is not a focus of this review.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients in PURSUIT-SC had to have moderate to severely active UC (Mayo score of 6 to 12, inclusive), including an endoscopic subscore of at least 2. They had to have demonstrated an inadequate response or be intolerant to at least one of a list of standard conventional therapies, including 5-aminosalicylic acid, corticosteroids, or immunosuppressants such as azathioprine or 6-mercaptopurine (MP), or demonstrate dependence on corticosteroids, defined as an inability to taper off corticosteroids without return of UC symptoms. Patients at imminent risk of colectomy were excluded, as were patients with a history of latent or active granulomatous infection, a predisposition to infection, or a history of or increased risk for malignancy. PURSUIT-MAINTENANCE was comprised of patients from either PURSUIT-SC or PURSUIT-IV (which had similar inclusion criteria to PURSUIT-SC), who had completed all study drug administration in these studies and had a week 6 Mayo score.

b) Baseline Characteristics

Across studies, patients were approximately 40 years of age, on average, and mostly male. Patients had had UC for a mean of approximately 6.5 years, and approximately 40% had extensive disease, rather than disease limited to the left side of the colon. Mayo scores ranged from a mean of 8.2 to 8.6 points and 8.1 ro 8.5 on a scale of 0 to 12 in PURSUIT-SC and PURSUIT-MAINTENCE, respectively. The majority (approximately 94%) of patients in both studies had received treatment with UC medications. There were no clear differences between treatment groups within each study.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	PURSUIT-SC				PURSUIT-MAINTENANCE		
	GO 100 mg–50 mg N = 72	GO 200 mg–100 mg N = 331	GO 400 mg–200 mg N = 331	Placebo N = 331	GO 50 mg N = 154	GO 100 mg N = 154	Placebo N = 156
Mean (SD) age, year	40.9 (12.2)	40.0 (13.5)	40.7 (13.8)	39.0 (13.0)	41.4 (13.8)	39.1 (13.1)	40.2 (14.1)
Median age (range), year	40.0 (21, 74)	39.0 (18, 78)	38.0 (18, 77)	37.0 (18, 72)	41.0 (18, 79)	37.0 (18, 72)	38.0 (18, 77)
Male gender, n (%)	40 (56)	180 (54)	201 (61)	175 (53)	77 (50)	89 (58)	75 (48)
Caucasian, n (%)	65 (90)	271 (82)	275 (83)	263 (80)	138 (90)	130 (84)	137 (88)
Black, n (%)	1 (1)	9 (3)	8 (2)	9 (3)	2 (1)	5 (3)	1 (1)
Asian, n (%)	4 (6)	36 (11)	36 (11)	50 (15)	12 (8)	14 (9)	12 (8)
Other, n (%)	2 (3)	15 (5)	12 (4)	9 (3)	2 (1)	5 (3)	6 (4)
UC disease duration in years, mean (SD)	6.6 (7.3)	6.4 (6.2)	6.4 (6.3)	6.0 (6.7)	6.8 (6.9)	7.2 (7.0)	6.9 (7.0)
Extent of disease							
Limited to left side of colon, n (%)	43 (60)	193 (58)	191 (58)	188 (57)	80 (52)	93 (60)	86 (55)
Extensive	29 (40)	138 (42)	140 (42)	142 (43)	74 (48)	61 (40)	70 (45)
Mayo score (0 to 12), mean (SD)	8.2 (1.4)	8.6 (1.5)	8.5 (1.5)	8.3 (1.5)	8.1 (1.4)	8.5 (1.3)	8.3 (1.4)
Concomitant medications at baseline							
Any UC medications, n (%)	70 (97)	302 (91)	308 (93)	310 (94)	144 (94)	143 (93)	148 (95)
CS (excluding BUD)	35 (49)	142 (43)	145 (44)	134 (41)	77 (50)	79 (51)	83 (53)
BUD	2 (3)	6 (2)	9 (3)	8 (2)	6 (4)	4 (3)	5 (3)
Immunostimulatory drug	27 (38)	105 (32)	107 (32)	106 (32)	47 (31)	48 (31)	52 (33)
Aminosalicylic acid	59 (82)	270 (82)	267 (81)	276 (83)	128 (83)	119 (77)	125 (80)
Patients refractory, dependent, or intolerant of CS, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refractory	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
to past treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
to current treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients dependent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients intolerant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BUD = budesonide; CS = corticosteroids; GO = golimumab; SD = standard deviation; UC = ulcerative colitis.

3.2.3 Interventions

In PURSUIT-SC, three SC golimumab induction dose regimens were evaluated in part 1: 100 mg at week 0 and 50 mg at week 2 (100 mg–50 mg); 200 mg at week 0 and 100 mg at week 2 (200 mg–100 mg); 400 mg at week 0 and 200 mg at week 2 (400 mg–200 mg). These SC induction dose regimens were selected based on: 1) clinical data from use of intravenous infliximab in Crohn disease and UC and 2) estimates of the potency of golimumab relative to infliximab based on clinical data in rheumatoid arthritis. Doses for part 2 were selected after an interim analysis of data from part 1, and the 200 mg to 100 mg and 400 mg to 200 mg regimens were retained.

There were no differences in appearance between the syringes of placebo and golimumab. The designated pharmacists, or other appropriately licensed and authorized personnel who dispensed the study drug, and independent drug monitors were unblinded to study drug. Patients, site monitors, principal investigator, and all other investigational site staff were blinded to study drug assignment.

3.2.4 Outcomes

The Mayo score is calculated as the sum of the four subscores of stool frequency, rectal bleeding, physician's global assessment, and endoscopy findings (Appendix 5: VALIDITY OF OUTCOME MEASURES for further details). A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severe disease. The partial Mayo score is the Mayo score excluding the endoscopy subscore. If one or more of the four Mayo subscores was missing at a specific visit, but not all four subscores were missing, the last available value for each missing subscore was carried forward to impute a full Mayo score and a partial Mayo score at that visit. If all four subscores were missing at a specific visit, the Mayo score and partial Mayo score were considered missing at that visit. Mayo scores were calculated at weeks 0 and 6. The baseline Mayo score is defined as the Mayo score calculated just before the first administration of study drug at week 0. The endoscopy subscore taken during the screening sigmoidoscopy (or colonoscopy) was used to calculate the baseline Mayo score. Partial Mayo scores were calculated at weeks 0, 2, 4, and 6 using data obtained at those visits.[6,7]

Clinical response was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.[6,7]

Clinical remission was defined as a Mayo score ≤ 2 points, with no individual subscore > 1.[6,7]

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a disease-specific instrument composed of 32 Likert-scaled items. The total score ranges from 32 to 224 using the 7-point response options, with higher scores indicating better health-related quality of life. The IBDQ scale contains four component subscales: bowel symptoms, systemic symptoms, emotional function, and social function. Each subscale can be computed with total scores ranging from 10 to 70, 5 to 35, 12 to 84, and 5 to 35, respectively. In addition, a cut-off of a more than 20-point improvement from baseline in the IBDQ score was chosen to be consistent with the definition of IBDQ response in the UC population. The individual IBDQ dimensions were calculated when ≤ 1 item was missing in the dimension. The missing item was estimated using the average value across the non-missing items. If any one of the dimensions within the IBDQ could not be calculated, then the total IBDQ score could not calculated.[6,7]

The Short-Form (36) Health Survey (SF-36) questionnaire is a self-administered multi-domain scale with 36 items. Eight subscales cover a range of functioning: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The scoring yields a physical component summary score, a mental component summary score, and subscale scores. Higher scores represent better outcomes. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the benefit of different treatments. A change of three points in any of the subscales or five points for the component score is associated with clinically meaningful change. Each of the individual SF-36 subscales was calculated whenever ≥ 50% of the items that comprise the individual subscale were available (non-missing). Any missing items were estimated using the average value across the non-missing items. If < 50% of the items that comprise the subscale were available, the subscale was not calculated. If any of the individual subscales that comprise the SF-36 were missing, then the physical and mental component summary scores were not calculated.[6,7]

The EuroQol 5-Dimension Quality of Life Questionnaire (EQ-5D) is a standardized non–disease-specific instrument for describing and valuing health-related quality of life. The EQ-5D consists of five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problem, some problem, or extreme problem. It also contains a visual analogue scale (VAS). Patients are asked to indicate the level that describes their current level of function or experience for each dimension. As a measure of health status, it provides a descriptive profile and can be used to generate a single index value for health status, where full health is equal to 1 and death is equal to 0. The VAS records the subject's assessment of his/her own health along a vertical 20 cm line, which has health state scores between 0 and 100.[6,7]

3.2.5 Statistical Analysis

The primary hypothesis in PURSUIT-SC is that golimumab (at the selected dose[s]) is superior to placebo in inducing clinical response at week 6 in patients with moderately to severely active UC. The proportions of patients in clinical response at week 6 were summarized and compared between the placebo and golimumab groups using a two-sided chi-square test. The comparison between the 400 mg–200 mg group and the placebo group was first tested at the two-sided 0.05 level of significance. Only if this test was positive was the 200 mg–100 mg group compared with the placebo group at the same level of significance. The study was considered positive if the test involving the 400 mg–200 mg group was positive, regardless of the result of the test for the 200 mg–100 mg group.

The primary hypothesis of PURSUIT-MAINTENANCE is that golimumab (100 mg or 50 mg) is superior to placebo in maintaining clinical response through week 54 in patients with moderately to severely active UC induced into clinical response with golimumab in the induction studies. In this testing procedure, the comparison between the 100 mg group and the placebo group was first tested at the two-sided 0.05 level of significance. Only if this test was positive was the 50 mg group compared with the placebo group at the same level of significance. The study was considered positive if the test involving the 100 mg group was positive, regardless of the result of the test for the 50 mg group.

In PURSUIT-MAINTENANCE, patients who had any of the following events were considered a treatment failure from the time of event onward:

- an ostomy or colectomy (partial or total)
- discontinuation of study drug due to lack of therapeutic effect
- dose adjustment
- a prohibited change in UC medication.

Treatment failure rules were applied to all efficacy end points unless otherwise specified. For dichotomous end points, patients who had a treatment failure were considered not to have achieved the respective end points. For continuous end points, with the exception of corticosteroid end points, patients who had a treatment failure had their week 0 value from the induction study carried forward from the time of the treatment failure onwards. For corticosteroid end points, the week 0 value from the maintenance study was carried forward.

a) Analysis Populations

Unless otherwise specified, efficacy analyses were based on an intent-to-treat principle. Therefore, patients were analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

In PURSUIT-SC, the primary analysis population was patients randomized in part 2 after the dose selection, excluding those from site 7257. In PURSUIT-MAINTENANCE, the primary analysis population was patients randomized at week 0 (i.e., patients in clinical response to golimumab induction at week 0 of this maintenance study as determined by the interactive voice response system, excluding those from sites 6706 and 7257).

3.3 Patient Disposition

There were no major issues with respect to patient disposition. The proportion of patients who withdrew from the study was similar between groups and reasonably low.

TABLE 6: PATIENT DISPOSITION

	PURSUIT-SC				PURSUIT-MAINTENANCE		
	GO 100 mg–50 mg	**GO 200 mg–100 mg**	**GO 400 mg–200 mg**	**Placebo**	**GO 50 mg**	**GO 100 mg**	**Placebo**
Screened, N	NR	NR	NR	NR	NA	NA	NA
Randomized, N	72	331	331	331	154	154	156
Randomized and treated	71	331	331	331	154	154	156
Discontinued study drug, N (%)	2 (3)	3 (1)	4 (1)	7 (2)	43 (28)	45 (29)	43 (28)
Adverse event	2 (3)	1 (< 1)	1 (< 1)	3 (1)	12 (8)	12 (8)	17 (11)
Unsatisfactory effect					17 (11)	22 (14)	19 (12)
Lost to follow-up					2 (1)	1 (1)	1 (1)
Death					0	0	0
Other					12 (8)	10 (7)	6 (4)
Completed study					NA	NA	NA
Completed 16 week placebo					NA	NA	NA
Terminated study					NA	NA	NA
Prior to week 6					NA	NA	NA
Between week 6 and 16					NA	NA	NA
Completed study drug					NA	NA	NA
Completed study					NA	NA	NA
Entered maintenance					NA	NA	NA
Completed 16 week placebo					NA	NA	NA
Terminated study					NA	NA	NA
Prior to week 6					NA	NA	NA
Between week 6 and 16					NA	NA	NA
Patients who terminated study participation	6 (8)	7 (2)	9 (3)	13 (4)	18 (12)	21 (14)	18 (12)
Withdrew consent	2 (3)	2 (1)	3 (1)	4 (1)	10 (7)	11 (7)	5 (3)
Lost to follow-up	0	0	1 (< 1)	0	2 (1)	2 (1)	3 (2)
Death	0	0	0	0	0	0	0
Other	4 (6)	5 (2)	5 (2)	9 (3)	6 (4)	8 (5)	10 (6)
ITT, N	NR	NR	NR	NR	NR	NR	NR
PP, N	NR	257	258	256	147	149	148
Safety, N	NR	NR	NR	NR	154	154	156

GO = golimumab; ITT = intention to treat; NA = not applicable; NR = not reported; PP = per protocol.

