Common Drug Review
Clinical Review Report

December 2016

Drug	Entyvio (vedolizumab)
Indication	Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a tumour necrosis factor-alpha antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids
Reimbursement request	As per indication
Dosage form	300 mg per vial for intravenous infusion
NOC date	2016-03-22
Manufacturer	Takeda Canada Inc.

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

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

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ABBREVIATIONS

CDAI	Crohn's Disease Activity Index
CDR	CADTH Common Drug Review
CI	confidence interval
CrI	credible interval
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions Questionnaire
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IDC	indirect comparison
ITT	intention-to-treat population
IV	intravenous
MCID	minimal clinically important difference
MCS	mental component summary
MD	mean difference
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
PCS	physical component summary
PY	patient-year
RD	risk difference
RR	relative risk
SF-36	Short Form (36) Health Survey
TNF	tumour necrosis factor
VAS	visual analogue scale

EXECUTIVE SUMMARY

Introduction

Crohn's disease is a chronic form of inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, but most commonly affects the ileum (i.e., small intestine) and colon (i.e., beginning of the large intestine). Common gastrointestinal symptoms experienced by patients with Crohn's disease include abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, itchiness or irritation around the anus, flatulence, and bloating.[1-3] According to Crohn's and Colitis Canada, there are approximately 129,000 Canadians living with Crohn's disease (one in 150 people), and it is estimated that 5,700 new cases of Crohn's disease are diagnosed each year.[1,4]

Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to the alpha4 beta7 integrin to inhibit leukocyte migration into the gut mucosa. Vedolizumab is currently approved by Health Canada for use in the following:

- Treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a tumour necrosis factor (TNF) alpha antagonist, or who have had an inadequate response with or intolerance to or have demonstrated dependence on corticosteroids
- Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or loss of response to or who were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.[5]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of vedolizumab intravenous (IV) infusion in accordance with the Health Canada–approved indication for the treatment of Crohn's disease. Vedolizumab has been previously reviewed through the CADTH Common Drug Review (CDR) for the treatment of ulcerative colitis.[6]

Vedolizumab is available in single-use vials containing 300 mg of vedolizumab. It is administered via IV infusion and must be reconstituted and diluted prior to administration.[5] For the treatment of Crohn's disease, the product monograph for vedolizumab recommends a dosage of 300 mg IV at initiation (i.e., week 0), two weeks, six weeks, and then every eight weeks thereafter. The product monograph states that therapy with vedolizumab should be discontinued for patients who fail to show evidence of therapeutic benefit by 14 weeks.[5]

Results and interpretation

Included studies

The CDR systematic review included two pivotal, phase 3, multi-centre, double-blind randomized controlled trials (GEMINI II and GEMINI III). Both studies enrolled adults with moderately to severely active Crohn's disease who had failed treatment with one or more TNF alpha antagonists, immunomodulators, and/or corticosteroids. The GEMINI II study included a six-week induction phase followed by a 46-week maintenance phase (i.e., total treatment duration of 52 weeks). The six-week induction phase of GEMINI II enrolled a total of 1,115 patients in the following two cohorts: A double-blind cohort randomized (3:2) to receive vedolizumab or placebo (n = 368) and an open-label cohort who were all treated with vedolizumab (n = 747). Patients in the double-blind cohort were scheduled to receive either 300 mg vedolizumab or placebo at weeks 0 and 2 (i.e., a total of two infusions). Those in the open-label cohort received unmasked 300 mg vedolizumab at weeks 0 and 2. In the maintenance phase of GEMINI II, patients from both the double-blind and open-label cohorts who received

vedolizumab in the induction phase and who demonstrated a clinical response at six weeks (i.e., a reduction in Crohn's Disease Activity Index [CDAI] score of at least 70 points) were randomized (1:1:1) to double-blind treatment with 300 mg vedolizumab every four weeks, 300 mg vedolizumab every eight weeks, or placebo. In accordance with the Health Canada–approved dosage regimen, the CDR review focused on the results of the 300 mg vedolizumab every eight weeks group. The maintenance phase began at the week 6 visit and concluded after 52 weeks.

The GEMINI III study was a multinational, randomized, double-blind, placebo-controlled study (N = 416). The study was designed such that 75% of the study population had failed previous treatment with at least one TNF alpha antagonist and 25% were naive to TNF alpha antagonist therapy. Patients were randomized (1:1) to receive either 300 mg vedolizumab or placebo at weeks 0, 2, and 6 (i.e., a total of three infusions).

Clinical remission (i.e., CDAI ≤ 150) at six weeks and enhanced clinical response (i.e., reduction in CDAI score of at least 100 points) at six weeks were the two primary end points of the induction phase of GEMINI II. Clinical remission in the overall study population at 52 weeks was the primary end point of the maintenance phase of GEMINI II. Clinical remission at six weeks in the TNF alpha-failure subpopulation was the primary end point in GEMINI III.

Efficacy

Induction treatment

Vedolizumab-treated patients were more likely to achieve clinical remission during the six-week induction phase than patients treated with placebo in both GEMINI II (15% versus 7%; adjusted risk difference [RD] 7.8%; 95% confidence interval [CI], 1.2 to 14.3) and GEMINI III (19% versus 12%; RD = 6.9%; 95% CI, 0.1 to 13.8); however, the difference was considered to be statistically significant only in GEMINI II, because of failure of the statistical testing hierarchy in GEMINI III. The proportion of vedolizumab-treated patients with clinical remission further increased at the week 10 evaluation compared with placebo (28.7% versus 13.0%; RD = 15.5%; 95% CI, 7.8 to 23.3) in GEMINI III. In the TNF alpha antagonist-failure subpopulation, there was no statistically significant difference between vedolizumab and placebo in the proportion of patients who achieved clinical remission (GEMINI II, RD = 6.2% [95% CI, −9.2 to 21.3]; and GEMINI III, RD = 3.0% [95% CI, −4.5 to 10.5]). This was the primary end point of GEMINI III; therefore, failure to demonstrate a statistically significant difference between vedolizumab and placebo stopped the statistical testing hierarchy at this end point. Similar to the evaluation conducted in the overall treatment population, the proportion of vedolizumab-treated patients with clinical remission increased at the 10-week evaluation compared with placebo (26.6% versus 12.1%; RD = 14.4%; 95% CI, 5.7 to 23.1) in GEMINI III. Although a large proportion of vedolizumab-treated patients failed to achieve clinical remission, the effect size was considered to be clinically relevant, particularly for patients who had failed treatment with one or more TNF alpha antagonists.

Enhanced clinical response at six weeks was one of the primary end points in the induction phase of GEMINI II, and there was no statistically significant difference between the vedolizumab and placebo treatment groups with respect to this outcome (31.4 % versus 25.7%; RD = 5.7%; 95% CI, −3.6 to 15.0; *P* = 0.2322). In GEMINI III, there was a greater proportion of vedolizumab-treated patients with enhanced clinical response compared with placebo at both week 6 and week 10 (RD = 16.4%; 95% CI, 7.7 to 25.2; and RD = 23.7%; 95% CI, 14.5 to 32.9). Results in the TNF alpha antagonist-failure subgroup analyses were similar to the overall populations in both studies. Both studies included a minority of patients (17% in GEMINI II and 3% in GEMINI III) with corticosteroids as their worst treatment failure

(i.e., naive to both TNF alpha antagonists and immunomodulators); subgroup data were not reported for these patients.

All patient-reported outcomes in the induction studies were considered exploratory by the manufacturer and no statistical testing was performed. Vedolizumab-treated patients demonstrated greater improvements from baseline in the Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form (36) Health Survey (SF-36) mental component summary (MCS), SF-36 physical component summary (PCS), EuroQol 5-Dimensions Questionnaire (EQ-5D) score, and EQ-5D visual analogue scale (VAS), although it is not known whether these differences were statistically significant.

Maintenance treatment

In GEMINI II, a statistically significantly greater proportion of vedolizumab-treated patients demonstrated clinical remission at 52 weeks compared with placebo (39.0% versus 21.6%; RD = 17.4%; 95% CI, 7.3 to 27.5; *P* = 0.0007). The proportion of patients achieving clinical remission was reduced in the TNF alpha antagonist-failure subgroup (28.0% with vedolizumab and 12.8% with placebo); however, the adjusted RD between the two groups was similar to the analysis using the overall treatment population (RD = 15.2%; 95% CI, 3.0 to 27.5). There was no statistically significant difference between the vedolizumab and placebo groups for the proportion of patients with durable clinical remission (i.e., clinical remission in at least 80% of study visits, including the visit at week 52) (21.4% versus 14.4%; RD = 7.2%; 95% CI, −1.5 to 16.0; *P* = 0.1036).

A statistically significantly greater proportion of vedolizumab-treated patients demonstrated enhanced clinical response at 52 weeks compared with placebo-treated patients (43.5% versus 30.1%; RD = 13.4%; 95% CI, 2.8 to 24.0; *P* = 0.0132) in GEMINI II. The proportion of patients achieving enhanced clinical response was reduced in the TNF alpha antagonist-failure subgroup, and the adjusted RD between the vedolizumab and placebo was 8.8% (95% CI, −4.6 to 22.1).

Patients who were being treated with concomitant corticosteroids at the start of the maintenance phase were to begin having their dosage of corticosteroids reduced according to a pre-specified tapering regimen. At the beginning of the maintenance phase, just more than half of the patients in the placebo (n = 82 [54%]) and vedolizumab (n = 82 [53%]) groups were receiving treatment with corticosteroids. A statistically significantly greater proportion of vedolizumab-treated patients achieved corticosteroid-free clinical remission at 52 weeks compared with the placebo group (31.7% versus 15.9%; RD = 15.9%; 95% CI, 3.0 to 28.7; *P* = 0.0154). In the TNF alpha antagonist-failure subgroup analysis, 24.4% of vedolizumab-treated patients achieved corticosteroid-free remission compared with no placebo-treated patients (RD = 24.4; 95% CI, 2.4 to 45.1).