3.4 Exposure to Study Treatments

In PURSUIT-SC, 16 patients received a single SC dose of golimumab or placebo but discontinued study treatment before the week 2 administration: seven in the placebo group, two in the 100 mg–50 mg group, three in the 200 mg–100 mg group, and four in the 400 mg–200 mg group.

In PURSUIT-MAINTENANCE, patients who subsequently lost response at any time during the study had their golimumab dose adjusted as follows:

- Placebo: Received golimumab 100 mg every four weeks
- Golimumab 50 mg: Re-randomized to receive golimumab 50 mg or 100 mg every four weeks
- Golimumab 100 mg: Before the implementation of Protocol Amendment 3, patients were re-randomized to receive golimumab 100 mg or 200 mg every four weeks. After the implementation of Protocol Amendment 3, patients received golimumab 100 mg every four weeks. Patients who had been re-randomized to golimumab 200 mg every four weeks before the implementation of Protocol Amendment 3 had their dose decreased to golimumab 100 mg every four weeks.

In PURSUIT-MAINTENANCE, 156 placebo patients received an average of 8.2 administrations, 154 GO 50 mg patients received an average of 11.1 administrations, and 154 GO 100 mg patients received an average of 11.3 administrations. A total of 115 out of 464 patients had a dose adjustment that resulted in an increased dose of golimumab. These patients received golimumab as follows from the time of dose adjustment onward:

- Placebo–100 mg: 76 patients received an average of 7.6 administrations
- 50 mg–100 mg: 25 patients received an average of 5.5 administrations
- 100 mg–200 mg: 14 patients received an average of 6.9 administrations.

3.5 Critical Appraisal

3.5.1 Internal Validity

The design of the PURSUIT studies was such that responders from the two induction studies were randomized into PURSUIT-MAINTENANCE. One would expect that the maintenance study should only include responders from the induction phase; however, this still represents a selected population of patients who both responded to and tolerated the drug. It appears that such a design is typical of biologics for UC. With respect to assessing harms, this design could bias results in favour of the study drug, as all enrolled patients had already demonstrated that they were able to tolerate the drug, at least in the short-term. With respect to efficacy, patients in PURSUIT-MAINTENANCE had already demonstrated that they responded to the drug, so the fact that all were proven responders might bias results in favour of golimumab. This bias might occur not only because of the enhanced response to golimumab, but also because of diminished responses with placebo. Patients in the placebo group had all been previously treated with golimumab in the induction study; thus withdrawing them from golimumab and replacing this with placebo might have led to even worse responses with placebo than if these patients had been treated with placebo throughout induction. On the other hand, a study design in which non-responders were included and no re-randomization occurred may have biased results in favour of golimumab, assuming the placebo group contained a larger proportion of non-responders from the induction phase.

Adequate measures appear to have been taken to maintain blinding. Patients in the placebo group received a placebo injection that was described as identical in appearance to golimumab. There do not appear to be any unique adverse effects of golimumab that occur with enough frequency to increase the

risk of patients being unblinded. Patients were made aware of the increased risk of cancer and serious opportunistic infections such as tuberculosis (TB) before the study; however, these events occurred infrequently and were not more common in any one group. Thus, it is unlikely that they would have impacted blinding in a meaningful way. Randomization was performed using an interactive voice response system, which would contribute to maintaining allocation concealment.

3.5.2 External Validity

The lack of an active control group is an important limitation of both PURSUIT studies. The natural comparator would be infliximab, the first monoclonal antibody to TNF approved for this indication. Because both drugs target TNF, the major difference between the two drugs would likely be the type of monoclonal antibody used, chimeric or human. These differences would likely be subtle, if evident at all, and thus a direct comparison between these two drugs is likely the optimal way to determine any differences between the two drugs. A longer follow-up might have also helped to uncover these differences.

The one year follow-up in PURSUIT-MAINTENANCE is likely not long enough to properly assess some of the key safety concerns associated with these drugs, particularly malignancy. Malignancies typically take years to develop, and there were very few events in the PURSUIT studies. Malignancies have been a key safety concern with the TNF inhibitors throughout their history, beginning with infliximab. The events are uncommon enough that it has proved challenging to characterize the extent of the risk, even with the many years of experience with infliximab.

Immune responses are also a key adverse effect associated with the use of monoclonal antibodies. However, the PURSUIT studies likely did not have a large enough sample size to assess a rare event such as anaphylaxis. Earlier monoclonal antibodies, such as infliximab, are thought to carry a higher risk of serious anaphylactic reactions because they are a hybrid of human and animal antibodies; however, this hypothesis has not been tested adequately in a comparison of infliximab and golimumab. As noted previously, there is no direct comparison of the two drugs; however, an indirect comparison would also be limited by the small sample size of the golimumab trials in UC.

Golimumab is approved for patients who "have had an inadequate response to or have medical contraindications for conventional therapies." [redacted][11] It is also not clear whether patients had an adequate trial of conventional therapies before an inadequate response was identified.

3.6 Efficacy

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

3.6.1 Clinical Response

More golimumab-treated patients achieved clinical response placebo-treated patients in both the induction (PURSUIT-SC) and maintenance studies (PURSUIT-MAINTENANCE). These differences were seen at both doses in PURSUIT-SC, although there was minimal difference in response between doses (GO 200 mg–100 mg: 52% of patients responded; GO 400 mg–200 mg: 55%), and both doses in PURSUIT-MAINTENANCE (GO 50 mg: 47%; GO 100 mg: 51%).

a) Subgroups: Disease Severity

In PURSUIT-SC, approximately 40% of patients had extensive disease. [redacted].

In PURSUIT-MAINTENANCE, most patients had moderate disease, thus complicating any analysis within these subgroups. Patients with moderate disease had results that were similar to those for the entire population, with a higher response rate in GO 50 mg (49%) and GO 100 mg (50%) groups versus placebo (32%). Patients with severe disease constituted < 10% of the overall population, and the response rate was low in the GO 50 mg group (22%), and much higher in the GO 100 mg group (55%) versus placebo (18%). It is not clear why such a relatively small number of patients in the maintenance study had severe disease.

b) Subgroups: Prior Steroid Responses

The majority of patients were refractory to, dependent on, or intolerant to oral corticosteroids in both studies. In PURSUIT-MAINTENANCE, statistically significant improvements versus placebo were seen only for the higher dose in each of the subgroups of refractory to, dependent on, or intolerant to oral corticosteroids (GO 100 mg 46% versus placebo 32%) or not (GO 100 mg 65% versus placebo 30%).

3.6.2 Clinical Remission

A higher proportion of golimumab-treated patients achieved remission compared with placebo-treated patients in both groups in PURSUIT-SC (GO 200 mg–100 mg: 19%; GO 400 mg–200 mg: 18%; placebo: 6%), and these differences were statistically significant. In PURSUIT-MAINTENANCE, a higher proportion of golimumab-treated patients also achieved remission compared with placebo-treated patients (GO 50 mg: 24%; GO 100 mg: 29%; placebo: 15%); however, these differences were only statistically significant at the higher 100 mg dose and not at 50 mg.

3.6.3 Quality of Life

Three separate instruments were used to assess quality of life in each of the included studies. [redacted]

3.6.4 Colectomy

The number of patients requiring colectomy was not reported in PURSUIT-SC. [redacted]

3.6.5 Other Efficacy Outcomes

In PURSUIT-MAINTENANCE, there was no difference between groups in the proportion of patients in remission and receiving concomitant steroids at week 0 but not at week 54. This outcome was not reported in the induction study.

A statistically higher proportion of golimumab-treated patients than placebo-treated patients had evidence of mucosal healing by end of treatment in PURSUIT-SC (GO 200 mg–100 mg: 43%; GO 400 mg–200 mg: 46%; placebo: 29%) and in PURSUIT-MAINTENANCE (GO 50 mg: 42%; GO 100 mg: 44%; placebo: 27%).

Several markers of disease activity were reported in the included studies. Change from baseline in C-reactive protein was improved with both golimumab doses versus placebo in the induction study;

[redacted]

TABLE 7: KEY EFFICACY OUTCOMES

Outcome[a]	PURSUIT-SC				PURSUIT-MAINTENANCE		
Clinical Response	**GO 200 mg–100 mg N = 331**	**GO 400 mg–200 mg N = 332**	**Placebo N = 330**		**GO 50 mg**	**GO 100 mg**	**Placebo**
N (%)	133/257 (52)	142/258 (55)	76/256 (30)	Week 54	72/153 (47)	78/154 (51)	49/156 (31)
RR (95% CI)	1.74 (1.40 to 2.18)	1.85 (1.49 to 2.31)			1.50 (1.13 to 2.00)	1.61 (1.22 to 2.13)	
NNT (95% CI)	5 (3 to 7)	4 (3 to 6)			6 (4 to 20)	5 (3 to 13)	
P value	*P* < 0.0001	*P* < 0.0001			*P* = 0.010	*P* < 0.001	
Clinical Remission							
N (%)	48/257 (19)	46/258 (18)	16/256 (6)	Week 30/54	36/153 (24)	44/154 (29)	24/156 (15)
RR (95% CI)	2.99 (1.74 to 5.12)	2.85 (1.66 to 4.90)			1.53 (0.96 to 2.44)	1.86 (1.19 to 2.90)	
NNT (95% CI)	8 (6 to 14)	8 (6 to 17)			NA	8 (5 to 25)	
P value	*P* < 0.0001	*P* < 0.0001			*P* = 0.091	*P* = 0.003	
QoL: IBDQ							
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]			[redacted]	[redacted]	
QoL: SF-36 PCS							
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	4.5 (7.1)	3.8 (7.6)	2.5 (7.2)		[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]			[redacted]	[redacted]	
QoL: SF-36 MCS							
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline	4.7 (10.7)	5.1 (10.3)	1.6 (8.8)		[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]			[redacted]	[redacted]	
QoL: EQ-5D							
Mean (SD) at baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

Outcome[a]	PURSUIT-SC			PURSUIT-MAINTENANCE			
Clinical Response	**GO 200 mg–100 mg N = 331**	**GO 400 mg–200 mg N = 332**	**Placebo N = 330**		**GO 50 mg**	**GO 100 mg**	**Placebo**
baseline							
P value	[redacted]	[redacted]			[redacted]	[redacted]	
Colectomy							
Patients with a colectomy (partial or full)[a]					[redacted]	[redacted]	[redacted]

CI = confidence interval; EQ-5D = EuroQol 5-Dimension Quality of Life Questionnaire; GO = golimumab; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = mental component summary; NA = not available; NNT = number needed to treat; PCS = physical component summary; QoL: quality of life; RR = relative risk; SD = standard deviation; SF-36 = Short-Form (36) Health Survey.

[a] Outcomes identified as important to the review (Section 2.2.1 for review protocol).

3.7 Harms

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

3.7.1 Adverse Events

The incidence of adverse events was relatively low and was similar between GO 200 mg–100 mg (38% of patients), GO 400 mg–200 mg (39%) and placebo (38%) groups in PURSUIT-SC. In PURSUIT-MAINTENANCE, 73% of patients in GO 50 mg and of GO 100 mg groups reported an adverse event versus 66% of those treated with placebo. The most common adverse event in the induction study was headache. The most common adverse event in the maintenance study was UC (GO 50 mg: 18%; GO 100 mg: 16%; placebo: 19%), followed by nasopharyngitis, headache, arthralgia, and abdominal pain.

3.7.2. Serious Adverse Events

There were a smaller number of golimumab-treated than of placebo-treated patients who experienced a serious adverse event in the induction study (3% in each golimumab group and 6% with placebo). In PURSUIT-MAINTENANCE, the incidence of serious adverse events was lower in the GO 50 mg group (8% of patients) and in the placebo group (8%) than in the GO 100 mg group (14%).

3.7.3 Withdrawals Due to Adverse Events

Few patients discontinued from study drug due to an adverse event in the induction study, and there was no difference between groups. [redacted]

3.7.4 Mortality

Across both studies there were two deaths, both in golimumab-treated patients. In the induction study, one patient in the GO 400 mg–200 mg group died of sepsis, while in PURSUIT-MAINTENANCE, one patient in the GO 100 group died of heart failure. This patient was in the GO 400 mg–200 mg group in the induction study.

3.7.5 Notable Harms

Infection is a potential harm associated with golimumab, and is due to golimumab's effects on TNF. In the induction study the incidence of infection was similar between groups (12% in each), but in PURSUIT-MAINTENANCE, the incidence of infection was higher with golimumab (39% of patients in each group) than with placebo (28%). No patients developed TB during the induction study, but a GO 100 mg patient and a placebo patient developed TB during PURSUIT-MAINTENANCE.

TABLE 8: HARMS

	PURSUIT-SC				PURSUIT-MAINTENANCE		
Adverse Events	**GO 200 mg–100 mg N = 331**	**GO 400 mg–200 mg N = 332**	**Placebo N = 330**		**GO 50 mg N = 154**	**GO 100 mg N = 154**	**Placebo N = 156**
Patients with > 0 AEs, N (%)	124 (37.5)	129 (38.9)	126 (38.2)		112 (72.7)	113 (73.4)	103 (66.0)
Most common AEs							
Headache	10 (3)	15 (5)	17 (5)	Ulcerative colitis	27 (18)	24 (16)	29 (19)
Nasopharyngitis	11 (3)	8 (2)	11 (3)	Nasopharyngitis	14 (9)	21 (14)	11 (7)
Pyrexia	6 (2)	10 (3)	7 (2)	Headache	12 (8)	12 (8)	14 (9)
Nausea	3 (1)	12 (4)	7 (2)	Arthralgia	11 (7)	8 (5)	12 (8)
				Abdominal pain	11 (7)	11 (7)	4 (3)
Serious adverse events							
Patients with >0 SAEs, N (%)	9 (2.7)	11 (3.3)	20 (6.1)		13 (8)	22 (14)	12 (8)
Most common SAEs							
Ulcerative colitis	[redacted]	[redacted]	[redacted]	Ulcerative colitis	[redacted]	[redacted]	[redacted]
Infections	1 (0.3)	3 (0.9)	6 (1.8)	Infections	5 (3.2)	4 (2.6)	3 (1.9)
Withdrawals due to adverse events							
Discontinued drug due to an AE, N (%)	1 (0.3%)	1 (0.3%)	3 (0.9%)		12 (8)	12 (8)	17 (11)
Most common reasons	NR	NR	NR		NR	NR	NR
Deaths							
Number of deaths, N (%)	0	1	0		0	1	0
Most common reasons							
Reason		Sepsis				Cardiac failure	

	PURSUIT-SC				PURSUIT-MAINTENANCE		
Adverse Events	**GO 200 mg–100 mg N = 331**	**GO 400 mg–200 mg N = 332**	**Placebo N = 330**		**GO 50 mg N = 154**	**GO 100 mg N = 154**	**Placebo N = 156**
Notable harms							
Infection	39 (11.8)	41 (12.3)	40 (12.1)		60 (39)	60 (39)	44 (28)
Tuberculosis	0	0	0		0	1	1
Other opportunistic infection	0	0	0		0	0	1 (CMV)
Injection-site reactions	11 (3.3)	10 (3.0)	5 (1.5)		3 (1.9)	11 (7.1)	3 (1.9)
Anaphylaxis	0	0	0		0	0	0
Malignancy	0	1 [redacted]	1 [redacted]			1 (lung)	
Markedly abnormal post baseline hematology							
Decreased Hb	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
WBC decreased	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
ANC decreased	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
ALC decreased	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

AE = adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; CMV = cytomegalovirus; Hb = hemoglobin; NR = not reported; SAE = serious adverse event; WBC = white blood cell count.

4. DISCUSSION

4.1 Summary of Available Evidence

Two double-blind RCTs met the inclusion criteria for this review. PURSUIT-SC (N = 1065) was a six-week induction study, and responders from this study were enrolled in PURSUIT-MAINTENANCE (N = 464), a 52-week study. Both studies compared more than one dose of golimumab versus placebo: in the induction study the approved 200 mg–100 mg dose was tested as well as a 400 mg–200 mg dose, and in the maintenance study both Health Canada-approved doses (50 mg and 100 mg) were tested. This design, in which only responders were enrolled into PURSUIT-MAINTENANCE, presents some important potential for bias, as it is a selected population. The primary outcome of both studies was clinical response, defined by Mayo scores, and in both studies there were statistically more golimumab-treated patients who achieved clinical response compared with placebo-treated patients. Clinical remission was also achieved by statistically more golimumab patients than placebo patients in the induction study but not in the lower 50 mg dose group in the maintenance study. [redacted]

Important events such as colectomy, serious opportunistic infections, malignancy, and anaphylactic reactions were infrequent and did not differ between groups in either of the studies.

4.2 Interpretation of Results

4.2.1 Efficacy

The two studies included in this review examined golimumab for induction and for maintenance of response in UC. The two studies, PURSUIT-SC (induction) and PURSUIT-MAINTENANCE, were interrelated, as responders from the induction study were enrolled in the maintenance study. As noted earlier in this review, this complicates analysis of findings from PURSUIT-MAINTENANCE; however, there is also an appropriate rationale for this design. The design allows for assessment of induction followed by maintenance regimens in the same population, and maintenance cannot be properly assessed unless these patients have responded to induction.

Health Canada has approved both the golimumab 50 mg and 100 mg doses for use as maintenance therapy in UC, and in fact, from the wording of the indication, it would appear that the 50 mg dose is first line, and the 100 mg dose is reserved as a secondary option. [redacted][11] Nonetheless, although the PURSUIT studies were not powered to detect differences between golimumab and placebo for secondary outcomes, statistically significant differences were consistently found for the higher 100 mg dose versus placebo, but — as mentioned previously — no statistically significant findings were reported for the 50 mg dose. Therefore, it remains to be determined whether golimumab in the 50 mg dose significantly improves a

patient's chance of remission or any quality of life parameters versus placebo, important considerations for patients who may rely on this drug for treatment of UC.

Clinical response (the primary outcome of both PURSUIT studies) and clinical remission, which were key efficacy outcomes of this review, are both based on results on the Mayo scoring system (Appendix 5). Clinical response is based on a minimum improvement in the Mayo system, while remission is based on a drop below a specific threshold on the Mayo score. First, it is not clear that either of these parameters— a change for clinical response or the threshold for remission — has been validated. It is not clear whether a 3-point reduction on the Mayo score has the same significance to the patient regardless of where they are on the scale. Furthermore, although the Mayo system is a widely used, validated scoring system, and is accepted by the US Food and Drug Administration, there are issues associated with its use. For instance, the physician assessment component is subjective, and the physician global assessment double-counts some of the symptoms in the scale. Additionally, stool frequency might not necessarily be an accurate reflection of disease activity, as the number of stools per day that would be considered "normal" can vary widely.

Quality of life is clearly a key issue of importance to patients with UC, and the PURSUIT studies assessed quality of life using three different instruments, including IBDQ, which is a disease-specific scale (for review of IBDQ, see Appendix 5). [redacted] The IBDQ has been validated and appears to be an accepted instrument for assessing health-related quality of life in IBD. [redacted] This might suggest that these scales are failing to capture characteristics of IBD that are of most importance to these patients. Nevertheless, it is surprising that neither of these validated and widely accepted scales was able to detect improvement in health-related quality of life with golimumab. Of note, the mean changes from baseline on all three quality of life scales were positive (showing improved quality of life) during PURSUIT-SC, both in the golimumab and the placebo arms. [redacted]

4.2.2 Harms

A number of serious safety issues have emerged with TNF monoclonal antibodies over their history. Several of these issues have a mechanistic rationale. Immunogenicity, for example, might be expected due to the monoclonal antibody technology. Immune reactions such as anaphylaxis have been a long-standing issue with monoclonal antibodies as a whole. TNF plays a role in immune function; thus, TNF inhibitors are expected to carry with them an increased risk of infection, including serious opportunistic infections, such as TB. There were more infections in the golimumab groups in PURSUIT-MAINTENANCE; however, the serious opportunistic infections such as TB occurred too infrequently to determine whether risk was altered with use of golimumab. The product monograph for golimumab does note the risk of serious infections with the TNF inhibitors, and it notes that these infections have also been observed with golimumab. The product monograph also states that all patients who plan to start golimumab must be assessed for both active and latent TB, and that patients with latent TB should be treated before initiating golimumab.

TNF also plays a role in cancer; thus, there has been a long-standing concern about TNF inhibition leading to an increased risk of malignancy, notably lymphoma. In the PURSUIT trials, there were very few occurrences of malignancy; too few to establish any trends. The 52 weeks of controlled treatment also comprise far too short a period to assess risk of malignancy with any drug, as cancer develops over a much longer time frame than that. The product monograph notes as a serious safety warning the increased risk of malignancies, particularly lymphoma, in children and adolescents. The monograph also notes the increased incidence of lymphoma with TNF inhibitors, as well as with golimumab in phase 2 and 3 clinical trials in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

Golimumab is the third monoclonal antibody to TNF to be used for UC. The main differences between the three drugs are the route of administration and the source of antibody. Infliximab, the oldest drug in the class, is chimeric-source and, thus, in theory might carry with it a higher risk of immune reactions; it is administered intravenously. Adalimumab does not have a Health Canada Notice of Compliance for UC but is approved for Crohn disease, and it appears that it is used off-label in clinical practice for UC. Adalimumab and golimumab are both human-source monoclonal antibodies to TNF and, thus might have a lower risk of immune reactions than infliximab. All three have demonstrated efficacy versus placebo (Appendix 7); however, there are no direct comparisons among these drugs. A number of the key harms of drugs in this class appear to be most logically explained by the fact that they inhibit TNF; thus, there is no reason to think that the risk of malignancy and serious infections would differ among any of these drugs. Only a well-designed direct comparison of sufficient duration would definitively determine whether one drug has an advantage over the other with respect to harms.

5. CONCLUSIONS

Two double-blind RCTs comparing golimumab to placebo, one using an induction regimen (PURSUIT-SC) and the other using a maintenance regimen (PURSUIT-MAINTENANCE), were included in this review. Results for the primary outcome, clinical response, were consistently statistically significantly in favour of golimumab versus placebo in each study. Remission was statistically significantly achieved only at the higher golimumab dose in the maintenance study, yet both this and the lower golimumab dose were approved by Health Canada. These results suggest that although a clinical response is attainable at the lower golimumab dose, remission might not be. [redacted]

The included studies had too small a sample and were too short in duration to adequately assess key outcomes such as need for colectomy, as well as infrequent harms such as malignancy, serious opportunistic infections, and serious immune reactions. No differences were detected between golimumab and placebo for any of these outcomes. The lack of a direct comparison with other TNF inhibitors is a limitation of this review.

APPENDIX 1: PATIENT INPUT SUMMARY

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

Brief Description of Patient Group(s) Supplying Input

The Crohn's and Colitis Foundation of Canada (CCFC) is a volunteer-based national charity consisting of approximately 65,000 supporters, dedicated to finding cures for Crohn disease and ulcerative colitis (UC), two of the primary forms of inflammatory bowel disease (IBD). The CCFC invests in IBD research, education and awareness and is Canada's top funder of IBD cure-related research. In the fiscal year 2013-2014 the organization received 9.5% of total revenues from the following manufacturers: AbbVie, Aptalis, Celltrian, Ferring, Janssen, Shire, Takeda, Vertex and Warner Chilcott. The funds are used to help sponsor patient education events, research and medical conferences, educational brochures, kids' camps and post-secondary scholarships for IBD patients. Pharmaceutical funding makes up less than 10% of the CCFC's total annual revenue. CCFC declared no conflict in the preparation of this submission.

The GI (Gastrointestinal) Society is the Canadian leader in providing evidence-based information on all areas of the GI tract and is committed to improving the lives of people with GI and liver conditions, supporting research, advocating for appropriate patient access to health care, and promoting GI and liver health. The GI Society gives lectures on various digestive conditions, has educational websites, provides patient information pamphlets, newsletters and other printed materials, and organizes support group meetings for those newly diagnosed as well of those who have lived with a GI condition for years. In the last two years, the GI Society has received funding from Abbott Laboratories Ltd, AbbVie Corporation, Amgen Canada Inc, Actavis (as Aptalis Pharma, Forest Laboratories, and Warner Chilcott), AstraZeneca Canada Inc., Bristol-Myers Squibb Canada, Canada's Research-Based Pharmaceutical Companies (Rx&D), Ferring Inc., Gilead Sciences Canada Inc., GlaxoSmithKline Inc., Hoffmann-La Roche Ltd., Janssen Canada, Merck Canada Inc., Medical Futures Inc., Novartis Pharma Canada Inc., Cubist Pharmaceuticals (as Optimer Pharma), Pfizer Canada Inc., Sanofi-Aventis Canada Inc., Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc. t declared no conflict of interest in preparation of this submission.

Condition and Current Therapy-Related Information

Information was compiled from patient interviews and conversations, a 2011 survey on the impacts of IBD completed by 430 Canadians, informational brochures, a recent questionnaire completed by 27 Canadians with UC, consultation with experts, and printed sources.