All patient-reported outcomes in the GEMINI II maintenance study were considered exploratory by the manufacturer, and no statistical testing was performed. After 52 weeks, treatment with vedolizumab was associated with greater improvements in the IBDQ (mean difference [MD] 15.1; 95% CI, 4.4 to 25.9), SF-36 PCS (MD 3.5; 95% CI, 1.1 to 5.9); EQ-5D (MD −0.5; 95% CI, −0.9 to −0.1), and EQ-5D VAS (MD 12.4; 95% CI, 7.0 to 17.8) compared with placebo. The mean improvement in EQ-5D VAS exceeded the published minimal clinically important difference (MCID) of 8.2, whereas the mean improvement in SF-36 PCS was below the MCID of 4.2. Although the difference between vedolizumab and placebo in the IBDQ did not exceed the published MCID for the IBDQ (i.e., an improvement of ≥ 16),[7] the European product monograph for vedolizumab states that improvements in IBDQ were clinically meaningful.[8]

The manufacturer submitted an indirect comparison of vedolizumab versus infliximab and adalimumab using the Bucher method, with placebo as the common comparator. The manufacturer reported that vedolizumab was noninferior to infliximab for inducing and maintaining clinical remission (relative risk [RR] 0.15 [95% CI, 0.02 to 1.11] and RR 0.87 [95% CI, 0.45 to 1.69], respectively), but inferior for inducing and maintaining clinical response (RR 0.29 [95% CI, 0.12 to 0.74] and RR 0.52 [95% CI, 0.30 to 0.92]). The manufacturer also reported that, compared with adalimumab, vedolizumab was noninferior for inducing and maintaining clinical remission (RR 0.61 [95% CI, 0.34 to 1.07] and RR 0.58 [95% CI, 0.33 to 1.01]) and corticosteroid-free clinical remission (RR 0.41; 95% CI, 0.13 to 1.28), and inducing clinical response (RR 0.87; 95% CI, 0.67 to 1.14). Vedolizumab was inferior to adalimumab for maintaining enhanced clinical response (RR 0.56; 95% CI, 0.35 to 0.90) and clinical response (RR 0.51; 95% CI, 0.32 to 0.79). The manufacturer's claims of noninferiority are limited by the absence of any pre-specified noninferiority margins or considerations of the statistical power required to make such conclusions. In addition, there is substantial heterogeneity in the study design and in patient characteristics across the studies included in the indirect comparison. Overall, given the limitations of the manufacturer's analysis and the heterogeneity across studies, the comparative efficacy of these drugs is uncertain in both the induction and maintenance phases of treatment. Therefore, there is uncertainty with the manufacturer's conclusions regarding the noninferiority or inferiority of vedolizumab compared with infliximab and adalimumab.

Harms

The manufacturer conducted safety analyses for the induction phase and for the combined induction and maintenance phases (induction/maintenance). Data from the induction phase of GEMINI III were pooled with data from the induction phase of GEMINI II for the manufacturer's induction safety analysis and data from both phases of GEMINI II were used in the evaluation of safety in the induction/maintenance population.

A similar proportion of patients in the vedolizumab and placebo groups experienced at least one adverse event in the induction population (57% and 60%, respectively) and in the induction/maintenance population (88% versus 84%, respectively). Crohn's disease was the most common adverse event in the induction/maintenance population and was more frequently reported in the placebo group compared with the vedolizumab group (0.293 events per patient-year [PY] versus 0.230 events/PY). The next most commonly reported adverse events, arthralgia and pyrexia, were also more frequently reported in the placebo group (0.275 events/PY versus 0.193 events/PY and 0.238 events/PY versus 0.166 events/PY, respectively). Nasopharyngitis (0.267 events/PY versus 0.165 events/PY), back pain (0.129 events/PY versus 0.064 events/PY), and fatigue (0.129 events/PY versus 0.101 events/PY) were more frequently reported in the vedolizumab group compared with the placebo group (respectively).

The proportion of patients who experienced at least one serious adverse event was the same in the vedolizumab and placebo groups in the induction population (7% in each group) and slightly greater with vedolizumab in the induction/maintenance population (18% versus 15%, respectively). Crohn's disease was the only serious adverse event that occurred in at least 1% of patients in the induction population and was more commonly reported in the placebo group compared with the vedolizumab group (5% versus 3%, respectively). Nearly all of the serious adverse events in both the vedolizumab and placebo groups were classified as gastrointestinal disorders (12% in both groups) or infections and infestations (4% and 3%, respectively).

Withdrawals due to adverse events were more common in the placebo group compared with the vedolizumab group in both the induction (5% versus 3%, respectively) and induction/maintenance

populations (10% versus 8%, respectively). Crohn's disease was the most commonly cited adverse event leading to discontinuation in both the induction (4% with placebo and 1% with vedolizumab) and induction/maintenance populations (5% with placebo and 4% with vedolizumab). For the vedolizumab group, there were no other adverse events leading to discontinuation that were reported for more than one patient. One vedolizumab-treated patient experienced an infusion-related adverse event that resulted in discontinuation from GEMINI II.

The manufacturer reported that there were no malignancies reported in GEMINI III. In GEMINI II, four patients (four of 815; 0.5%) in the combined vedolizumab group (i.e., both dosage groups of vedolizumab) were diagnosed with a malignancy; there were no malignancies reported for the placebo group.[9]

The manufacturer conducted a number of indirect comparisons for safety end points in both the induction and maintenance phase. The manufacturer reported that vedolizumab was noninferior to the comparators for all safety end points with the exception of being associated with a reduced risk of withdrawals due to adverse events compared with infliximab in the maintenance phase, and a greater risk of serious adverse events compared with infliximab and adalimumab in the maintenance phase. These indirect comparisons were conducted with relatively short-term trials that were not individually powered to evaluate safety end points and were limited by substantial heterogeneity across the studies; therefore, the results may not be reflective of the comparative safety profile that would be observed in larger patient populations exposed for a greater duration of treatment.

Other considerations

Vedolizumab and infliximab are currently available only as solutions for IV administration, whereas adalimumab can be administered via subcutaneous injection. The manufacturer of vedolizumab is currently enrolling patients in phase 3 randomized controlled trials to evaluate the efficacy of a subcutaneous formulation of vedolizumab for the maintenance treatment of patients with Crohn's disease[10] and ulcerative colitis[11] and is planning a longer-term safety study for the subcutaneous formulation.[12] Patient group input indicated that IV infusion was not considered to be a major issue for most patients, noting that IV administration is currently required for some currently available treatments (e.g., infliximab). It should be noted that the product monograph for vedolizumab recommends that the infusion occur over 30 minutes,[5] which is less time than currently required for infliximab (i.e., not less than two hours).[13,14]

GEMINI II included a minority of patients with a draining fistula at baseline (n = 35) and the trial demonstrated that a greater proportion of vedolizumab-treated patients had closure of the fistula at week 52 (seven of 17, 47%) compared with placebo-treated patients (two of 18, 11.1%).[15] Vedolizumab is not currently indicated in the treatment of fistulizing Crohn's disease,[5] whereas infliximab is approved for use in the treatment of fistulizing Crohn's disease.[13,14] The clinical expert consulted by CDR noted that, for patients who fail to respond to conventional therapy, a TNF alpha antagonist would likely be used, although vedolizumab would be considered as an alternative if treatment with a TNF alpha antagonist is considered to be inappropriate for safety reasons or has shown to be ineffective. The manufacturer for vedolizumab is currently recruiting patients for a phase 4, double-blind randomized controlled trial to evaluate the use of vedolizumab in the treatment of fistulizing Crohn's disease (ENTERPRISE; N = 126 [estimated]).

The Australian Pharmaceutical Benefits Advisory Committee recommended the reimbursement of vedolizumab for the treatment of adults with severe Crohn's disease,[16-18] whereas the National Institute

for Health and Care Excellence and the Scottish Medicines Consortium have both accepted vedolizumab for use for the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a TNF alpha antagonist.[19,20]

Conclusions

Three phase 3, placebo-controlled, double-blind randomized controlled trials investigated the effects of vedolizumab on treatment induction (GEMINI II and GEMINI III) or maintenance (GEMINI II) in patients with moderate to severe Crohn's disease. Clinical remission was defined as a CDAI ≤ 150. Regulatory agencies and the clinical expert consulted by CDR noted that the definition of clinical remission was reflective of a clinically meaning improvement.

Patients who received vedolizumab were more likely to achieve clinical remission at six weeks than those who were treated with placebo in both GEMINI II and GEMINI III. The proportion of vedolizumab-treated patients who achieved clinical remission was greater at 10 weeks compared with that at six weeks in GEMINI III. In the subpopulation of patients who had previously failed treatment with at least one TNF alpha antagonist, treatment with vedolizumab was not associated with a statistically significant difference compared with placebo for inducing clinical remission at six weeks in either GEMINI II or GEMINI III, but a greater proportion of vedolizumab-treated patients in this subgroup did achieve clinical remission compared with placebo at 10 weeks in GEMINI III. The proportion of patients with an enhanced clinical response (defined as an improvement of at least 100 in CDAI) was greater at six and 10 weeks in GEMINI III, but there was no such difference versus placebo at six weeks in GEMINI II. In the maintenance phase of GEMINI II, a greater proportion of vedolizumab-treated patients demonstrated clinical remission and corticosteroid-free clinical remission at 52 weeks compared with placebo in both the overall population as well as the subpopulation of patients who had previously failed treatment with at least one TNF alpha antagonist. Compared with placebo-treated patients, a greater proportion of vedolizumab-treated patients demonstrated enhanced clinical response at 52 weeks in GEMINI II in the overall population, but not in the TNF alpha antagonist population. Vedolizumab-treated patients demonstrated greater improvements from baseline in the IBDQ, SF-36, EQ-5D, and EQ-5D VAS, although it is not known whether these differences were statistically significant. The improvement in EQ-5D VAS exceeded the published MCID, whereas the improvements in SF-36 and IBDQ did not. The included studies were not designed to investigate the efficacy of vedolizumab for mucosal healing or reducing the need for surgical intervention and efficacy end points.

The proportion of patients who experienced at least one adverse event or serious adverse event, or who discontinued due to an adverse event was similar between the vedolizumab and placebo groups across all of the included studies. Nasopharyngitis, back pain, and fatigue were more frequently reported in vedolizumab-treated patients compared with placebo treatment, but these did not lead to discontinuation of treatment. Infusion-related reactions were relatively rare and occurred at a similar frequency in the placebo and vedolizumab groups.

There were no studies in which vedolizumab has been compared directly to the TNF alpha antagonists, adalimumab and infliximab, for induction or maintenance treatment of Crohn's disease. Five indirect comparisons that were reviewed by CDR included comparisons of vedolizumab against other biologic treatments for Crohn's disease. However, each of these comparisons was limited by substantial heterogeneity associated with the study designs and patient characteristics of the studies included in the indirect comparisons, which precluded any definitive conclusions about the comparative efficacy and safety of vedolizumab compared with TNF alpha antagonists.