UC is a serious IBD consisting of fine ulcerations in the inner mucosal lining of the large intestine. Inflammation starts just above the anus and extends upward in a continuous manner, to variable distances. There is no cure. UC can occur at any point in life; however, evidence suggests a peak of onset in the early 20s and again in later years. The increasing rate of diagnosis has been greatest in young children. Canada has the highest reported prevalence and incidence in the world, with approximately 104,000 diagnosed with UC.

Rectal bleeding occurs in most UC patients; diarrhea, cramping abdominal pain, and constipation are common. If the diarrhea and blood loss are severe, anemia can result. Some patients have extra-intestinal manifestations of UC, including fever, inflammation of the eyes or joints, ulcers of the mouth or skin, tender inflamed nodules on the shins, reduced fertility in women, as well as other conditions.

Anxiety and stress are major factors. After 10 to 15 years, patients with UC have increased risk for colorectal cancer.

UC often has a profound effect on lives, physically, emotionally, and socially. It is particularly difficult for children and young adults, since it often affects a person's sense of self. Approximately half of the 2011 IBD survey respondents felt they missed out on each of the following activities: playing sports, school trips, family vacations, parties, and special events like graduations and weddings. One interviewee no longer uses public transportation as she once had a humiliating experience soiling herself due to a lack of washroom availability.

There are also financial impacts. According to the 2012 *Impact of Inflammatory Bowel Disease in Canada Final Report and Recommendations*, the economic costs of IBD are estimated at $2.8 billion in Canada. Indirect costs are dominated by work absences and patient out-of-pocket expenses and are higher than direct costs, which totalled $1.2 billion, a figure including medications, hospitalization, and physician visits. It is conservatively estimated that $11,900 annually is spent per person living with IBD in Canada. In the words of individual patients: *"*I miss work on a regular basis and it is affecting my chances of obtaining permanent employment as a teacher" and "I have low energy; I'm tired often. My employer does not understand and it affects my attendance.*"*

IBD affects the whole family. Caregivers often manage the patient's health and well-being, especially as there are increasing numbers of children being diagnosed. Challenges for caregivers include absences from work, which may jeopardize job security, high costs of care, and negative emotional and mental health effects, such as fatigue, stress, and depression. Caregivers may need to devote more resources to family members who are unable to complete day-to-day tasks such as errands, cooking, hygiene, etc., due to flaring IBD. The *Impact of Inflammatory Bowel Disease in Canada Final Report and Recommendations* estimated caregiver costs for parents of the 5,900 children in Canada with IBD at $7 million and overall caregiving cost for those severely affected at $86 million annually.

UC patients have reported that sustained remission/treatment response is more important than relieving any one symptom. The current treatment of UC includes managing the symptoms and consequences of the disease as well as attempting to reduce the underlying inflammation. Aminosalicylic acid helps settle acute inflammation and, for some patients, keep the inflammation inactive when taken long term. Oral prednisone and budesonide can help in moderate to severe UC, but prednisone tends to have greater side effects, including moon face, weight gain, skin thinning, low energy, and mood swings. Rectal formulations of corticosteroids are also available for topical relief, although these are inconvenient, making it difficult for patients to keep to routines, and may be ineffective if a patient has significant diarrhea. Immunosuppressants may reduce dependence on steroids and help patients with steroid-resistant disease, but it may take six or more months to see results.

Infliximab is the only biologic previously approved by Health Canada for UC and is dosed through intravenous infusions that can take from two to five hours every eight weeks and must be administered by a nurse, leading to extra travel time and expense. Rural patients find access to the drug and to specialists challenging. When UC causes the digestive system to cease proper functioning, a colectomy may be required. This removes diseased tissue, but is not a cure; the systemic disease remains. Patients are left with an external appliance to collect waste, which may become infected, and elimination remains frequent as the colon no longer reabsorbs water. For women, surgery may not be a viable solution as there is an increased risk of infertility.

Related Information About the Drug Being Reviewed

Patients have seen remarkable results from biologics when other treatments have failed; however, not everyone responds to the currently available treatments, so more options are essential. As an injectable biologic for moderate to severe UC, golimumab has the potential to improve the health and quality of life for many individuals currently suffering from ineffective treatments. All patients interviewed who had experience with golimumab through clinical trials felt that they had responded and saw significant improvements where previous medications had failed. Patients stated their washroom visits were less frequent, and abdominal pain, fatigue, and rectal bleeding were reduced. They also highlighted the lack of lengthy infusion treatments and reduced need for regular health care appointments, as golimumab can be administered at home once every four weeks by self-injection. Many were concerned about the cost of the drug and the possibility that they would no longer be able to afford the treatment at the end of their trials.

All patients who responded to the recent questionnaire would rather receive a biologic medication, despite the potential risks and side effects, than undergo a colectomy, even if their disease became very severe. It is expected with new and proven biologics that many patients will be able to have a more normal life in remission, and IBD will be a minor inconvenience. Individuals will no longer need to plan their activities around the availability of washrooms, and, in women who have experienced infertility due to flare-ups, research has shown similar fertility to the general population when their disease is in remission. Patients would require fewer hospital visits and would be more functioning members of society.

“The use of biologics has restored our child’s quality of life. He is now able to attend school on a regular basis. He has recently started extracurricular activities such as skating. He still has to manage [some] symptoms…but biologics have made it possible for our child to regain some sense of normalcy.”

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:	Aug 28, 2013
Alerts:	Weekly search updates until January 15 2013
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.hw	Searches for this word in within a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
*	Truncation symbol for one character
?	Truncation symbol for one or no characters only
.ti	Title
.ab	Abstract
.ot	Original title
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(simponi* or golimumab* or cnto148 or cnto-148 or 91X1KLU43E).ti,ab,mi,tn,ot,rn,hw,nm
2	476181-74-5.rn.
3	1 or 2
4	use pmez
5	(simponi* or golimumab* or cnto148 or cnto-148 or 91X1KLU43E).ti,ab.
6	*golimumab/
7	or 6
8	use oemezd
9	4 or 8
10	(colitis or bowel*).ti,ab,hw.
11	9 and 10
12	remove duplicates from 11

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

Grey Literature

Dates for Search:	August 2013
Keywords:	Simponi, golimumab
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
Hutas G. Curr Opin Mol Ther 2008;10(4):393-406.	Narrative Review
Smith K. Nat Rev Gastroenterol Hepatol. 2013 Jul;10(7):386.	News

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 9: OTHER OUTCOMES

	PURSUIT-SC				PURSUIT-MAINTENANCE		
	GO 200 mg–100 mg	**GO 400 mg–200 mg**	**Placebo**		**GO 50 mg N = 154**	**GO 100 mg N = 154**	**Placebo N = 156**
Patients n/N (%) in remission and receiving concomitant corticosteroids at week 0 but not at week 54					22/79 (28) *P* = 0.299	19/83 (23) *P* = 0.464	16/87 (18)
Patients n/N (%) with mucosal healing at week 6	[redacted]	[redacted]	[redacted]	At weeks 30 and 54	64 (42) *P* = 0.011	67 (44) *P* = 0.001	42 (27)
GOL-Ab positive at any time, patients, n					4	5	11
Markers of disease activity							
Fecal lactoferrin, mcg/mL							
Mean (SD) baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline, week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CRP, mg/L							
Mean (SD) baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline, week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fecal calprotectin							
Mean (SD) baseline	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline, week 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	PURSUIT-SC				PURSUIT-MAINTENANCE		
	GO 200 mg–100 mg	**GO 400 mg–200 mg**	**Placebo**		**GO 50 mg N = 154**	**GO 100 mg N = 154**	**Placebo N = 156**
Clinical response: Subgroups, n/N (%)							
Limited disease	[redacted]	[redacted]	[redacted]	Moderate disease	71/144 (49) *P* = 0.012	71/143 (50) *P* < 0.001	46/145 (32)
Extensive disease	[redacted]	[redacted]	[redacted]	Severe disease	2/9 (22) *P* = NE	6/11 (55) *P* = NE	2/11 (18)
Refractory to, dependent on or intolerant to oral CS							
Yes	[redacted]	[redacted]	[redacted]		50/113 (44) *P* = 0.124	54/117 (46) *P* = 0.014	38/119 (32)
No	[redacted]	[redacted]	[redacted]		22/40 (55) *P* = 0.070	24/37 (65) *P* = 0.013	11/37 (30)

CRP = C-reactive protein; CS = corticosteroids; GO = golimumab; GOL-Ab = golimumab antibodies; NE = not evaluable; SD = standard deviation.

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize evidence concerning the reliability, validity, scoring, and minimally clinically important difference of the following scales used to assess changes in ulcerative colitis (UC) disease activity and outcome measurement in the clinical trials:

- Mayo scoring system
- Inflammatory Bowel Disease Questionnaire (IBDQ).

Findings

Mayo Scoring System

The Mayo scoring system is one of the most commonly used disease activity indices in placebo-controlled trials in UC. In its complete form, it is composed of four parts: bleeding, stool frequency, physician assessment, and endoscopy findings. Each part is rated from 0 to 3, yielding a total score of 0 to 12. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severe disease. Two abridged versions have been developed and validated: the partial Mayo score that excludes the endoscopy subscore and the non-invasive 6-point score comprising only the bleeding and stool frequency portions.[12] The Mayo score and partial Mayo score were used in both PURSUIT-SC and PURSUIT-MAINTENANCE to assess clinical response to treatment. The Mayo score and the partial Mayo score have been demonstrated to correlate with patient assessment of change in UC activity.[12] Lewis et al. reported that a reduction of ≥ 3 points on the Mayo score and the partial Mayo score reflect a clinically meaningful change.[12] Lewis et al. also recommended clinical remission of UC be defined using a Mayo score of ≤ 2 points.[12]

Although the Mayo score is a widely recognized UC activity index and is accepted by regulatory bodies, including Health Canada and the US Food and Drug Administration, it may not be optimal. Cooney et al. argue that two components of the Mayo score — the physician global assessment and the endoscopy subscore — are subjective and introduce variability and lack of precision into the index. The physician's global assessments also includes a sigmoidoscopy score, which introduces double counts of some elements.[13]

Inflammatory Bowel Disease Questionnaire

The IBDQ was developed by Guyatt et al.[14] as a physician-administered questionnaire, and it is widely used for health-related quality of life (HRQoL) assessment in patients with inflammatory bowel disease (UC and Crohn disease).[15] It is a 32-item Likert-based questionnaire divided into four dimensions: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). Response to each of the questions is graded from 1 to 7 (1 being the worst situation and 7 the best). Therefore, the total IBDQ score ranges between 32 and 224, with higher scores representing better quality of life. The scores of patients in remission usually range from 170 to 190. An increase in IBDQ score of 16 to 32 points constitutes the upper and lower bounds of the clinically meaningful improvement in HRQoL in patients with Crohn disease.[16] Information on whether this correlation between score and levels of clinical improvement translates directly to UC was not available through the literature search for this summary.

A systematic review[16] of nine validation studies on the IBDQ for UC reported that the IBDQ was able to differentiate clinically important differences by demonstrating significant differences in score between patients with disease remission and patients with disease relapse in seven studies.[15] The IBDQ can also discriminate changes in the social and emotional state of patients; however, the correlation of this dimension with disease activity is not as high as the correlation with remission of bowel symptoms.[15] The IBDQ also demonstrated high test–retest reliability in all the four IBDQ dimensional scores. Six studies evaluated IBDQ for sensitivity to change, and all suggested it is a sensitive instrument to quantify changes in HRQoL relative to clinical activity changes in UC.[15]

Summary

The Mayo score and the partial Mayo score are commonly used disease activity indices in placebo-controlled trials in UC. Both have demonstrated correlation with patient assessment of change in UC activity. Mild, moderate, and severe disease activities are indicated by score ranges of 3 to 5 points, 6 to 10 points, and 11 to 12 points, respectively. Lewis et al. reported that a reduction of ≥ 3 points on the Mayo score and the partial Mayo score reflects a clinically meaningful change.[12] The IBDQ is a physician-administered 32-item questionnaire used to assess HRQoL in patients with inflammatory bowel disease (UC and Crohn disease).[15] It evaluates bowel and systemic symptoms, as well as emotional and social functions. Response to each of the questions is graded from 1 to 7 with overall score ranging from 32 (very poor HRQoL) to 224 (perfect HRQoL). Patients in symptomatic remission usually have a score of 170 or greater. An increase in IBDQ score of 16 to 32 points constitutes the upper and lower bounds of the clinically meaningful improvement in HRQoL in patients with Crohn disease.

APPENDIX 6: SUMMARY OF OTHER STUDIES

Aim

To summarize the PURSUIT-IV study, a phase 2 and 3, multicentre, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of golimumab induction therapy, administered intravenously, in patients with moderately to severely active ulcerative colitis (UC). This study was excluded from the systematic review because intravenous (IV) administration of golimumab is not approved by Health Canada.

Description of Study

PURSUIT-IV was divided into two parts. Part 1 was a phase 2 dose-ranging study used to evaluate the dose response of IV golimumab induction regimens and to determine the IV induction dose(s) of golimumab for further evaluation in part 2.[17] Part 2 was a phase 3 dose-confirming study to examine the safety and efficacy of the IV induction dose(s) that were selected for further evaluation based on part 1.

[redacted][17][redacted][17][redacted] Patients already enrolled in the study were followed per the protocol and were also eligible to enter PURSUIT-MAINTENANCE. A total of 291 patients were randomized to treatment, 214 patients to golimumab (62, 75, and 77 patients to the 1 mg/kg, 2 mg/kg, and 4 mg/kg groups, respectively) and 77 patients to placebo.[17]

The primary objectives of the study were:

- To evaluate the efficacy of IV induction regimens of golimumab in inducing clinical response in patients with moderately to severely active UC and
- [redacted]

Secondary objectives were:

- To evaluate the efficacy of IV induction regimens of golimumab in inducing clinical remission
- [redacted]
- [redacted]
- [redacted]

Inclusion and Exclusion Criteria

Study participants were adults aged 18 years or older. Further details of inclusion and exclusion have been provided in Table 10.

TABLE 10: DETAILS OF INCLUDED STUDIES

		PURSUIT-IV
Designs and Populations	Study design	DB RCT
	Locations	[redacted]
	Randomized (N)	291 [redacted]
	Inclusion criteria	Men or women 18 years of age or older with moderately to severely active UC as defined by a Mayo score of 6 to 12 inclusive at baseline (week 0), including an endoscopic subscore of ≥ 2. A biopsy result consistent with the diagnosis of UC, and patient must have been ambulatory (i.e., not at imminent risk of colectomy). Patient must have demonstrated an inadequate response to, or have failed to tolerate, at least one of the following conventional therapies: oral 5- aminosalicylic acid, oral corticosteroids, or the immunomodulators azathioprine or 6-mercaptopurine. Must have demonstrated corticosteroid dependence (i.e., an inability to successfully taper corticosteroids without a return of the symptoms of UC).
	Exclusion criteria	Imminent risk for colectomy, UC limited to the rectum only or < 20 cm of the colon, a stoma, a fistula, an obstruction, or adenomatous colonic polyps that were not removed. A history of latent or active granulomatous infection (including TB), a predisposition to infections, or a history of or increased potential for malignancy. A diagnosis or history of CHF, lymphoproliferative disease, SLE, or demyelinating disease.
Drugs	Intervention	Part 1 Golimumab solution for IV injection: 1 mg/kg, 2 mg/kg, and 4 mg/kg Part 2 Golimumab solution for IV injection: 2 mg/kg, and 4 mg/kg
	Comparator(s)	Placebo as IV injection identical in appearance to corresponding golimumab dose.
Duration	Run-in	NR
	Double-blind	6 weeks
	Follow-up	6 weeks (16 weeks follow-up for patients who did not enroll in PURSUIT-Maintenance)
	Primary end point	Clinical response at week 6, as measured by decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.
Outcomes	Other end points	Clinical remission (Mayo score ≤ 2 points, with no individual subscore > 1), and [redacted]
	Publications	None

DB = double-blind; CHF = congestive heart failure; IV = intravenous; NR = not reported; RCT = randomized controlled trial; SLE = systemic lupus erythematosus; UC = ulcerative colitis.
Source: PURSUIT-IV clinical study report.[17]

Baseline Characteristics

In general, baseline demographic characteristics were well balanced across patients randomized to placebo and golimumab groups. [redacted][17] Table 11 summarizes baseline characteristics of study participants.

TABLE 11: SUMMARY OF BASELINE CHARACTERISTICS OF RANDOMIZED PATIENTS

Title	Placebo N = 77	GO 1 mg/kg N = 62	GO 2 mg/kg N = 75	GO 4 mg/kg N = 77	Combined GO N = 214
Demographics					
Age, mean (SD)	40.9 (12.58)	40.7 (15.51)	42.3 (13.14)	39.9 (14.07)	41.0 (14.16
Male n (%)	47 (61.0)	41 (66.1)	36 (48.0)	50 (54.9)	127 (59.3)
White n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (kg), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Height (cm), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease characteristics					
Duration (years), mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Limited to left side of colon, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extensive, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mayo score, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication					
Any UC medications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS (excluding budesonide)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budesonide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunomodulatory drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6-MP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aminosalicylic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CS = corticosteroids; GO = golimumab; MP = mercaptopurine; SD = standard deviation; UC = ulcerative colitis.
Source: PURSUIT-IV clinical study report.[17]

Table 12 summarizes patient disposition. A total of 291 patients were randomized to treatment, with 214 to golimumab and 77 to placebo.[17] Breakdown of patients randomized to golimumab is as follows: 62 to 1 mg/kg, 75 to 2 mg/kg, and 77 to 4 mg/kg. One patient in the 2 mg/kg group was randomized but never treated. One patient randomized to the 4 mg/kg group received 0.4 mg/kg of golimumab because the infusion was stopped due to an adverse event; all other patients received the assigned treatment.[17]

[redacted][17]

TABLE 12: PATIENT DISPOSITION

	PURSUIT-IV				
	Placebo	GO 1 mg/kg	GO 2 mg/kg	GO 4mg/kg	Combined GO
Screened, N	291				
Randomized, N (%)	77	62	75	77	214
Completed study, n (%)	69 (89.6)	57 (91.9)	70 (93.3)	74 (96.1)	201 (93.9)
Entered MP, n (%)	[redacted]				
Completed 16 week visit	[redacted]				
Total withdrawals, n (%)	8 (10.4)	5 (8.1)	5 (6.7)	3 (3.9)	13.6 (6.1)
Most common reason for withdrawal					
Withdrawal of consent, n (%)	1 (1.3)	1 (1.6)	2 (2.7)	0	3 (1.4)
Lost to follow-up, n (%)	0	0	1 (1.3)	1 (1.3)	2 (0.9)
Other, n (%)	[redacted]				
ITT, N	NR	NR	NR	NR	NR
PP, N	NR	NR	NR	NR	NR
Safety, N	NR	NR	NR	NR	NR

GO = golimumab; ITT = intention to treat; MP = maintenance phase; PP = per protocol; NR = not reported.
Source: PURSUIT-IV clinical study report.[17]

Efficacy

[redacted][17]

At week 6, a greater proportion (44.0% and 41.6%) achieved clinical response in the part 1 and part 2 combined population among the 2 mg/kg and 4 mg/kg golimumab groups, respectively, compared with 30.1% in the placebo group, [redacted] (Table 13)[17]

[redacted][17]

TABLE 13: SUMMARY OF KEY EFFICACY OUTCOMES

Outcome	PURSUIT-IV				
	Placebo N = 73	GO 1 mg/kg N = 61	GO 2 mg/kg N = 75	GO 4 mg/kg N = 77	Combined GO N = 213
Primary outcome					
Clinical response, n (%)	22 (30.1)	22 (36.1)	33 (44.0)	32 (41.6)	87 (40.8)
P value		[redacted]	[redacted]	[redacted]	[redacted]
Secondary outcomes					
Clinical remission, n (%)	8 (11.0)	6 (9.8)	12 (16.0)	10 (13.0)	28 (13.1)
P value		[redacted]	[redacted]	[redacted]	[redacted]
Mucosal healing, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value		[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline in Mayo score at week 6					
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 6, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QoL: IBDQ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QoL: SF-36					
PCS: Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MCS: Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QoL: EQ-5D					
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outcome	PURSUIT-IV				
	Placebo N = 73	GO 1 mg/kg N = 61	GO 2 mg/kg N = 75	GO 4 mg/kg N = 77	Combined GO N = 213
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Colectomy, partial or full					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

GO = golimumab; EQ-5D = EuroQol 5-Dimension Quality of Life Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = mental component summary score; NR = not reported; NA = not applicable; PCS = physical component summary score; QoL = quality of life; SD = standard deviation; SF-36 = Short-Form (36) Health Survey.
Source: PURSUIT-IV clinical study report.[17]

Harms

The proportion of patients with treatment-emergent adverse events was slightly higher in the golimumab combined group (36.6%) compared with the placebo group (31.2%) through week 6.[17] [redacted][17] The most frequently reported system-organ class for adverse events in placebo-treated patients was general disorders and administration site conditions (9.1% in the placebo group and 4.2% in the golimumab combined group). Leukopenia was reported in 3 (1.4%) golimumab-treated patients and no placebo-treated patients. None of these events were serious or resulted in withdrawal of patients from the study.[17]

Generally, incidence of serious adverse events through week 6 was low and comparable in the golimumab combined and placebo groups (3.8% and 2.6%, respectively). The only serious adverse event that occurred in more than one patient was UC, occurring in four (1.9%) golimumab-treated patients and no placebo-treated patients.[17] [redacted]

[redacted][17]

Adverse events of special interest and severe intensity included severe sepsis in one patient in the 4 mg/kg golimumab group, [redacted][17]

TABLE 14: HARMS

	PURSUIT-IV				
AEs	**Placebo N = 77**	**GO 1 mg/kg N = 63**	**GO 2 mg/kg N = 74**	**GO 4 mg/kg N = 76**	**Combined GO N = 213**
Patients with > 0 AEs, N (%)	24 (31.2)	26 (41.3)	22 (29.7)	30 (39.5)	78 (36.6)
Most common AEs					
Colitis ulcerative, n (%)	2 (2.6)	3 (4.8)	5 (6.8)	0	8 (3.8)
Cough, n (%)	0	2 (3.2)	3 (4.1)	1 (1.3)	6 (2.8)
Headache, n (%)	1 (1.3)	1 (1.6)	3 (4.1)	2 (2.6)	6 (2.8)
Nasopharyngitis, n (%)	1 (1.3)	1 (1.6)	0	2 (2.6)	3 (1.4)
Nausea, n (%)	2 (2.6)	0	1 (1.4)	2 (2.6)	3 (1.4)
Pyrexia	0	1 (1.6)	2 (2.7)	0	3 (1.4)
SAEs					
Patients with > 0 SAEs, n (%)	2 (2.6)	2 (3.2)	3 (4.1)	3 (3.9)	8 (3.8)
Most common SAEs					
Colitis ulcerative, n (%)	0	2 (3.2)	2(2.7)	0	4 (1.9)

	PURSUIT-IV				
AEs	**Placebo N = 77**	**GO 1 mg/kg N = 63**	**GO 2 mg/kg N = 74**	**GO 4 mg/kg N = 76**	**Combined GO N = 213**
Gastrointestinal hemorrhage, n (%)	0	0	1 (1.4)	0	1 (0.5)
Cellulitis, n (%)	0	0	0	1 (1.3)	1 (0.5)
Sepsis, n (%)	0	0	0	1 (1.3)	1 (0.5)
Nephrolithiasis, n (%)	0	0	0	1 (1.3)	1 (0.5)
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Notable harms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; GO = golimumab; NR = not reported; SAEs = severe adverse events; WDAEs = withdrawal due to adverse events.
Source: PURSUIT-IV clinical study report.[17]

Summary

PURSUIT-IV was a phase 2 and 3 multicentre, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of golimumab induction therapy, administered intravenously, in patients with moderately to severely active UC. This study was excluded from the systematic review because IV administration of golimumab is not approved by Health Canada. [redacted][17] IV golimumab was generally well tolerated in this population, and the safety profile was similar to that observed with the subcutaneous route of administration and with other TNF inhibitor therapies. Enrolment in the study was terminated and [redacted][17]

APPENDIX 7: SUMMARY OF COMPARATORS

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

Aim

To summarize evidence from systematic reviews and randomized controlled trials (RCTs) on the use of conventional drugs (5-aminosalicylate [5-ASA], corticosteroids, azathioprine, 6-mercaptopurine, and probiotics) and TNF inhibitors other than golimumab (infliximab and adalimumab) for the treatment of ulcerative colitis (UC).

Findings

A focused search (with main concepts appearing in title or major subject heading) was conducted on key resources, including MEDLINE. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, RCTs, non-randomized studies, and guidelines. The search was also limited to English-language documents published between October 1, 2003, and October 10, 2013.

Conventional Therapies for Ulcerative Colitis

The literature search yielded six studies for this summary. One systematic review and meta-analysis[18] and another meta-analysis[19] assessed the efficacy of 5-ASAs in UC patients, and one Cochrane review[20] evaluated azathioprine and 6-mercaptopurine for maintenance of remission in UC. A meta-analysis[21] and a Cochrane review[22] evaluated probiotic use in induction and maintenance therapy for UC. Use of corticosteroids in UC was assessed by another review[23] evaluating onset of UC therapy. The six studies that met the selection criteria are summarized in Table 15.