TABLE 1: SUMMARY OF RESULTS FROM THE GEMINI II AND GEMINI III INDUCTION PHASE STUDIES

End Point	Time Point	Parameter	Overall Population				TNF Alpha-Failure Population			
			GEMINI II		GEMINI III		GEMINI II		GEMINI III	
			Placebo	VDZ	Placebo	VDZ	Placebo	VDZ	Placebo	VDZ
Clinical remission	6 weeks	n (%)	10 (7)	32 (15)	25 (12.1)	40 (19.1)	3 (4.3)	11 (10.5)	19 (12.1)	24 (15.2)
		RD (95% CI)	7.8 (1.2 to 14.3)		6.9 (0.1 to 13.8)		6.2 (−9.1 to 21.3)		3.0 (−4.5 to 10.5)	
		RR (95% CI)	2.1 (1.1 to 4.2)		1.6 (1.0 to 2.5)		NA		1.2 (0.7 to 2.2)	
		P value	0.021		0.0478				0.4332	
	10 weeks	n (%)	NA		27 (13.0)	60 (28.7)	NA		19 (12.1)	42 (26.6)
		RD (95% CI)			15.5 (7.8 to 23.3)				14.4 (5.7 to 23.1)	
		RR (95% CI)			2.2 (1.4 to 3.3)				2.2 (1.3 to 3.6)	
		P value			< 0.0001				0.0012	
Enhanced clinical response	6 weeks	n (%)	38 (25.7)	69 (31.4)	47 (22.7)	82 (39.2)	15 (20.8)	23 (20.7)	35 (22.3)	62 (39.2)
		RD (95% CI)	5.7 (−3.6 to 15.0)		16.4 (7.7 to 25.2)		−0.1 (−12.1 to 11.9)		16.9 (6.7 to 27.1)	
	10 weeks	n (%)	NA		50 (24.2)	100 (47.8)	NA		39 (24.8)	74 (46.8)
		RD (95% CI)			23.7 (14.5 to 32.9)				22.0 (11.4 to 32.6)	
IBDQ	6 weeks	BL mean (SE)	114.5 (2.5)	122.1 (2.2)	122.7 (2.2)	122.7 (2.5)	NA		121.2 (2.4)	122.1 (2.8)
		Change from baseline (SE)	16.5 (2.75)	23.1 (2.28)	14.9 (2.16)	24.1 (2.14)			14.6 (2.45)	24.0 (2.42)
		MD (95% CI)	6.5 (−0.5 to 13.6)		9.1 (3.1 to 15.1)				9.4 (2.6 to 16.2)	
SF-36 PCS	6 weeks	BL mean (SE)	35.7 (0.59)	36.4 (0.54)	36.4 (0.59)	36.7 (0.60)	NA		35.7 (0.69)	36.4 (0.70)
		Change from baseline (SE)	2.4 (0.56)	3.5 (0.47)	2.2 (0.48)	3.3 (0.47)			2.2 (0.53)	3.3 (0.52)
		MD (95% CI)	1.0 (−0.4 to 2.5)		1.1 (−0.2 to 2.4)				1.1 (−0.4 to 2.5)	
SF-36 MCS	6 weeks	BL mean (SE)	35.0 (0.96)	36.4 (0.79)	36.6 (0.77)	37.4 (0.91)	NA		36.6 (0.88)	37.8 (1.06)
		Change from baseline (SE)	2.4 (0.86)	4.6 (0.71)	3.3 (0.70)	3.9 (0.70)			3.0 (0.80)	4.1 (0.79)

End Point	Time Point	Parameter	Overall Population				TNF Alpha-Failure Population			
			GEMINI II		GEMINI III		GEMINI II		GEMINI III	
			Placebo	VDZ	Placebo	VDZ	Placebo	VDZ	Placebo	VDZ
		MD (95% CI)	2.2 (0.0 to 4.4)		0.6 (−1.3 to 2.6)				1.1 (−1.1 to 3.3)	
EQ-5D	6 weeks	BL mean (SE)	8.2 (0.14)	8.0 (0.11)	7.8 (0.11)	7.9 (0.11)	NA		7.9 (0.12)	7.9 (0.13)
		Change from baseline (SE)	−0.3 (0.12)	−0.5 (0.10)	−0.2 (0.10)	−0.4 (0.10)			−0.1 (0.11)	−0.4 (0.11)
		MD (95% CI)	−0.2 (−0.5 to 0.1)		−0.2 (−0.5 to 0.1)				−0.2 (−0.5 to 0.1)	
EQ-5D VAS	6 weeks	BL mean (SE)	46.6 (1.72)	48.8 (1.38)	51.3 (1.27)	50.3 (1.47)	NA		51.1 (1.46)	50.0 (1.68)
		Change from baseline (SE)	5.4 (1.65)	6.9 (1.38)	4.8 (1.36)	9.6 (1.35)			3.9 (1.58)	9.7 (1.56)
		MD (95% CI)	1.5 (−2.8 to 5.7)		4.8 (1.0 to 8.6)				5.8 (1.4 to 10.2)	

BL = baseline; CI = confidence interval; EQ-5D = EuroQol Five Dimensions Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = mental component summary; MD = mean difference; NA = not applicable; PCS = physical component summary; RD = risk difference; RR = relative risk; SE = standard error; SF-36 = Short Form (36) Health Survey; TNF alpha = tumour necrosis factor alpha; VAS = visual analogue scale; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

TABLE 2: SUMMARY OF RESULTS FROM THE GEMINI II MAINTENANCE PHASE STUDY

End Point	Parameter	Overall Population		TNF Alpha-Failure Population	
		Placebo	VDZ	Placebo	VDZ
Clinical remission at 52 weeks	n (%)	33 (21.6)	60 (39.0)	10 (12.8)	23 (28.0)
	RD (95% CI)	17.4 (7.3 to 27.5)		15.2 (3.0 to 27.5)	
	RR (95% CI)	1.8 (1.3 to 2.6)		NA	
	P value	0.0007			
Enhanced clinical remission at 52 weeks	n (%)	46 (30.1)	67 (43.5)	16 (20.5)	24 (29.3)
	RD (95% CI)	13.4 (2.8 to 24.0)		8.8 (−4.6 to 22.1)	
	RR (95% CI)	1.4 (1.1 to 1.9)		NA	
	P value	0.0132			
Corticosteroid-free clinical remission at 52 weeks	n (%)	13 (15.9)	26 (31.7)	0 (0)	10 (24.4)
	RD (95% CI)	15.9 (3.0 to 28.7)		24.4 (2.4 to 45.1)	
	RR (95% CI)	2.0 (1.1 to 3.6)		NA	
	P value	0.0154			
Durable clinical remission at 52 weeks	n (%)	22 (14.4)	33 (21.4)	8 (9.8)	17 (19.3)
	RD (95% CI)	7.2 (−1.5 to 16.0)		9.6 (−0.9 to 20.0)	
	RR (95% CI)	1.5 (0.9 to 2.4)		NA	
	P value	0.1036			
IBDQ score at 52 weeks	BL mean (SE)	122.6 (3.42)	126.6 (3.52)	NA	
	Change from baseline (SE)	35.5 (3.81)	50.7 (3.88)		
	MD (95% CI)	15.1 (4.4 to 25.9)			
SF-36 PCS at 52 weeks	BL mean (SE)	37.5 (0.87)	37.9 (0.89)	NA	
	Change from baseline (SE)	5.9 (0.86)	9.4 (0.88)		
	MD (95% CI)	3.5 (1.1 to 5.9)			
SF-36 MCS at 52 weeks	BL mean (SE)	36.7 (1.18)	36.7 (1.24)	NA	
	Change from baseline (SE)	7.8 (1.15)	10.7 (1.17)		
	MD (95% CI)	3.0 (−0.3 to 6.2)			
EQ-5D at 52 weeks	BL mean (SE)	8.0 (0.18)	8.0 (0.17)	NA	
	Change from baseline (SE)	−1.0 (0.15)	−1.5 (0.15)		
	MD (95% CI)	−0.5 (−0.9 to −0.1)			
EQ-5D VAS at 52 weeks	BL mean (SE)	51.4 (2.12)	51.5 (2.13)	NA	
	Change from baseline (SE)	14.2 (1.91)	26.6 (1.94)		
	MD (95% CI)	12.4 (7.0 to 17.8)			

BL = baseline; CI = confidence interval; EQ-5D = EuroQol Five Dimensions Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = mental component summary; MD = mean difference; NA = not applicable; PCS = physical component summary; RD = risk difference; RR = relative risk; SE = standard error; SF-36 = Short Form (36) Health Survey; TNF alpha = tumour necrosis factor alpha; VAS = visual analogue scale; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II.[15]

TABLE 3: SUMMARY OF ADVERSE EVENTS IN THE SAFETY POPULATIONS

AEs, n (%)	Induction (GEMINI II and GEMINI III)		Induction/Maintenance (GEMINI II)	
	VDZ (N = 1,176)	PLA (N = 355)	VDZ (N = 154)	PLA[a] (N = 153)
Any AE	668 (57)	212 (60)	135 (88)	128 (84)
WDAE	37 (3)	17 (5)	12 (8)	15 (10)
SAE	86 (7)	25 (7)	28 (18)	23 (15)
Serious infection	13 (1)	2 (< 1)	6 (4)	5 (3)
WDSAE	24 (2)	10 (3)	9 (6)	7 (5)
Deaths	1 (< 1)	0	1 (< 1)	0

AE = adverse event; PLA = placebo; SAE = serious adverse event; VDZ = vedolizumab; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.

[a] Patients received VDZ during induction phase and were randomized to PLA for maintenance phase.

Source: Common Technical Document, section 2.7.4,[22] and Clinical Study Report for GEMINI II.[15]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Crohn's disease is a chronic form of inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, but most commonly affects the ileum (i.e., small intestine) and colon (i.e., beginning of the large intestine). Common gastrointestinal symptoms experienced by patients with Crohn's disease include abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, itchiness or irritation around the anus, flatulence, and bloating.[1-3] Crohn's disease–associated inflammation can also manifest outside the gastrointestinal tract, affecting the joints, eyes, and skin of the patient. Complications associated with Crohn's disease can include malnutrition, weight loss, anemia, bowel obstructions, fistulas, anal fissures, and ulcers.[3] In addition, patients with colonic Crohn's disease have been shown to have an increased risk of developing colon cancer.[3] According to Crohn's and Colitis Canada, there are approximately 129,000 Canadians living with Crohn's disease (one in 150 people), and it is estimated that 5,700 new cases of Crohn's disease are diagnosed each year.[1,4]

TABLE 4: CLASSIFICATION OF DISEASE SEVERITY IN CROHN'S DISEASE

Status	CDAI Score	Description from ACG Guidelines
Remission	< 150	Asymptomatic or without any symptomatic inflammatory sequelae
Mild to moderate	150 to 220	Ambulatory and able to tolerate oral alimentation without manifestations of dehydration, systemic toxicity, abdominal tenderness, painful mass, intestinal obstruction, or > 10% weight loss
Moderate to severe	220 to 450	Failed to respond to treatment for mild to moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting, or significant anemia
Severe	> 450	Persistent symptoms despite the introduction of conventional corticosteroids or biologic drugs as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess

ACG = American College of Gastroenterology; CDAI = Crohn's Disease Activity Index.
Source: American College of Gastroenterology.[23]

1.2 Standards of Therapy

Currently, there is no cure for Crohn's disease, and the therapeutic goals include inducing and maintaining clinical and endoscopic remission, reducing the need for long-term corticosteroid use, and preventing the development of colon cancer. Several drug classes are used in the treatment of Crohn's disease, including aminosalicylates, immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate), corticosteroids (e.g., prednisone), and tumour necrosis factor (TNF) alpha antagonists (e.g., infliximab and adalimumab).[3] All, except the TNF alpha antagonists, are commonly referred to as conventional therapies. Current medical management is based on a stepwise approach, with treatments being used sequentially and escalated to either newer therapies or higher doses as patients fail to respond to each step of treatment.[23] Most drugs have important adverse effects that may have short-term or long-term consequences.[3] Surgery, including total colectomy and ileostomy, may be considered for patients with serious complications or medically refractory disease.[23]

1.3 Drug

1.3.1 Indication and requested reimbursement criteria

Vedolizumab is a humanized IgG1 monoclonal antibody that binds to the alpha4 beta7 integrin to inhibit leukocyte migration into the gut mucosa. Vedolizumab is currently approved by Health Canada for use in the following:

- Treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, loss of response to, or were intolerant to immunomodulators or a TNF alpha antagonist, or who have had an inadequate response with or intolerance to or have demonstrated dependence on corticosteroids.
- Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or loss of response to or who were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.[5]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of vedolizumab intravenous (IV) infusion in accordance with the Health Canada–approved indication for the treatment of Crohn's disease. Vedolizumab has been previously reviewed through the CADTH Common Drug Review (CDR) for the treatment of ulcerative colitis.[6]

TABLE 5: INDICATION AND REQUESTED REIMBURSEMENT CRITERIA

Indication under review
Treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF-alpha antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids
Reimbursement criteria requested by the applicant
As per indication

CD = Crohn's disease; TNF = tumour necrosis factor.