5-Aminosalicylic Acid

Together, the two systematic reviews[18,19] that examined 5-ASA in the treatment of UC included data from a total of 86 RCTs involving 8,576 patients with UC. One review[18] examined the efficacy of 5-ASA compared with placebo in the treatment of UC. Failure of remission in active UC and relapse of disease activity in quiescent UC were outcomes of interest. In these regards, endoscopic evidence and clinical assessments (including using scoring systems such as Truelove and Witt scores) or other author-defined criteria were used to establish remission and relapse. 5-ASA resulted in less failure to achieve remission compared with placebo, with relative risk (RR) of 0.79 (95% confidence interval [CI], 0.73 to 0.85; $P = 0.009$). The 5-ASAs were also reported to prevent more relapse than placebo (RR 0.65; 95% CI, 0.55 to 0.76; $P = 0.02$). The study also compared efficacy of standard daily doses (≥ 2 g to 2.5 g) with high doses (> 2.5 g per day) and low doses (< 2 g per day) in inducing remission in active UC or preventing relapse in quiescent UC. The proportion of failure in the standard and high-dose groups (58.7%) was lower than that in the low-dose group (69.8%). However, the study also found that, in pooled data analysis, rates of failure to induce remission were not significantly different between the standard dose group (70.2%) and the high-dose group (69.1%). It was concluded that 5-ASAs are highly effective for inducing remission and preventing relapse in UC with doses greater than 2.0 g per day, although doses greater than 2.5 g per day do not appear to lead to higher remission rates.

The other review[19] evaluated the ability of various 5-ASA preparations (including oral versus rectal administration) to accomplish mucosal healing (MH) in UC patients. One limitation of this analysis was the variable clinical and endoscopic definitions for MH used in the reviewed studies. Of the patients

treated with oral 5-ASAs, 36.9% achieved MH, while 50.3% of those in the rectal-administration group achieved MH. Overall, 43.7% of UC patients treated with 5-ASA achieved MH. Pooled data from head-to-head comparisons showed that MH rates were higher in patients receiving higher doses, but rates were statistically significantly different only in the orally treated group. In the oral 5-ASA treated group, a head-to-head comparison of tablets and granulated treatment revealed no significant difference between treatments, though the granulated treatment seemed to be associated with higher MH (49%) than the tablets (34.9%) using original article definitions of MH. In the rectal-treatment group, higher MH rate was achieved by suppositories (62%) than by foam (51%) and by enema (46%). However, a statistically significant difference was not observed in head-to-head comparisons of studies using both 5-ASA foam and enema. The study concludes that 5-ASA preparations achieve MH in almost 50% of patients without a significant difference between oral or rectal treatment options.

TABLE 15: SUMMARY OF STUDIES ON CONVENTIONAL ULCERATIVE COLITIS TREATMENTS

First Author, Year; Study Design	Ford et al., 2011;[18] SR and MA	Romkens et al., 2012;[19] SR and MA	Timmer et al., 2012;[20] SR and MA (Cochrane)	Naidoo et al., 2011;[22] SR and MA (Cochrane)	Sang et al., 2010;[21] SR and MA	Masson et al., 2005a;[23] Review
Number and type of studies	37 RCTs	49 RCTs	6 RCTs	4 RCTs	13 RCTs	127 Studies
Patient characteristics	2,086 adult patients with mildly to moderately active UC	6,490 patients with UC	286 patients with UC in remission treated with AZA or 6-MP	664 patients with UC in remission	1,108 patients with UC	Patients with active UC
Intervention	Various 5-ASAs	Various 5-ASAs administered orally or rectally	AZA and 6-MP	Probiotics single species or as a cocktail species	Probiotics single species or as a cocktail species	Corticosteroids
Comparator	Placebo and an alternative dose of the same 5-ASA	Various 5-ASAs compared among each other	Placebo, 5-ASA, sulfasalazine, or methotrexate	No treatment, placebo, or any other intervention	Standard therapy for UC, or placebo	Placebo, 5-ASAs
Clinical outcomes measured	Failure to achieve remission in active UC and to prevent relapse in quiescent UC	Per cent (%) MH	Failure to maintain remission, any AE, and withdrawal due to AE	Clinical relapse Secondary: any AE	Remission rate and recurrence rate	Induction of remission
Adverse events	Nausea, vomiting, headache, and abdominal pain	NR	Pancreatitis, jaundice or hepatitis, and bone marrow suppression	Diarrhea, bloody stools, nausea and vomiting, and headache	NR	Adrenal suppression, osteoporosis
Conclusions	5-ASAs show a clear benefit over placebo in both the induction of remission of active UC and in	"5-ASA preparations achieved MH in nearly 50% of UC patients. There were no	"Azathioprine may be effective treatment for patients who have failed or cannot tolerate standard	"The available evidence does not support the use of probiotics as maintenance therapy in	"Compared with standard treatments, such as 5-ASA or mesalazine, the effect of	"In more severe active disease, systemic corticosteroids continue to dominate

First Author, Year; Study Design	Ford et al., 2011;[18] SR and MA	Romkens et al., 2012;[19] SR and MA	Timmer et al., 2012;[20] SR and MA (Cochrane)	Naidoo et al., 2011;[22] SR and MA (Cochrane)	Sang et al., 2010;[21] SR and MA	Masson et al., 2005a;[23] Review
	preventing relapse in quiescent UC. "Increasing the total daily dose of 5-ASA used, to at least 2.0 g, appears to both increase the likelihood of achieving remission and reduce the risk of disease relapse". P. 614	significant differences in MH between the various 5-ASA drugs, either in the oral or the rectal treatment groups". P. 2190	maintenance therapy with mesalazine or sulfasalazine or for patients who require repeated courses of corticosteroid to induce remission." P. 16	quiescent UC. No evidence was found to support the use of probiotics as an alternative to mesalazine for maintenance of remission in UC." P. 11	probiotics auxiliary therapy was not significantly different, but was obviously better than placebo therapy." P. 1909	treatment, although this is the area that is perhaps most lacking in evidence from clinical trials." P. 2080

5-ASA = 5-aminosalicylate; 6-MP = 6-mercaptopurine; AE = adverse event; AZA = azathioprine; MA = meta-analysis; MH = mucosal healing; RCT = randomized controlled trial; SR = systematic review; UC = ulcerative colitis.

[a] This is an extensive review of UC therapy chosen because of lack of recent literature evaluating corticosteroids in UC.

Corticosteroids

Despite the long-established efficacy of corticosteroids in the treatment of UC, there is a paucity of RCTs or systematic reviews in recent literature in this regard. The reviews found in the literature search for this summary often made reference to older studies, including many from 1950s and 1960s. In the selected review,[23] the author references several such dated studies to support the efficacy of corticosteroids to induce remission in mildly to moderately active disease that is not responsive to other therapy, or as primary therapy in severe disease. In one such reference, oral prednisone at 20 mg per day is reported to achieve a higher remission rate (77%) compared with sulfasalazine 8 g per day (48%). Locally acting corticosteroids with limited systemic absorption leading to reduced adverse events have been discussed. In this regard, budesonide is reported to demonstrate efficacy similar to that of prednisolone but without suppression of plasma cortisol levels. Although beclomethasone, another locally acting corticosteroid, was not found to be more effective than mesalazine in inducing remission, a combination of the two was more effective than mesalazine alone. The authors caution about the adverse events associated with corticosteroid use, including adrenal suppression and osteoporosis, which require that benefit of treatment be weighed against the risks. Corticosteroids are not recommended for use in maintenance therapy of UC. A prompt treatment of active disease with corticosteroids to achieve rapid symptomatic improvements followed by withdrawal of treatment is described as usually appropriate.

Immunomodulators (Azathioprine and 6-Mercaptopurine)

A Cochrane review[20] evaluating azathioprine (AZA) and 6-mercaptopurine for maintenance of remission in UC included six RCTs. The authors report that all the studies were small and there were various quality issues including three studies with unsatisfactory methodological quality, one study labelled as unclear risk on method of randomization, and a further four graded as unclear risk for issues with allocation concealment. In addition two of the included studies were rated as high risk of bias for lack of blinding and three studies were rated unclear risk for selective reporting. The authors state that based on four trials azathioprine was shown to be superior to placebo for prevention of relapse in UC, and the difference is statistically significant. The 6-mercaptopurine was compared with 5-ASA and methotrexate in one of the included trials. It was reported that 50% (7/14) of 6-mercaptopurine patients failed to maintain remission compared with 100% (8/8) of 5-ASA patients and 92% (11/12) of methotrexate patients. However, the authors of the Cochrane review[20] state that the results should be interpreted with caution as the study was unblinded and had a small sample size. They add that considering the well-established efficacy and safety of aminosalicylic acid for the maintenance of remission in UC, "antimetabolites cannot be recommended for first-line treatment for this purpose."[20] They conclude that there is insufficient evidence to assess superiority of azathioprine alone, or in addition to standard maintenance; and that given the potential for serious adverse events azathioprine may not be an ideal first-line therapy in quiescent UC.[20]

Probiotics

One Cochrane review[22] and one meta-analysis[21] assessed the use of probiotics in the treatment of UC. The Cochrane review included four studies involving patients with UC in remission. In two of the studies, patients were randomized to receive a probiotic preparation or mesalazine. Another trial randomized patients to receive a probiotic or placebo, and the fourth study had three arms with patients randomized to receive probiotics or mesalazine, or a combination of probiotic and mesalazine. The primary outcome measure in all the studies was relapse, which was defined variously as clinical activity index greater than four, or greater than six, endoscopic index greater than four, histological signs of acute inflammation, simple clinical colitis activity index score greater than four, and appearance of UC symptoms needing additional medical treatment. Two of the studies were rated as unclear risk of bias

for sequence generation in allocation of participants, all four studies were graded as unclear for allocation concealment, and one study was rated high risk of bias for being an open-label study. All other quality aspects of the included studies were rated as low risk. The systematic review found no evidence to support the use of probiotics as an alternative to mesalazine for the maintenance of remission in UC. The overall quality of evidence gathered from pooled analysis comparing probiotics to mesalazine was described as low due to high risk of bias and sparse data. Adverse events in probiotic-treated patients included diarrhea, nausea and vomiting, abdominal discomfort, distended abdomen, and flatulence. These adverse events were described as mild and well tolerated. Incidence of adverse events for patients treated with probiotics was not statistically significantly different from mesalazine.

The meta-analysis[21] involved 13 studies. While the quality of included study was not evaluated in the same manner as in the Cochrane review, the authors reported heterogeneity and a publication bias in included studies using inverted funnel plot analysis. Remission rates were 68.2% in the probiotic-treated group and 60.4% in the placebo group. There was no significant difference (remission rate 1.35; 95% CI, 0.98 to 1.85; *P* = 0.07). However, probiotics achieved lower recurrence rates (27.9%) than placebo group (39.2%). The difference was significant (recurrence rate 0.69; 95% CI, 0.47 to 1.01; *P* = 0.05).

Tumour Necrosis Factor-alpha Inhibitors for Ulcerative Colitis

The literature search yielded three studies: one Cochrane systematic review and meta-analysis[24] that assessed the efficacy and safety of infliximab versus placebo or corticosteroids for UC, and two RCTs that evaluated adalimumab versus placebo for UC.[25,26]

Infliximab

The Cochrane review[24] used for this summary included seven RCTs involving patients with moderate to severe UC who responded poorly to oral corticosteroids and who were given infliximab for the induction of remission in UC. The sample sizes were small except in two trials (ACT1 and ACT),[27] which had 364 participants each.

One study involving 20 patients was methylprednisolone-controlled with infliximab administered as 5 mg/kg at 0, 2, and 6 weeks followed by 8 weekly doses compared with methylprednisolone at 0.7 to 1 mg/kg daily for 1 week, then tapered.[24] The primary outcome was remission, defined as disease activity index (DAI) less than 3 within two weeks. All patients in both arms of this studies achieved remission.[24] The methylprednisolone-controlled trial was open label and was graded together with one double-blind placebo-controlled trial as unclear risk of bias. The remaining five studies were all A-rated in this regard.[24]

Another study involving 13 patients was prednisolone-controlled, with infliximab 5 mg/kg at 0, 2, and 6 weeks compared with prednisolone administered as 1.5 mg/kg daily for two weeks, then tapered.[24] Outcome measures were a) remission at 13 weeks, defined as absence of inflammatory symptoms in conjunction with MH, and b) therapy success, defined as a decrease of more than 5 points from baseline on the modified Truelove and Witts activity score, and to less than 10 points total at three weeks, as well as at 13 weeks.[24] No statistically significant difference was observed between infliximab and prednisolone (RR 0.70; 95% CI 0.28 to 1.77).[24] Five of seven patients receiving oral prednisolone developed Cushing-like symptoms, two developed facial acne, and one developed dysphoria. Adverse events were not mentioned in the methylprednisolone-controlled study.