1.3.2 Recommended dosage

Vedolizumab is available in single-use vials containing 300 mg vedolizumab. It is administered via IV infusion and must be reconstituted and diluted prior to administration.[5] For the treatment of Crohn's disease, the product monograph for vedolizumab recommends a dosage of 300 mg IV at initiation (i.e., week 0), two weeks, six weeks, and then every eight weeks thereafter. The product monograph states that therapy with vedolizumab should be discontinued for patients who fail to show evidence of therapeutic benefit by 14 weeks.[5]

1.3.3 Key comparators

Vedolizumab is the first integrin inhibitor approved for the treatment of Crohn's disease in Canada. There are currently two TNF alpha antagonists (infliximab and adalimumab) approved for use in Canada for the treatment of Crohn's disease. Similar to vedolizumab, infliximab is administered via IV infusion, whereas adalimumab is administered subcutaneously. The Crohn's disease indication for vedolizumab is limited to adult patients, which is more restrictive than the indications for infliximab and adalimumab (Table 6). Infliximab currently has the broadest indication for use in the treatment of Crohn's disease, being approved for use in the treatment of adults, children, and patients with fistulizing Crohn's disease. Adalimumab is approved for use in both adults and children with Crohn's disease.

The Health Canada–approved dosage regimens are similar for vedolizumab and infliximab, with administration occurring at weeks 0, 2, and 6 during the induction phase and every eight weeks during maintenance treatment.[5,13,14] Administration of adalimumab occurs more frequently during maintenance treatment (i.e., once every two weeks).[24] Dosing of infliximab is based on the patient's weight (i.e., 5 mg/kg), whereas dosing of vedolizumab and adalimumab is not adjusted based on the weight of the patient. The product monographs for adalimumab and infliximab indicate that the dosage of these products can be escalated in the event of non-response, incomplete response, and/or a disease flare.[13,14,24] In contrast, the dosage and administration section of the product monograph for vedolizumab does not specify that the dosage can be escalated.[5]

1.4 Previous Reviews by the CADTH Common Drug Review

Vedolizumab has been reviewed through the CDR process for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response or loss of response to or who were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist. The CADTH Canadian Drug Expert Committee (CDEC) recommended that vedolizumab be listed with clinical criteria and/or conditions for the above-noted indication.[6] Adalimumab for the treatment of moderately to severely active Crohn's disease was reviewed through the CDR process in 2007 and received a recommendation from the Canadian Expert Drug Advisory Committee to list with clinical criteria and conditions.[25,26] Infliximab (Remicade) has not been reviewed through the CDR process for the treatment of Crohn's disease; however, a CDR submission is currently pending for a subsequent entry biologic, infliximab (Inflectra), for the treatment of Crohn's disease.[14,27]

TABLE 6: KEY CHARACTERISTICS OF VEDOLIZUMAB, INFLIXIMAB, AND ADALIMUMAB

	Vedolizumab[5]	Infliximab[13]	Adalimumab[24]
Mechanism	Anti-integrin inhibitor	TNF alpha antagonist	
Indications[a]	**Adult CD** • Treatment of adults with moderately to severely active CD who have had an inadequate response to, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or who have had an inadequate response to, an intolerance to, or demonstrated dependence on CS	**Adult CD** • Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction of CS use in adults with moderately to severely active CD who have had an inadequate response to a CS and/or aminosalicylate. **Pediatric CD** • Reduction of signs and symptoms and induction and maintenance of clinical remission in children with moderately to severely active CD who have had an inadequate response to conventional therapy **Fistulizing CD** • Treatment of fistulizing CD in adults who have not responded despite conventional treatment	**Adult CD** • Reduction of signs and symptoms and induction and maintenance of clinical remission in adults with moderately to severely active CD who have had an inadequate response to conventional therapy • Reduction of signs and symptoms and induction of clinical remission in adults with moderately to severely active CD who have lost response to or are intolerant to infliximab **Pediatric CD** • Reduction of signs and symptoms and induction and maintenance of clinical remission in children with severely active CD and/or who have had an inadequate response to or were intolerant to conventional therapy and/or a TNF alpha antagonist
Administration	IV		SC
Recommended Dose	**Adults (moderate to severe CD)** • Induction: 300 mg at weeks 0, 2, 6[b] • Maintenance: 300 mg q8w starting at week 6	**Adults (moderate to severe CD)** • Induction: 5 mg/kg at weeks 0, 2, 6 • Maintenance: 5 mg/kg q8w; 10 mg/kg for incomplete responders **Adults (fistulizing CD)** • Induction: 5 mg/kg at weeks 0, 2, 6 • Maintenance: 5 mg/kg q8w or 10 mg/kg q8w for those with relapse following an initial response **Pediatrics (moderate to severe CD)** • Induction: 5 mg/kg at weeks 0, 2, 6 • Maintenance: 5 mg/kg q8w	**Adult CD** • Induction: 160 mg at week 0; 80 mg at week 2 • Maintenance: 40 mg q2w beginning at week 4; dose escalation for patients with a disease flare or non-response **Pediatrics CD** • Induction: 160 mg at week 0; 80 mg at week 2 • Maintenance: 20 mg q2w beginning at week 4; 40 mg q2w for patients with a disease flare or non-response
Serious Side Effects or Safety Issues	• Serious infections • Infusion and serious allergic reactions	• Serious infections • Malignancy • Infusion and serious allergic reactions	• Serious infections • Malignancies, particularly lymphoma

	Vedolizumab[5]	Infliximab[13]	Adalimumab[24]
Other	• Not indicated for use in the treatment of children with CD	• Subsequent entry biologic available (Inflectra)[14] • CD indication has not been reviewed through the CDR process	• CD indication has been reviewed through the CDR process[25,26]

CD = Crohn's disease; CDR = CADTH Common Drug Review; CS = corticosteroids; IV = intravenous; SC = subcutaneous; TNF alpha = tumour necrosis factor alpha; q2w = every two weeks; q8w = every eight weeks.

[a] Health Canada indication.

[b] The Health Canada–approved product monograph for vedolizumab does differentiate between induction and maintenance dosage regimens; however, the manufacturer's pharmacoeconomic evaluation states that the standard dose of vedolizumab is 300 mg at weeks 0, 2, and 6 (induction) and every 8 weeks thereafter (maintenance).

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of vedolizumab IV infusion in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, have lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist, or who have had an inadequate response or intolerance to or have demonstrated dependence on corticosteroids.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 7.

TABLE 7: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

PATIENT POPULATION	Adult patients with moderately to severely active CD who have had an inadequate response to, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist or who have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids. Potential subgroups: • Disease severity at baseline • Previous therapy with a TNF alpha antagonist • Treatment-naive with both immunomodulators and TNF alpha antagonists
INTERVENTION	Vedolizumab (300 mg) administered as an IV infusion at 0, 2, 6 weeks and then every 8 weeks
COMPARATORS	• Infliximab • Adalimumab • Placebo

OUTCOMES	***Efficacy outcomes:***
	• Clinical remission
	• Clinical response
	• Mucosal healing determined by histology or endoscopy
	• Health-related quality of life
	• Need for surgery for CD
	
	Harms outcomes:
	• Mortality
	• SAEs
	• WDAEs
	• AEs including but not limited to:
	  ○ Injection-site reactions
	  ○ Hypersensitivity reactions
	  ○ Malignancy
	  ○ Hepatotoxicity
	  ○ Hematologic

STUDY DESIGN	Published and unpublished phase 3 RCTs

AE = adverse events; CD = Crohn's disease; IV = intravenous; RCT = randomized controlled trial; SAE = serious adverse events; TNF alpha = tumour necrosis factor alpha; WDAE = withdrawal due to adverse event.

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946 to present) with epub ahead of print, in-process records and daily updates via Ovid; Embase (1974 to 2016 May 18) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Entyvio and vedolizumab.

No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 19, 2016. Regular alerts were established to update the search until the CDEC meeting on September 21, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free) and Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two 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 8; 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 8 and described in section 3.2. A list of excluded studies is presented in Appendix 3: Excluded Studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