Data for the two corticosteroid studies were not pooled. The authors stated that there is no evidence that infliximab is more effective than high-dose corticosteroids for inducing remission, although these two RCTs were quite small in sample size.[24]

Five studies in the Cochrane review involved a total of 827 participants, and they compared infliximab with placebo for the induction of remission of acute UC in patients who had failed to respond to conventional treatment using corticosteroids and immunosuppressants. Two studies (ACT1 and ACT 2), which had similarly relatively larger sample sizes, showed statistically significant benefit for infliximab. The results of a meta-analysis showed that infliximab was superior to placebo in achieving clinical remission at eight weeks (RR 3.2; 95% CI, 2.18 to 4.76), and was also superior in producing a clinical response (RR 1.99; 95% CI; 1.65 to 2.41).[24] No statistically significant benefit was demonstrated for the studies using smaller sample sizes in these regards.[24] Data were available from one study (n = 45) showing significant reduction in colectomy rates with infliximab (RR 0.44; 95% CI, 0.22 to 0.87).[24] No serious adverse events or infusion reactions were observed with infliximab, although a few patients receiving infliximab developed pruritus, headache, and upper respiratory or urinary tract infection.[24] One patient treated with placebo developed life-threatening sepsis. The authors report that in extension studies one patient treated with infliximab developed tuberculosis in ACT1 and one patient treated with infliximab developed histoplasmosis and died from acute respiratory distress syndrome in ACT 2.[24] Newly positive results for antinuclear antibodies and double-stranded anti-DNA antibodies occurred more frequently in the infliximab group than in placebo in both studies. There were two reports of possible delayed hypersensitivity reactions in patients receiving infliximab.[24]

The results of the systematic review and meta-analysis suggest that infliximab is effective in patients with moderate to severe UC with disease resistant to conventional therapy, including corticosteroids and or immunosuppressive drugs. The authors found that it was more effective than placebo for inducing clinical and endoscopic remission, achieving clinical response, and helping to avoid colectomy in the short-term.[24]

Adalimumab

This summary of adalimumab is based on two pivotal phase 3 double-blind RCTs, ULTRA 1 and ULTRA 2, in which adalimumab was studied in moderately to severely active UC that was resistant to conventional therapy. ULTRA 1 examined the efficacy of two induction doses of adalimumab (160–40 mg versus 80–40 mg) administered every other week, compared with placebo for eight weeks. The patients had all failed therapy with corticosteroids and/or immunosuppressants, but none had previously been exposed to a TNF inhibitor. A Mayo score of less than 2, with no individual score more than 1 at week 8, defined clinical remission. The study found that remission rates among patients with moderate to severe UC treated with the higher initial doses of adalimumab were twice as high as those for placebo at week 8 (19% versus 9%, respectively; $P = 0.031$).[25] The lower adalimumab dose was not more effective than placebo for inducing remission (10% versus 9%, respectively).[25]

ULTRA 2 was a longer-term (one year) investigation of the efficacy and safety of adalimumab in patients with moderate to severe UC (defined by Mayo score 6 to 12 points).[26] It involved 518 patients, all of whom were concurrently receiving oral corticosteroids, azathioprine, or 6-mercaptopurine. Unlike in ULTRA 1, 40% of patients had previously been exposed to infliximab, which had been discontinued for more than eight weeks before the start of ULTRA 2 because of loss of response or drug intolerance.[26] Participants were randomized 1:1 to receive placebo or adalimumab, administered at doses of 160 mg and 80 mg at week 0 and week 2, respectively, and then 40 mg at week 4 and every other week thereafter.[26] Patients treated with adalimumab achieved a significantly higher rate of clinical remission

than patients receiving placebo at week 8 (17% versus 9%, respectively; *P* = 0.019) and at week 52 (17% versus 9%, respectively; *P* = 0.004).[26] There was also a significant improvement in the clinical response rate among patients treated with adalimumab compared with placebo at week 8 (50% versus 35%, respectively; *P* < 0. 001) and at week 52 (30% versus 18%, respectively; *P* = 0.002).[26] In addition, more patients in the adalimumab arm achieved MH (41% versus 32%, respectively, at week 8; *P* = 0.032; and 25% versus 15%, respectively, week 52; *P* = 0.009)[26] The difference in clinical remission rates between adalimumab and placebo in infliximab-exposed patients did not reach statistical significance at week 8 (9% versus 7%, respectively). The difference was significant at week 52 for both the infliximab-naive group (22% versus 12% for placebo; *P* = 0.0290) and the infliximab-experienced group (10% versus 3% for placebo; *P* = 0.039).

The incidence of treatment-related adverse events was 33% in the adalimumab arm and 39% in the placebo arm.[26] Severe adverse events were 16% in the adalimumab arm and 14 % in the placebo arm, and serious adverse events were 12 % in both groups.[26] Discontinuation was slightly higher in the placebo group (13%) than in the adalimumab group (9%).[26] Significantly more patients receiving adalimumab than those receiving placebo had injection-site reactions (12% versus 4%, respectively; *P* < 0.001) or hematologic adverse events (2% versus 0%, respectively; *P* = 0.003%).[26]

Summary

The 5-aminosalicylic acid in the various dosage forms demonstrated efficacy and safety in induction and maintenance of remission in UC. They have also demonstrated effectiveness in inducing MH in mild to moderate UC. Corticosteroids are suitable for remission of severe disease and conditions that fail to respond to other drugs because of their effectiveness and rapid onset of action. Despite the long-standing wide acceptance of the importance of corticosteroids in this regard, evidence from clinical trials to buttress the position is lacking, more especially in recent literature. There was no conclusive evidence to support the role of probiotics in the treatment of UC. There was not enough evidence for meaningful conclusions to be made about the effectiveness of azathioprine or 6-mercaptopurine in UC. The available evidence suggests that infliximab and adalimumab are superior to placebo for the induction of clinical response and remission in UC that persists despite an adequate trial of conventional therapies. Both drugs were safe and well tolerated by patients. Infliximab also reduced the risk of colectomy compared with placebo. In two small studies comparing infliximab to high-dose corticosteroids, no significant difference in rates of clinical remission was observed.

APPENDIX 8: SUMMARY AND CRITICAL APPRAISAL OF MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS

Aim

The manufacturer conducted a network meta-analysis (NMA) based on a systematic review to evaluate the relative safety and efficacy end points of golimumab, infliximab, and adalimumab for the treatment of moderate to severe ulcerative colitis (UC) with inadequate response to conventional therapy. For efficacy, the following end points — clinical remission, clinical response, and mucosal healing (MH) at induction (week 6 or 8), maintenance (week 54) — were considered. This supplemental issue provides a summary and critical appraisal of the methods and main findings of the NMA.

Summary of Network Meta-Analysis

Rationale

The manufacturer indicated that the systematic review and NMA were undertaken because none of the randomized controlled trials (RCTs) compared golimumab head-to-head, and thus relative efficacy is unclear. The systematic review, meta-analysis, and NMA were also conducted to facilitate the development of health economic models for the Common Drug Review (CDR) submission.

Methods

Eligibility Criteria

The inclusion criteria for the systematic review were the following: RCTs with adult patients who have moderately to severely active UC with an inadequate response to conventional treatment (e.g., aminosalicylates, corticosteroids, and immunosuppressants). Treatment with one of the three tumour necrosis factor (TNF)-alpha drugs and the placebo and active treatment arms of included trials could each include concomitant therapy treatments such as aminosalicylates, corticosteroids, and immunosuppressants. RCTs reporting only outcomes among patients with no prior anti-TNF-alpha experience were included. RCTs must have reported on at least one of five efficacy outcomes (clinical remission, clinical response, mucosal healing, IBDQ response, and colectomy) and reported outcomes at eight weeks or later.

Intervention and Comparators

Golimumab:

- For the outcomes after induction the 200 mg/100 mg dosing was used from PURSUIT
- For the 54-week outcomes 100 mg every four weeks.

Infliximab:

- 5 mg/kg at week 0, 2, 6, and then at every eight weeks.

Adalimumab:

- Initial dose of 160 mg, two weeks later a dose of 80 mg, and maintenance dose of 40 mg every other week.

Outcomes

Data on the following key efficacy outcomes were extracted:

1) Clinical remission — defined as a Mayo score ≤ 2 with no individual subscore > 1 or as a Seo index < 120 points

2) Clinical response — defined as decrease from baseline in the total Mayo score by ≥ 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1 mucosal healing — defined as an endoscopy subscore of 0 or 1.

Data on two key safety outcomes were also extracted: serious adverse events (SAEs) and discontinuation due to adverse events.

Analysis

Bayesian indirect treatment comparison meta-analyses were performed for the outcomes described above. All outcomes were binary and were therefore modelled in a logistic regression model. Random-effects model using empirically informed heterogeneity priors due to the small number of trials for outcome after induction. With only three trials on three treatments for sustained outcomes at 54 weeks a fixed-effect model was used, as heterogeneity could not be estimated. For all outcomes, we recorded odds ratio (OR) with the associated 95% credible interval (CrI) for the control comparisons as well as the comparisons.

Results

Study and Patient Characteristics

Five RCTs (N = 2039) were included in the NMA. All the studies were parallel RCTs, placebo-controlled and double blind. The golimumab trial, PURSUIT, combined PURSUIT-SQ, a six-week study, and PURSUIT-maintenance, a subsequent 54-week study. PURSUIT-Maintenance included two major arms: those who responded to any golimumab dose regimen from either of the induction studies were randomized into the "target group"; and those who were golimumab non-responders or placebo responders and non-responders from the induction studies were followed in the "non-randomized group." Only golimumab induction responders were blinded throughout the 60-week study period; the remaining patients were unblinded at six weeks. Two trials assessed infliximab: ACT 1, a 54-week study, and ACT 2, a 30-week study; and two studies assessed adalimumab: ULTRA 1, an eight-week study, and ULTRA 2, a 52-week study.

The RCTs included patient populations consisting of adult patients (> 18 years of age) with UC, having moderately to severely active disease despite a trial of conventional therapies. At baseline for each study, the Mayo score was between 6 and 12 and endoscopy score of $\underline{\geq}$ 2, and no patients were treated previously with TNF-alpha inhibitors. All studies allowed use of open-label background therapy such as salicylates, corticosteroids, and immunosuppressants. The proportion of male patients enrolled in the studies ranged from 52.9% to 64.5%, and mean age was approximately 40 years; duration of UC was about six to seven years, except in the two ULTRA studies, in which the mean duration of UC was greater than eight years.

Results of the Network Meta-Analysis

Each TNF inhibitor had statistically significantly greater efficacy compared with placebo for each outcome, with the exception of adalimumab for mucosal healing. Golimumab was not statistically significantly different compared with infliximab and adalimumab. Infliximab was superior to adalimumab for all three outcomes. Relative efficacy between the comparators after induction is presented in Table 16.

TABLE 16: RELATIVE EFFICACY BETWEEN GOLIMUMAB, INFLIXIMAB, AND ADALIMUMAB AFTER INDUCTION (WEEK 6 OR WEEK 8) FOR REMISSION, RESPONSE, AND MUCOSAL HEALING

Comparison	Clinical Remission After Induction OR (95% CrI)	Clinical Response After Induction OR (95% CrI)	Mucosal Healing After Induction OR (95% CrI)
Golimumab versus placebo	**3.53 (1.68, 7.83)**	**2.54 (1.44, 4.53)**	**2.06 (1.17, 3.67)**
Infliximab versus placebo	**5.26 (2.94, 9.99)**	**4.15 (2.53, 6.82)**	**3.26 (2.21, 0.84)**
Adalimumab versus placebo	**2.22 (1.23, 3.98)**	**1.87 (1.18, 2.97)**	1.51 (0.96, 2.39)
Golimumab versus infliximab	0.68 (0.25, 1.80)	0.61 (0.29, 1.30)	0.62 (0.29, 1.31)
Golimumab versus adalimumab	1.59 (0.61, 4.23)	1.35 (0.65, 2.84)	1.36 (0.65, 2.84)
Adalimumab versus infliximab	**0.42 (0.17-0.97)**	**0.45 (0.23-0.89)**	**0.46 (0.25-0.84)**

CI = confidence interval; CrI = credible interval; OR = odds ratio.

For 54-week maintenance outcomes, each treatment had statistically significantly greater efficacy compared with placebo for each outcome. Additionally, golimumab was statistically significantly superior to adalimumab in clinical response (OR 1.80; 95% CrI, 1.01 to 3.21) and mucosal healing (OR 1.88; 95% CrI, 1.01 to 3.49).