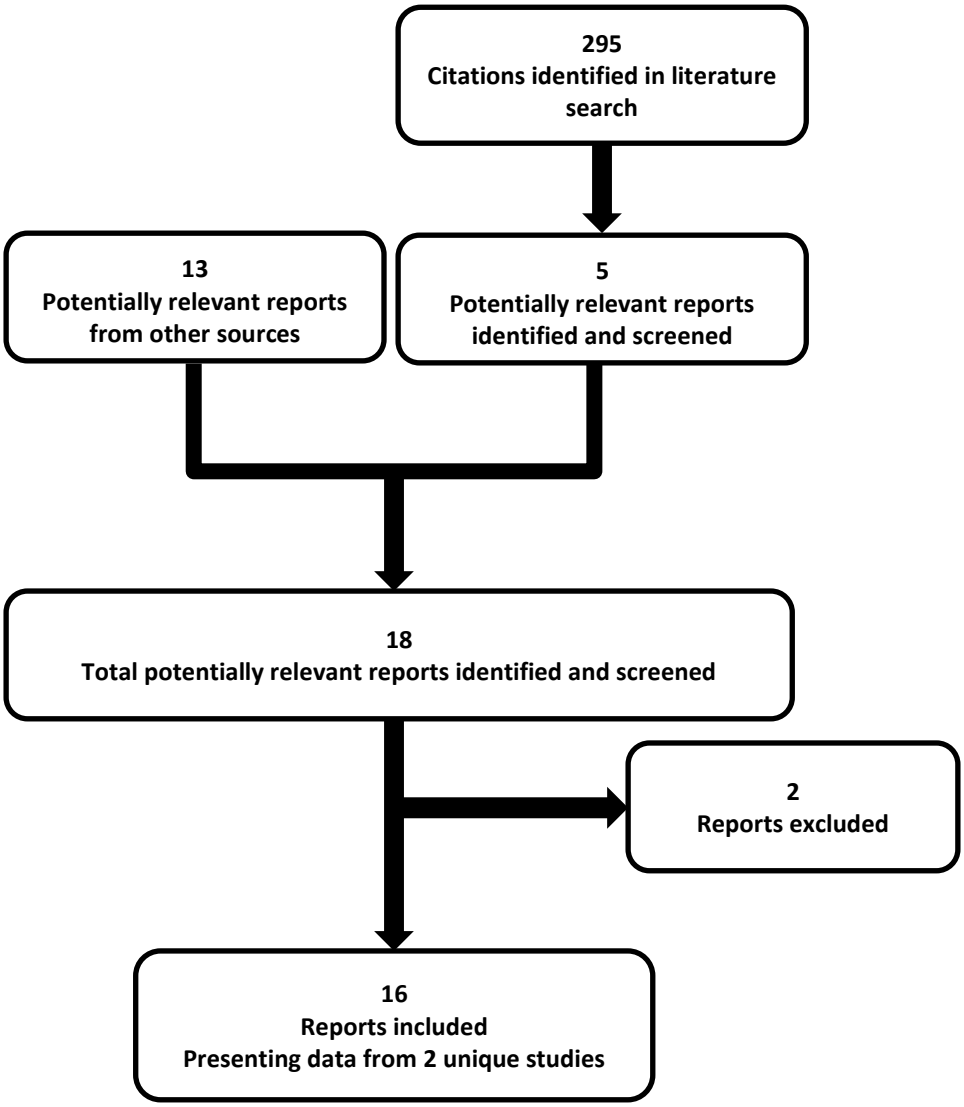


TABLE 8: DETAILS OF INCLUDED INDUCTION STUDIES

		GEMINI II (INDUCTION STUDY)[15]	GEMINI III[21]
DESIGNS AND POPULATIONS	**Study Design**	• Cohort 1: two-arm, 6-week, phase 3, placebo-controlled, DB RCT • Cohort 2: single-arm, 6-week, OL, uncontrolled, study	• Two-arm, 10-week, phase 3, placebo-controlled, DB RCT
	Locations	US, Canada, Europe, Asia, Australia	US, Canada, Europe, Asia, Australia

	Randomized (N)	• 1,115 enrolled:
		  ○ 368 randomized (3:2)
		  – 220 VDZ
		  – 148 placebo
		  ○ 748 non-randomized (OL VDZ)
			• 416 randomized (1:1):
			  ○ 209 VDZ
			  ○ 207 placebo

	Inclusion Criteria	• Age 18 to 80 years • Moderate to severe active CD • CD involvement of the ileum and/or colon • Inadequate response[a] or intolerance to ≥ 1: immunomodulator, TNF alpha antagonist, or CS	• Age 18 to 80 years • Moderate to severe active CD • CD involvement of the ileum and/or colon • Inadequate response[a] or intolerance to ≥ 1: immunomodulator, TNF alpha antagonist, or CS
	Exclusion Criteria	• Abdominal abscess at screening, other than a minimum of 10 aphthous ulcerations involving a minimum of 10 cm of intestine • Extensive colonic resection; colectomy • > 3 small bowel resections • Short bowel syndrome • Ileostomy, colostomy, or fixed symptomatic stenosis of the intestine • Active or latent tuberculosis	• Abdominal abscess at screening, other than a minimum of 10 aphthous ulcerations involving a minimum of 10 cm of intestine • Extensive colonic resection; colectomy • > 3 small bowel resections • Short bowel syndrome • Ileostomy, colostomy, or fixed symptomatic stenosis of the intestine • Active or latent tuberculosis
DRUGS	**Intervention**	• 300 mg VDZ (IV) at weeks 0, 2, 6	• 300 mg VDZ (IV) at weeks 0, 2, 6
	Comparator(s)	• Placebo	• Placebo
DURATION	**Phase**		
	Screening	20 days	20 days
	Induction	6 weeks	10 weeks
	Follow-up	Maintenance study (46 weeks)	2 years (if not participating in GEMINI-LTS)
OUTCOMES	**Primary End Points**	• Clinical remission at week 6 • Enhanced clinical response at week 6	• Clinical remission at week 6 (TNF alpha failure)
	Other End Points	• CRP levels at week 6 • IBDQ, SF-36, and EQ-5D at week 6 • AE, SAE, WDAE	• Clinical remission at week 6 (Overall) • Clinical remission at week 10 (TNF alpha failure; overall) • Sustained clinical remission at weeks 6 and 10 (TNF alpha failure; overall) • Enhanced clinical response (TNF alpha failure) • Closure of draining fistulas • CRP levels at weeks 6 and 10 • Fecal calprotectin levels at week 6

			• IBDQ, SF-36, and EQ-5D at weeks 6 and 10 • AE, SAE, WDAE
NOTES	**Publications**	• Sandborn et al., 2013[28,29] • ClinicalTrials.gov (NCT00783692)[30]	• Sands et al., 2013[31] • ClinicalTrials.gov (NCT01224171)[32]

AE = adverse event; CD = Crohn's disease; CRP = C-reactive protein; CS = corticosteroid; DB = double-blind; EQ-5D = EuroQol Five Dimensions Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; LTS = long-term study; OL = open-label; RCT = randomized controlled trial; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab; WDAE = withdrawal due to adverse event.
[a] Includes patients with a loss of response.

TABLE 9: DETAILS OF INCLUDED MAINTENANCE STUDY

		GEMINI II MAINTENANCE STUDY[15]
DESIGNS AND POPULATIONS	**Study Design**	Three-arm, phase 3, placebo-controlled, DB RCT
	Locations	US, Canada, Europe, Asia, Australia
	Randomized (N)	461 (1:1:1)
	Inclusion Criteria	Clinical response in either the DB or open-label phase of the induction phase
	Exclusion Criteria	As per induction phase.
DRUGS	**Intervention**	• 300 mg VDZ (IV) q8w • 300 mg VDZ (IV) q4w
	Comparator(s)	Placebo
DURATION	**Phase**	
	Induction	Weeks 0 to 6 (induction phase)
	Maintenance	Weeks 6 to 52
	Follow-up	2 years (if not participating in GEMINI-LTS)
OUTCOMES	**Primary End Points**	• Clinical remission at week 52
	Other End Points	• Enhanced clinical response at week 52 • Corticosteroid-free clinical remission at week 52 • Durable clinical remission • Time to disease worsening • Closure of draining fistulas • CRP levels • Extraintestinal manifestations of CD • Reduction in oral corticosteroid use • Time to major CD-related events • IBDQ, SF-36, and EQ-5D • AE, SAE, WDAE
NOTES	**Publications**	• Sandborn et al., 2013[28,29] • ClinicalTrials.gov (NCT00783692)[30]

AE = adverse event; CD = Crohn's disease; CRP = C-reactive protein; DB = double-blind; EQ-5D = EuroQol Five Dimensions Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; LTS = long-term study; q4w = every four weeks; q8w = every eight weeks; SAE = serious adverse event; SF-36 = Short Form (36) Health Survey; VDZ = vedolizumab; WDAE = withdrawal due to adverse event.

3.2 Included Studies

3.2.1 Description of studies

a) Induction studies

The CDR systematic review included two pivotal, multi-centre, double-blind randomized controlled trials (GEMINI II and GEMINI III). As shown in Figure 2, the GEMINI II study included a six-week induction phase followed by a 46-week maintenance phase (i.e., total treatment duration of 52 weeks). The six-week induction phase of GEMINI II enrolled a total of 1,115 patients in the following two cohorts:

- A double-blind cohort who were randomized (3:2) to receive vedolizumab or placebo (n = 368)
- An open-label cohort who were all treated with vedolizumab (n = 748).

The eligibility criteria for both the double-blind and open-label cohorts were identical. Patients in the double-blind cohort were scheduled to receive either 300 mg vedolizumab or placebo at weeks 0 and 2 (i.e., a total of two infusions). Those in the open-label cohort received unmasked 300 mg vedolizumab at weeks 0 and 2.[15] Only patients who were enrolled in the double-blind cohort were used in the efficacy evaluations for the induction phase of GEMINI II. The manufacturer reported that the open-label cohort of patients was used to ensure that there was a large enough cohort of induction phase responders who could be subsequently randomized into the maintenance phase (i.e., to ensure that the maintenance study was adequately powered).

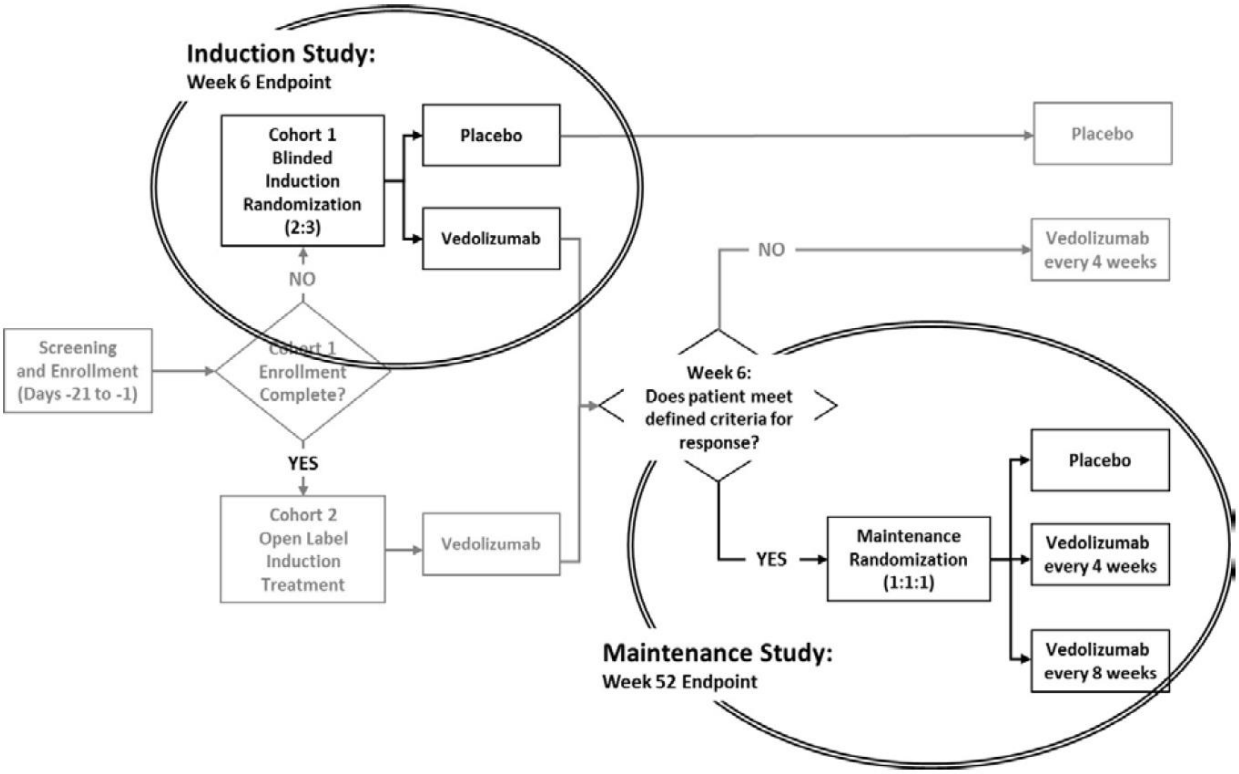
There were six protocol amendments during the GEMINI II trial, two of which resulted in changes that influenced the end points of the trial and the characteristics of the study population. Protocol amendment 2 was applied only to sites in the US and limited enrolment to patients who had previously demonstrated an inadequate response to, loss of response to, or intolerance to immunomodulators or TNF alpha antagonists.[15] Patients with corticosteroids as their worst treatment failure were not permitted at US sites after this protocol amendment. This amendment appears to have been required by the FDA due to concerns about the potential risk of progressive multifocal leukoencephalopathy.[33] Protocol amendment 5/6 specified enhanced clinical response as a primary end point of the GEMINI II induction phase (as opposed to the first key secondary end point), and lowered the upper threshold for the Crohn's Disease Activity Index (CDAI) score from 480 to 450.[15] These modifications to study protocol were made based on blinded demographic data from the first 50 patients who were enrolled in the study, where the levels of disease duration, activity, and severity were greater than anticipated by the manufacturer.[15] The manufacturer indicated that the inclusion of patients with more severe disease could negatively affect the ability of the trial to demonstrate efficacy based on clinical remission; therefore, the primary end point of clinical response was added and the upper CDAI threshold was lowered.[15] As shown in Table 4, a CDAI score greater than 450 is characterized as severe Crohn's disease, which is outside the Health Canada–approved indication for vedolizumab;[5] therefore, the protocol amendment does not limit the generalizability of GEMINI II with respect to the target population for this review.