TABLE 17: RELATIVE EFFICACY BETWEEN GOLIMUMAB, INFLIXIMAB, AND ADALIMUMAB FOR 54-WEEK CLINICAL REMISSION, CLINICAL RESPONSE, AND MUCOSAL HEALING

Comparison	Clinical Remission After Induction OR (95% CrI)	Clinical Response After Induction OR (95% CrI)	Mucosal Healing After Induction OR (95% CrI)
Golimumab versus placebo	**2.53 (1.77, 3.64)**	**3.28 (2.45, 4.44)**	**3.58 (2.62, 4.96)**
Infliximab versus placebo	**2.73 (1.50, 5.09)**	**3.40 (1.93, 6.15)**	**3.77 (2.14, 6.85)**
Adalimumab versus placebo	**2.00 (1.09, 3.91)**	**1.83 (1.10, 3.02)**	**1.99 (1.12, 3.31)**
Golimumab versus infliximab	0.93 (0.45, 1.88)	0.96 (0.50, 1.83)	0.95 (0.48, 1.81)
Golimumab versus adalimumab	1.26 (0.59, 2.60)	**1.80 (1.01, 3.21)**	**1.88 (1.01, 3.49)**
Adalimumab versus infliximab	0.72 (0.31-1.76)	0.54 (0.25-1.13)	0.50 (0.23-1.11)

CI = confidence interval; CrI = credible interval; OR = odds ratio.

Data were also reported for sustained clinical response and clinical remission. Sustained clinical response was defined as achieving response at the end of the maintenance study (52 to 54 weeks) conditional on also achieving response at the end of the induction studies (six to eight weeks). The same definition was used for clinical remission. Data extraction for this outcome is not described.
For safety results, discontinuation due to adverse events and serious adverse events was reported. There was no significant difference for discontinuation due to adverse events between any of the

comparisons. There were statistically significantly greater serious adverse events with golimumab compared with placebo and compared with infliximab.

TABLE 18: RELATIVE SAFETY END POINTS BETWEEN GOLIMUMAB, INFLIXIMAB, AND ADALIMUMAB FOR DISCONTINUATIONS DUE TO ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Comparison	Discontinuations Due to Adverse Events OR (95% CrI)	Serious Adverse Events OR (95% CrI)
Golimumab versus placebo	1.29 (0.60, 2.77)	**1.69 (1.22, 2.37)**
Infliximab versus placebo	0.90 (0.36, 2.29)	0.96 (0.57, 1.64)
Adalimumab versus placebo	0.64 (0.36, 1.13)	0.79 (0.44, 1.63)
Golimumab versus infliximab	1.45 (0.43, 4.81)	**2.12 (1.08, 4.23)**
Golimumab versus adalimumab	2.01 (0.78, 5.23)	1.76 (0.75, 3.29)
Adalimumab versus infliximab	0.72 (0.20-2.53)	1.23 (0.43-3.47)

CI = confidence interval; CrI = credible interval; OR = odds ratio.

Critical Appraisal of Network Meta-Analysis

The quality of the manufacturer's network meta-analysis was assessed according to the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.

Limitations

The network meta-analyses were based on study-level data, which does not allow for as complete an adjustment for differences in patient characteristics as could be achieved with patient-level data. Only five RCTs were included, limiting the precision of the effect size for each intervention. Safety outcomes, particularly in the ULTRA 2 trial and in PURSUIT, were not reported separately for anti-TNF-naive and anti-TNF-inadequate responders. Patients with previous inadequate clinical response to anti-TNF therapy made up about 40% of the total trial population in ULTRA 2. The PURSUIT study used a different design from the other clinical trials with re-randomization after four weeks. Patients in the golimumab arm of PURSUIT were proven responders, which might bias results in favour of golimumab. This bias might not occur only due to the enhanced response to golimumab, but due to diminished responses with placebo. Patients in the placebo group had all been previously treated with golimumab in the induction study and, hence, switching them from golimumab to placebo might have led to even worse responses with placebo than if these patients had been treated with placebo all through the induction phase. To adjust for this different design, both intention-to-treat and per-protocol analyses were completed using a Bayesian approach with prior distributions based on non-PURSUIT data to correct bias introduced from applying the ITT or PP approach.

Strengths

The network meta-analysis appears to have been well conducted and well reported, according to the ISPOR criteria. There was clear rationale for conducting the NMA. The details of the individual RCTs were well reported and in general have very similar patient characteristics, follow-up, and reporting of outcomes. The outcome measures assessed in the network meta-analysis were appropriate and consistent with the key efficacy assessments included in the CDR review, which were selected based on input from the clinical expert consulted for this review.

Summary

In the absence of adequate head-to-head trial data, the manufacturer conducted an NMA using study-level data for the TNF inhibitors, golimumab, infliximab, and adalimumab for the treatment of moderate to severe UC. Five placebo-controlled RCTs were included in the NMA, one for golimumab, and two each for infliximab and adalimumab. The NMA found that following induction, each TNF inhibitor was statistically superior versus placebo for each outcome (clinical response, clinical remission, and mucosal healing) at six or eight weeks, with the exception of adalimumab for mucosal healing. Golimumab was not statistically significantly different compared with infliximab and adalimumab for all three outcomes; infliximab was superior to adalimumab for all three outcomes. Likewise, there appeared to be little difference between the TNF inhibitors for outcomes at 54 weeks, except that golimumab showed superiority over adalimumab for clinical remission and mucosal healing. There was no significant difference for discontinuation due to adverse events between any TNF inhibitors. However, there were statistically significantly more serious adverse events with golimumab compared with placebo and with infliximab. Although the NMA was overall well conducted and reported, it was based on few RCTs with some variability in study design. Hence, it is uncertain, in the absence of supportive results from head-to-head trials, how meaningful these results are, which should be interpreted with caution.

TABLE 19: APPRAISAL OF NETWORK META-ANALYSIS USING INTERNATIONAL SOCIETY FOR PHARMACOECONOMICS AND OUTCOMES RESEARCH CRITERIA

ISPOR Checklist Item	Details and Comments
1. Are the rationale for the study and the objectives stated clearly?	The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2. Does the methods section include the following? • eligibility criteria • information sources • search strategy • study selection process • data extraction • validity/quality assessment of individual studies	• The eligibility criteria for individual RCTs were clearly stated. • Databases searched were clearly outlined along with the search time frame. • Search strategy was reported. • Inclusion and exclusion criteria were reported. • The items extracted from the included studies were clearly described. Data extraction methods were clearly described. Studies were assessed narratively and no objective tool was used for quality assessment. The specific design-issues of the PURSUIT trial were discussed at length in the report.
3. Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated. Each outcome is clearly defined with objective scores that were used in each of the included trials. One outcome that was reported, sustained clinical response and clinical remission, was not defined in the methods section.
4. 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 dichotomous outcome measures. • Odds ratios were reported and a rationale for the selection of random and fixed effects model was provided for induction and maintenance outcomes. • The handling of the PURSUIT study design was described narratively and the solution was to use a Bayesian approach with prior distributions obtained from non-PURSUIT data (sources not explicitly described). The analysis would then include both an intention-to-treat (60-week follow-up) and per-protocol (54-week) to minimize bias introduced by unblinding and non-randomization.

ISPOR Checklist Item	Details and Comments
	The use of sequential indirect comparisons was used.
5. Are sensitivity analyses presented?	No sensitivity analyses were performed.
6. Do the results include a summary of the studies included in the network of evidence? • individual study data? • network of studies?	• A table with patient characteristics was provided and the characteristics appear to be similar across the individual studies. • Trial duration of all included studies ranged from 6 to 8 weeks with induction phase and from 30 to 60 weeks for maintenance phase. • A figure showing the network of studies was provided. Outcomes in the network were assessed at 54 weeks.
7. Does the study describe an assessment of model fit?	• No assessment of the model fit was described.[a]
8. Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure including point estimates and 95% credible intervals as a measure of uncertainty.
9. Sensitivity/scenario analyses	• No sensitivity analyses were presented in the report.

ISPOR = International Society for Pharmacoeconomics and Outcomes Research; RCT = randomized controlled trial.

[a] According to the manufacturer, model fit analyses were not done due to the differential trial designs of PURSUIT versus ACT/ULTRA. A Bayesian approach using prior distributions of non-PURSUIT data was employed to minimize the bias. This prior consideration of adjusting the model made it clear which would be the optimal solution, so it was deemed by the manufacturer that a model fit statistic would not provide the appropriate answer. Also, according to the manufacturer, data were sparse, so there was no possibility to control for effect-modifiers.

REFERENCES

1. Fast facts: the impact of IBD in Canada 2012 [Internet]. Toronto: Crohn's and Colitis Foundation of Canada (CCFC); 2012. [cited 2013 Oct 15]. Available from: http://www.isupportibd.ca/pdf/ccfc.ca-impact-report-fast-facts.pdf
2. Simponi® (golimumab): 50 mg/0.5 mL, 100 mg/1.0 mL [product monograph]. Toronto: Janssen Inc.; 2013 Sep 19.
3. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association; 2013 [cited 2013 Oct 24]. Available from: https://www.e-therapeutics.ca Subscription required.
4. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate to severe ulcerative colitis. Gastroenterology. 2014;146(1):85-95.
5. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146(1):96-109.
6. Clinical study report C0524T17. A phase 2/3 multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of golimumab induction therapy, administered subcutaneously, in subjects with moderately to severely active ulcerative colitis [**CONFIDENTIAL** internal manufacturer's report]. Toronto: Janssen Inc.; 2011 Aug 11.
7. Clinical study report C0524T18. A phase 3 multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of golimumab maintenance therapy, administered subcutaneously, in subjects with moderately to severely active ulcerative colitis [**CONFIDENTIAL** internal manufacturer's report]. Toronto: Janssen Inc.; 2012 Jun 12.
8. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) [Internet]. In: Simponi (Golimumab) Injection. Company: Centocor Ortho Biotech Inc. NDA: 125289. Approval date: 4/24/2009. Rockville (MD): The Center; 2009 [cited 2013 Aug 13]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125289s0000TOC.cfm.
9. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Simponi (Golimumab) Injection. Company: Centocor Ortho Biotech Inc.. NDA: 125289. Approval date: 4/24/2009. Rockville (MD): The Center; 2009 [cited 2013 Aug 13]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125289s0000TOC.cfm.
10. CDR submission binder. Simponi® (golimumab) solution for injection 50mg/0.5mL, 100mg/1.0mL; Company: Janssen Inc. [**CONFIDENTIAL** manufacturer's submission]. Toronto (ON): Janssen Inc.; 2013.
11. Janssen response to October 8, 2013 request for additional information regarding the Simponi® UC CDR review. [**CONFIDENTIAL** additional manufacturer's information]. Toronto: Janssen Inc.; 2013 Oct 16.

12. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis [Internet]. 2008 Dec [cited 2013 Oct 7];14(12):1660-6. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2597552/pdf/nihms65682.pdf

13. Cooney RM, Warren BF, Altman DG, Abreu MT, Travis SP. Outcome measurement in clinical trials for ulcerative colitis: towards standardisation. Trials. 2007;8:17.

14. Guyatt G, Mitchell A, Irvine EJ, Singer J, Williams N, Goodacre R, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology. 1989 Mar;96(3):804-10.

15. Pallis AG, Mouzas IA, Vlachonikolis IG. The inflammatory bowel disease questionnaire: a review of its national validation studies. Inflamm Bowel Dis. 2004 May;10(3):261-9.

16. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. Gastroenterology. 1994 Feb;106(2):287-96.

17. Clinical study report C0524T16. A phase 2/3 multicenter, randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of golimumab induction therapy, administered intravenously, in subjects with moderately to severely active ulcerative colitis [**CONFIDENTIAL** internal manufacturer's report]. Toronto: Janssen Inc.; 2009 May 10.

18. Ford AC, Achkar JP, Khan KJ, Kane SV, Talley NJ, Marshall JK, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol. 2011 Apr;106(4):601-16.

19. Romkens TE, Kampschreur MT, Drenth JP, van Oijen MG, de Jong DJ. High mucosal healing rates in 5-ASA-treated ulcerative colitis patients: results of a meta-analysis of clinical trials. Inflamm Bowel Dis. 2012 Nov;18(11):2190-8.

20. Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012;9:CD000478.

21. Sang LX, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. World J Gastroenterol [Internet]. 2010 Apr 21 [cited 2013 Oct 7];16(15):1908-15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2856834

22. Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2011;(12):CD007443.

23. Masson S, Nylander D, Mansfield JC. How important is onset of action in ulcerative colitis therapy? Drugs. 2005;65(15):2069-83.

24. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;(3):CD005112.

25. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011 Jun;60(6):780-7.

26. Sandborn WJ, Van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65.

27. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.