The GEMINI III study was a multinational, randomized, double-blind, placebo-controlled study (N = 416). The study was designed such that 75% of the study population had failed previous treatment with at least one TNF alpha antagonist and 25% were naive to TNF alpha antagonist therapy. Patients were randomized (1:1) to receive either 300 mg vedolizumab or placebo at weeks 0, 2, and 6 (i.e., a total of three infusions). Randomization was stratified by prior exposure to TNF alpha antagonists (failure or naive), concomitant use of oral corticosteroids, and concomitant use of immunomodulators.

b) Maintenance study

The maintenance phase of GEMINI II was the only maintenance study for vedolizumab identified in the CDR systematic review. In the maintenance phase of GEMINI II, patients from both the double-blind and open-label cohorts of the induction phase who received vedolizumab in the induction phase and who demonstrated a clinical response (CDAI ≥ 70) at six weeks were randomized (1:1:1) to double-blind treatment with 300 mg vedolizumab every four weeks, 300 mg vedolizumab every eight weeks, or placebo. The maintenance phase began at the week 6 visit and concluded after 52 weeks. Randomization was stratified by enrolment in the double-blind or open-label cohort in the induction phase, concomitant use of oral corticosteroids, previous exposure to TNF alpha antagonists, or concomitant immunomodulator use.

FIGURE 2: DESIGN OF GEMINI II RANDOMIZED CONTROLLED TRIAL (INDUCTION AND MAINTENANCE STUDIES)



Note: The circled portions of the figure represent the double-blind treatment phases.
Source: Reproduced from Common Technical Document, section 2.7.3.[34]

3.2.2 Populations

a) Inclusion and exclusion criteria

Patients could be eligible for the GEMINI studies if they had failed treatment with one or more TNF alpha antagonists, immunomodulators, and/or corticosteroids. Because patients enrolled in the studies had typically failed more than one of the above-noted options, the manufacturer used a hierarchical approach to categorize patients according to their "worst treatment failure." Within this hierarchy, TNF alpha antagonist-failure was considered the worst scenario, followed by immunomodulators, and then corticosteroids. As shown in Table 10, there was further classification within each treatment category based on the type of failure experienced by the patient. Within each category, inadequate response was considered the worse scenario, followed by loss of response, and then intolerance.

TABLE 10: HIERARCHY AND DEFINITIONS FOR ESTABLISHING WORST TREATMENT FAILURE

Category	Subcategories and Definitions
1. TNF alpha antagonist	a) Inadequate response: persistently active disease despite induction treatment b) Loss of response: recurrence of symptoms during maintenance treatment following prior clinical benefit c) Intolerance: treatment-related toxicity
2. Immunomodulators	a) Inadequate response: persistently active disease despite an 8-week regimen b) Intolerance: treatment-related toxicity
3. Corticosteroids	a) Inadequate response: persistently active disease despite a 4-week regimen b) Intolerance: treatment-related toxicity

TNF alpha = tumour necrosis factor alpha.

b) Baseline characteristics

Induction studies

Key baseline and demographic characteristics from the induction phase studies are summarized in Table 11. In both studies, North America represented the most common region for recruiting patients, and both trials included Canadian patients (80 in GEMINI III, 115 in the induction phase of GEMINI II, and 43 in the maintenance phase of GEMINI II).[15,21] Slightly more females than males were enrolled in the two studies. The vast majority of patients in the induction studies were white (89% to 90%). The mean age was similar in the two studies (36.1 years in GEMINI II and 37.9 years in GEMINI III). Mean body weight was slightly greater in GEMINI III (70.4 kg) than in GEMINI II (66.2 kg); however, mean body mass index (BMI) was similar in the two studies (24.3 kg/m^2 in GEMINI III and 23.9 kg/m^2 in GEMINI II). The mean duration of disease was 10.3 years in GEMINI III compared with 9.0 years in GEMINI II, which is likely a reflection of enrolling a greater proportion of patients who had previously failed treatment with a TNF alpha antagonist (i.e., 75% in in GEMINI III and 50% in GEMINI II).

Mean baseline CDAI scores were lower in GEMINI III (307.7) compared with GEMINI II (323.6). Baseline CDAI scores were similar in the placebo group (324.6) and vedolizumab group (327.3) of GEMINI II; however, in GEMINI III, the mean baseline CDAI score was significantly higher in the vedolizumab group (313.9) compared with the placebo group (301.3), with 37% of vedolizumab-treated patients having a baseline CDAI score greater than 330 compared with 29% of the placebo-treated patients. Baseline fecal calprotectin levels were similar in GEMINI II and GEMINI III (1,254.2 and 1,288.0, respectively). A majority of patients in both studies had disease activity in both the ileum and the colon in GEMINI II and GEMINI III (55% and 61%, respectively). Prior surgeries for Crohn's disease were similar in GEMINI II and GEMINI III (42% and 54%, respectively). The majority of the patients in both treatment groups had no history of fistulizing disease, and only 12% of the patients had a draining fistula at baseline.

Prior exposure to IBD treatments and "worst failure" for the induction studies are summarized in Table 12. The manufacturer noted that the baseline data for prior exposure were obtained from the interactive voice response service, whereas the data for "worst failure" were obtained from the prior medications electronic case report forms.[15] Hence, there are slight differences in the reported proportions of patients with prior exposure to TNF alpha antagonists, depending on the source of the data. In accordance with the study designs, prior TNF alpha antagonist exposure was reported for approximately half of the patients in GEMINI II and approximately 75% of the patients in GEMINI III.[15,21] Of the patients in the induction studies with prior exposure to a TNF alpha antagonist, failure with one TNF alpha antagonist was reported for 21% of patients in GEMINI II and 25% in GEMINI III. Failure with two TNF alpha antagonists was less common in GEMINI II (21%) than in GEMINI III (41%), and failure

with three TNF alpha antagonists was reported in only a minority of patients in both trials (5% in GEMINI II and 8% in GEMINI III).[15,21] Data about the proportion of patients having failed treatment with multiple TNF alpha antagonists were not reported for the maintenance phase. A summary of baseline and demographic characteristics based on prior exposure to TNF alpha antagonists is provided in Table 35 for the GEMINI III study.

TABLE 11: SUMMARY OF BASELINE AND DEMOGRAPHIC CHARACTERISTICS FROM THE INDUCTION STUDIES

Parameter	GEMINI II		GEMINI III	
	PLA (N = 148)	VDZ (N = 220)	PLA (N = 207)	VDZ (N = 209)
Gender, n (%)				
Male	69 (47)	105 (48)	89 (43)	91 (44)
Female	79 (53)	115 (52)	118 (57)	118 (56)
Race, n (%)				
White	124 (84)	182 (83)	186 (90)	188 (90)
Black	3 (2)	3 (1)	5 (2)	4 (2)
Asian	19 (13)	35 (16)	9 (4)	9 (4)
Other	2 (1)	0	7 (3)	6 (3)
Age (y), mean (SD)	38.6 (13.16)	36.3 (11.57)	37.1 (13.15)	38.6 (12.14)
Body weight (kg), mean (SD)	68.7 (18.90)	67.1 (19.07)	71.3 (19.22)	69.5 (17.76)
BMI (kg/m^2), mean (SD)	23.7 (5.77)	23.1 (5.62)	24.6 (6.13)	24.0 (5.13)
Geographic region, n (%)				
North America	50 (34)	64 (29)	95 (46)	102 (49)
Western/Northern Europe	22 (15)	28 (13)	37 (18)	38 (18)
Central Europe	30 (20)	45 (20)	46 (22)	41 (20)
Eastern Europe	17 (11)	31 (14)	15 (7)	10 (5)
Asia/Australia/Africa	29 (20)	52 (24)	14 (7)	18 (9)
Duration of CD (y)				
mean (SD)	8.2 (7.80)	9.2 (8.18)	10.0 (7.98)	10.6 (8.75)
< 1 year, n (%)	12 (8)	12 (5)	12 (6)	11 (5)
≥ 1 to < 3 y, n (%)	27 (18)	48 (22)	25 (12)	28 (13)
≥ 3 to < 7 y, n (%)	45 (30)	49 (22)	52 (25)	52 (25)
≥ 7 y, n (%)	64 (43)	111 (50)	118 (57)	118 (56)
CDAI, mean (SD)	324.6 (78.08)	327.3 (70.67)	301.3 (54.97)	313.9 (53.17)
CDAI ≤ 330	81 (55)	119 (54)	148 (71)	132 (63)
CDAI > 330	66 (45)	100 (45)	59 (29)	77 (37)
CRP (mg/L), mean (SD)	23.6 (27.85)	24.1 (27.23)	18.5 (21.98)	19.0 (23.17)
Fecal calprotectin (mcg/g), mean (SD)	1,421.2 (2076)	1,839.9 (2625)	1,426.5 (2358)	1,148.1 (1879)
Disease localization, n (%)				
Ileum-only	21 (14)	37 (17)	29 (14)	33 (16)
Colon-only	43 (29)	62 (28)	52 (25)	48 (23)
Ileocolonic	84 (57)	121 (55)	126 (61)	128 (61)
Prior surgery for CD, n (%)	54 (36)	98 (45)	89 (43)	92 (44)
Smoking status, n (%)				
Current smoker	34 (23)	54 (25)	58 (28)	65 (31)

Parameter	GEMINI II		GEMINI III	
	PLA (N = 148)	VDZ (N = 220)	PLA (N = 207)	VDZ (N = 209)
Never smoked	85 (57)	120 (55)	102 (49)	93 (44)
Former smoker	29 (20)	46 (21)	47 (23)	51 (24)
History of fistulizing CD, n (%)	56 (38)	90 (41)	77 (37)	71 (34)
Draining fistula, n (%)	23 (16)	38 (17)	25 (12)	25 (12)
Extraintestinal manifestations, n (%)	107 (72)	133 (60)	130 (63)	116 (56)

BMI = body mass index; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; PLA = placebo; SD = standard deviation; y = years; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

TABLE 12: PRIOR EXPOSURE TO INFLAMMATORY BOWEL DISEASE TREATMENTS IN GEMINI II AND GEMINI III IN THE INDUCTION STUDIES

Parameter, n (%)	GEMINI II		GEMINI III	
	PLA (N = 148)	VDZ (N = 220)	PLA (N = 207)	VDZ (N = 209)
Prior Exposure[a]				
Any systemic CS	140 (95)	200 (91)	188 (91)	190 (91)
Only systemic CS	26 (18)	28 (13)	4 (2)	10 (5)
Any immunomodulators	113 (76)	174 (79)	193 (93)	176 (84)
Only immunomodulators	3 (2)	11 (5)	10 (5)	6 (3)
Any TNF alpha antagonists	75 (51)	117 (53)	158 (76)	156 (75)
Only TNF alpha antagonists	1 (< 1)	3 (1)	1 (< 1)	4 (2)
Failed 1 TNF alpha antagonist	28 (19)	49 (22)	45 (22)	59 (28)
Failed 2 TNF alpha antagonists	31 (21)	48 (22)	90 (43)	82 (39)
Failed 3 TNF alpha antagonists	11 (7)	8 (4)	21 (10)	14 (7)
Immunomodulators and TNF alpha antagonists	66 (45)	101 (46)	148 (71)	133 (64)
Worst Failure[b]				
TNF alpha antagonist(s)	70 (47)	105 (48)	157 (76)	158 (76)
Inadequate response	41 (59)	56 (53)	69 (44)	66 (43)
Loss of response	22 (31)	40 (38)	69 (44)	71 (46)
Intolerance	7 (10)	9 (9)	18 (12)	18 (12)
Immunomodulators	50 (34)	76 (35)	45 (22)	44 (21)
Inadequate response	35 (70)	53 (70)	28 (62)	33 (75)
Intolerance	15 (30)	23 (30)	17 (38)	11 (25)
CS only	27 (18)	36 (17)	5 (2)	9 (4)
Inadequate response	23 (85)	31 (86)	5 (100)	8 (89)
Intolerance	4 (15)	5 (14)	0	1 (11)

CS = corticosteroid; PLA = placebo; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab.
[a] These data for prior exposure were obtained from the interactive voice response service.
[b] These data for worst failure were obtained from the prior medications electronic case report forms.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

Maintenance study

Key baseline and demographic characteristics of the maintenance study are summarized in Table 13. The study enrolled slightly more females than males, and the majority of trial participants were white (88% with vedolizumab and 90% with placebo). The baseline and demographic characteristics were generally well balanced between the groups. Mean baseline CDAI (325.5 and 325.2), body weight (68.5 kg and 69.0 kg), and BMI (23.6 kg/m^{2}and 24.0 kg/m^2) were similar in the vedolizumab and placebo groups (respectively). Patients in the placebo group had a greater duration of disease than those in the vedolizumab group (9.6 versus 8.4 years).[15]

There were some differences between the placebo and vedolizumab groups with respect to the disease locations (e.g., colon-only Crohn's disease in 28% in the placebo group versus 18% in the vedolizumab group); however, the majority of patients in both groups had ileocolonic Crohn's disease at baseline (64% with vedolizumab and 59% with placebo). There was some variation between the groups with regard to the geographic location of enrolment: More patients in the vedolizumab groups were enrolled at sites in North America (38%) compared with the placebo group (24%), and more patients in the placebo group were enrolled at sites in Western and Northern Europe (35%) compared with the vedolizumab groups (19%).[15]

Prior exposure to IBD treatments and "worst failure" for the maintenance study are summarized in Table 13. Of the patients in the maintenance phase of GEMINI II, 55% in the vedolizumab group and 51% in the placebo group had previously failed treatment with a TNF alpha antagonist (similar to the overall proportion in the induction phase of GEMINI II). For those with prior exposure to a TNF alpha antagonist, 19% had failed one TNF alpha antagonist, 25% had failed two TNF alpha antagonists, and 7% had failed all three TNF alpha antagonists.[21]

TABLE 13: BASELINE AND DEMOGRAPHIC CHARACTERISTICS FROM THE GEMINI II MAINTENANCE STUDY

Parameter	PLA (N = 153)	VDZ q8w (N = 154)
Gender, n (%)		
Male	72 (47)	68 (44)
Female	81 (53)	86 (56)
Race, n (%)		
White	140 (92)	136 (88)
Black	4 (3)	4 (3)
Asian	9 (6)	14 (9)
Age (y), mean (SD)	37.2 (11.95)	35.1 (12.23)
Body weight (kg), mean (SD)	69.0 (18.15)	68.5 (18.56)
BMI (kg/m^2), mean (SD)	24.0 (5.93)	23.6 (5.67)
Geographic region, n (%)		
North America	37 (24)	58 (38)
Western/Northern Europe	54 (35)	30 (19)
Central Europe	35 (23)	31 (20)
Eastern Europe	9 (6)	13 (8)
Asia/Australia/Africa	18 (12)	22 (14)
Duration of CD (y), mean (SD)	9.6 (8.85)	8.4 (7.28)
CDAI, mean (SD)	325.2 (65.58)	325.5 (68.76)

Parameter	PLA (N = 153)	VDZ q8w (N = 154)
CDAI ≤ 330	86 (56)	78 (51)
CDAI > 330	67 (44)	75 (49)
CRP (mg/L), mean (SD)	17.2 (21.86)	17.9 (29.47)
Fecal calprotectin, mean (SD)	1,142.5 (1429.3)	1,044.6 (1502.0)
CD localization, n (%)		
Ileum-only	19 (12)	29 (19)
Colon-only	43 (28)	27 (18)
Ileocolonic	91 (59)	98 (64)
Prior surgery for CD, n (%)	57 (37)	57 (37)
Prior fistulizing CD, n (%)	57 (37)	47 (31)
Draining fistula at baseline, n (%)	18 (12)	17 (11)
Smoking status, n (%)		
Current smoker	48 (31)	48 (31)
Non-smoker (never smoked)	64 (42)	74 (48)
Former smoker	41 (27)	31 (20)
Extraintestinal manifestations, n (%)	95 (62)	87 (56)

BMI = body mass index; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; PLA = placebo; q8w = every 8 weeks; SD = standard deviation; y = years; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II.[15]

TABLE 14: PRIOR EXPOSURE TO INFLAMMATORY BOWEL DISEASE TREATMENTS IN THE GEMINI II MAINTENANCE STUDY

Parameter, n (%)	PLA (N = 153)	VDZ (N = 154)
Prior Exposure		
Prior TNF alpha antagonist	82 (54)	88 (57)
No prior TNF alpha antagonist	71 (46)	66 (43)
Worst Failure		
TNF alpha antagonist(s)	78 (51)	82 (55)
Inadequate response	35 (45)	37 (45)
Loss of response	29 (37)	35 (43)
Intolerance	14 (18)	10 (12)
Immunomodulators	49 (32)	48 (32)
Inadequate response	34 (69)	29 (60)
Intolerance	15 (31)	19 (40)
Corticosteroids only	25 (16)	20 (13)
Inadequate response	22 (88)	19 (95)
Intolerance	3 (12)	1 (5)

PLA = placebo; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II.[15]

3.2.3 Interventions

a) Study treatments

During the induction phase of GEMINI II, patients in the double-blind randomized phase were scheduled to receive either 300 mg vedolizumab or placebo at weeks 0 and 2 (i.e., a total of two infusions).[15] Those in the open-label cohort received unmasked 300 mg vedolizumab at weeks 0 and 2.[15] The GEMINI III induction trial included a third infusion of 300 mg vedolizumab or placebo at week 6, so all patients were scheduled to receive a total of three infusions (i.e., at weeks 0, 2, and 6).[21]

During the maintenance phase of GEMINI II, patients in all three treatment groups were scheduled to receive infusions of either 300 mg vedolizumab or placebo every four weeks. Those randomized to the vedolizumab every four weeks group were to receive a total of 12 infusions of vedolizumab during the maintenance phase, beginning at the week 6 visit and then every four weeks until their final infusion at week 50. Those randomized to the vedolizumab every eight weeks group were to receive a total of six infusions of vedolizumab and six placebo infusions during the maintenance phase (see Table 15). Those randomized to the placebo group were to receive matching placebo infusions every four weeks from week 6 to week 50.[15]

In both studies, the placebo infusions consisted of 250 mL of 0.9% sodium chloride, and the infusion bags of all treatments were masked to maintain blinding.[15,21] All infusions were to be administered over approximately 30 minutes, or up to 60 minutes for individuals who demonstrated intolerance to shorter infusion times (e.g., experienced adverse events during or after an infusion).[15,21]

TABLE 15: DOSAGE SCHEDULE FOR GEMINI II AND GEMINI III

Phase	Study	Dosage Schedule
Induction	GEMINI II	• VDZ at weeks 0 and 2 • PLA at weeks 0 and 2
	GEMINI III	• VDZ at weeks 0, 2, and 6 • PLA at weeks 0, 2, and 6
Maintenance	GEMINI II	• 300 mg VDZ q4w (i.e., weeks 6 to 50) • 300 mg VDZ q8w (i.e., weeks 6, 14, 22, 30, 38, and 46) and PLA on weeks 10, 18, 26, 34, 42, and 50 • PLA Q4W (i.e., weeks 6 to 50)

PLA = placebo; q4w = every four weeks; q8w = every eight weeks; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

b) Concomitant medications

Both GEMINI II and GEMINI III permitted patients to continue to use a variety of concomitant medications for the treatment of Crohn's disease, provided the patient was receiving a stable dosage at baseline. In general, the dosages of the concomitant medications were to remain stable throughout the trial, with the exception of tapering corticosteroids as result of toxicity in GEMINI III (up to a maximum reduction of 2.5 mg/week daily prednisone equivalent)[21] or in accordance with the corticosteroid-tapering protocol in GEMINI II.[15] Both studies also permitted the dosage of immunomodulators (i.e., azathioprine, 6-mercaptopurine, or methotrexate) to be reduced as a result of toxicity.

There was regional variation in the protocol for GEMINI II with regard to whether or not patients were permitted to use immunomodulators (i.e., azathioprine, 6-mercaptopurine, or methotrexate) during the study. Patients enrolled at US sites were permitted to use these drugs in the double-blind phase only

until week 6 (i.e., they had to be discontinued for enrolment in the maintenance phase) and were not permitted to use them in the open-label cohort of GEMINI II.[15] The rationale for this difference was not stated in the clinical study report for GEMINI II.

TABLE 16: CONCOMITANT MEDICATIONS PERMITTED IN GEMINI II AND GEMINI III

Medication	Enrolment Criteria	Permitted or Required Adjustments During the Studies
Induction Studies		
• Azathioprine • 6-MP • Methotrexate	• Stable dose for 8 weeks[a]	• GEMINI II: Stable throughout the induction phase; however, tapering permitted as a result of toxicity[b] • GEMINI III: Stable through week 10; however, tapering permitted as a result of toxicity
• Oral CS	• Stable dose for 4 weeks or 2 weeks if tapering	• GEMINI II: Stable throughout the induction phase • GEMINI III: Stable through week 10; however, tapering permitted as a result of toxicity (up to a maximum reduction of 2.5 mg/week daily prednisone equivalent)
• 5-ASA • Probiotics • Antibiotics	• Stable dose at baseline	• GEMINI II: Stable throughout the induction phase • GEMINI III: Stable through week 10
• Antidiarrheals	• As necessary for control of chronic diarrhea; stable doses were encouraged	
Maintenance Study		
• Azathioprine • 6-MP • Methotrexate	• US sites: not permitted[b] • Other sites: as per induction phase	• Discontinued at week 6 for US patients and stable throughout the maintenance phase for patients at non-US sites (tapering permitted due to toxicity)
• Oral CS	• As per induction phase	• Stable until the patient met the criteria for initiating a CS-tapering regimen, then tapered as follows: ▪ prednisone (> 10 mg/day or equivalent): rate of 5 mg/week until a 10 mg/day dose was reached ▪ prednisone (≤ 10 mg/day or equivalent): rate of 2.5 mg/week until discontinuation ▪ budesonide: rate of 3 mg every 3 weeks until discontinuation
• 5-ASA • Probiotics • Antibiotics	• Stable dose at baseline	• Stable throughout the maintenance phase
• Antidiarrheals	As necessary for control of chronic diarrhea; stable doses were encouraged	

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; CS = corticosteroid.
[a] Patients in the open-label cohort of GEMINI II participating at US sites were not permitted to use azathioprine, 6-MP, or methotrexate during the induction phase.
[b] Patients in the double-blind cohort GEMINI II participating at US sites were required to discontinue use of azathioprine, 6-MP, or methotrexate at week 6.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

3.2.4 Outcomes

a) Crohn's Disease Activity Index

The CDAI is an instrument used to evaluate and quantify the severity of symptoms for patients with Crohn's disease. The CDAI consists of the following eight factors, each of which is summed after adjustment with a weighting factor:

- Number of liquid or soft stools each day for seven days
- Abdominal pain each day for seven days (0 [none] to 3 [severe])
- General well-being each day for seven days (0 [well] to 4 [terrible])

- Presence of complications
- Taking diphenoxylate/atropine or opiates for diarrhea
- Presence of an abdominal mass (0 [none], 2 [questionable], 5 [definite])
- Hematocrit of < 0.47 in men and < 0.42 in women
- Percentage deviation from standard weight.

The total CDAI score ranges from 0 to 600, with higher scores indicating greater Crohn's disease activity.

b) Clinical remission

Clinical remission was defined as a CDAI score ≤ 150 points. All participants who prematurely discontinued for any reason were counted as not achieving clinical remission. Clinical remission in the overall study population was a primary end point in the induction phase of GEMINI II (evaluated at six weeks) and the primary end point of the maintenance phase (evaluated at 52 weeks). Durable clinical remission was a secondary end point in the maintenance phase and was defined as a CDAI score ≤ 150 points at 80% or more of study visits during the maintenance phase, including the week-52 visit (11 of 13 study visits).[15]

In GEMINI III, clinical remission at week 6 in the TNF alpha antagonist-failure subpopulation was the primary end point. Pre-specified secondary end points of GEMINI III included clinical remission at week 6 in the overall population and clinical remission at week 10 in both the overall and TNF alpha antagonist-failure populations.[21]

c) Corticosteroid-free clinical remission

Patients in the maintenance study who were using oral corticosteroids at baseline and achieved clinical response at week 6 were to initiate tapering of their corticosteroid dosage. The tapering schedule was as follows:

- prednisone (> 10 mg/day or equivalent): tapered at a rate of 5 mg per week until a 10 mg/day dose was reached
- prednisone (≤ 10 mg/day or equivalent): tapered at a rate of 2.5 mg/week until discontinuation
- budesonide: tapered at a rate of 3 mg every three weeks until discontinuation.[15]

Those who were able discontinue corticosteroids and were in clinical remission (i.e., had a CDAI score ≤ 150) at 52 weeks were considered to have corticosteroid-free clinical remission. All participants who prematurely discontinued for any reason were counted as not achieving corticosteroid-free clinical remission.[15]

d) Enhanced clinical response

Enhanced clinical response was defined as a reduction in CDAI score of at least 100 points from baseline. This was evaluated at six weeks in the induction studies and 52 weeks in the maintenance study.[15,21] All participants who prematurely discontinued for any reason were considered to have not achieved enhanced clinical response.[30] The FDA noted that the term "enhanced" was selected for this end point because the required decrease in CDAI is greater than the ≥ 70 point improvement that has been used in previous registration trials as a threshold for "clinical response."[35]

Inflammatory Bowel Disease Questionnaire

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a 32-item questionnaire that aims to capture how the patient felt during the two weeks before the measurement time point. Questions are related to

the symptoms of Crohn's disease, how the patient felt in general and their mood over the previous two weeks, and social or employment problems that may have occurred as a result of Crohn's disease.[36,37] An increase in IBDQ score indicates an improvement in health-related quality of life, while a decrease indicates a deterioration. The minimal clinically important difference (MCID) for the IBDQ is considered to be ≥ 16 points.[7]

Short Form (36) Health Survey

The Short Form (36) Health Survey (SF-36) is a generic instrument that was used to assess health-related quality of life in GEMINI II and GEMINI III. An increase in SF-36 score indicates an improvement in health-related quality of life. The physical component summary (PCS) reflects the physical function, role physical, general health, and pain domains. The mental component summary (MCS) reflects the mental health, role emotional, social functioning, and vitality domains. Scores for each component range from 0 (poorest health) to 100 (best health). The MCID for the PCS and the MCS has been estimated to be 4.1 and 3.9 in the Crohn's disease patient population, respectively.[38]

EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D) is a generic, preference-based index measure of 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. 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 which can be used to generate a single index value for health status using a scoring algorithm, where full health is equal to 1 and death is equal to 0. Negative scores are also possible. The EQ-5D also contains a visual analogue scale (VAS), which records the patient's assessment of their own health along a vertical 20 cm line (ranging from 0 to 100).[39,40]

Adverse events

The pivotal studies defined adverse events as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not it was considered to be study drug–related. This included any increase in severity or frequency of a pre-existing condition. Signs and symptoms of IBD were to be collected only if they developed or worsened during the studies. The severity of adverse events was categorized as follows:[35]

- Mild: awareness of event but easily tolerated
- Moderate: discomfort enough to cause some interference with usual activity
- Severe: inability to carry out usual activity
- Serious: resulted in death, life threatening, required hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or an important medical event (e.g., an event that may have jeopardized the patient and may have required medical intervention to prevent one of the outcomes listed previously).[15,21]

3.2.5 Statistical analysis

a) Analysis of efficacy end points

In both GEMINI II and GEMINI III, the primary end points (i.e., clinical remission) and all other proportion-based end points were tested using the Cochran–Mantel–Haenszel chi-square test at a 5% significance level, with stratification according to the randomization stratification factors. The Cochran–Mantel–Haenszel chi-square *P* value, risk difference (RD) with 95% confidence interval (CI), and relative risk were reported for these end points.[15,21] Changes from baseline end points (e.g., IBDQ, SF-36, and EQ-5D) were analyzed using an analysis of covariance (ANCOVA) model.[21] The manufacturer conducted

a number of sensitivity analyses to investigate the robustness of the imputation method used for the primary and key secondary end points (e.g., observed case, per-protocol, last observation carried forward, and multiple imputation).[35]

b) Power calculations

Sample size calculations for GEMINI II and GEMINI III are summarized in Table 17.

TABLE 17: SUMMARY OF POWER CALCULATIONS FROM GEMINI II AND GEMINI III

Study	Hierarchy	End Point	Assumed Response (%)	Patients	Power
GEMINI II (Induction)	Primary	Clinical remission at week 6	PLA (21), VDZ (37)	PLA (148) VDZ (222)	91%
		Enhanced clinical response at week 6	PLA (31), VDZ (46)		82%
	Secondary	Change in CRP at week 6	PLA (21), VDZ (12)		77%
GEMINI II (Maintenance)	Primary	Clinical remission at week 52	PLA (22), VDZ (38)	167 in each	89%
	Key secondary	Enhanced clinical response at week 52	PLA (24), VDZ (40)		88%
		CS-free remission at week 52	PLA (11), VDZ (30)	83 in each	86%
		Durable clinical remission at week 52	PLA (12), VDZ (24)	167 in each	81%
GEMINI III (Induction)	Primary	Clinical remission at week 6 (TNF alpha failure)	PLA (5), VDZ (17)	148 in each	91%
	Secondary	Clinical remission at week 6 (overall)	PLA (10), VDZ (23)	198 in each	93%
		Clinical remission at week 10 (TNF alpha failure)	PLA (7), VDZ (19)	148 in each	87%
		Clinical remission at week 10 (overall)	PLA (13), VDZ (26)	198 in each	90%
		Sustained clinical remission at week 6 and 10 (TNF alpha failure)	PLA (4), VDZ (14)	148 in each	85%
		Sustained clinical remission at week 6 and 10 (overall)	PLA (8), VDZ (19)	198 in each	89%
		Enhanced clinical response (TNF alpha failure)	PLA (21), VDZ (36)	148 in each	81%

CRP = C-reactive protein; CS = corticosteroid; PLA = placebo; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III[21] and FDA Statistical Review.[33]

c) Multiple comparisons

In both the induction and maintenance phases of GEMINI II, the manufacturer used the Hochberg method to control the overall type I error rate at the 0.05 significance level for the multiple comparisons of the primary and secondary end points. A similar approach was used in GEMINI III (Table 18).

TABLE 18: SUMMARY OF PROCEDURES FOR MULTIPLE COMPARISONS

Study	Multiplicity Procedure
Induction Phase	
GEMINI II	1. If both *P* values were ≤ 0.05, both primary end points were to be declared significant. 2. If one of the *P* values for the primary end points was ≤ 0.05, the other *P* value was to be tested at the 0.025 level and declared significant only if the *P* value was ≤ 0.025. 3. If neither primary was significant, no testing on the secondary end point was to be conducted. 4. If at least one of the primary end points was significant, the sequential procedure was to be used to test the secondary end point (i.e., changes in CRP at 6 weeks) for significance.[15]
GEMINI III	1. If the *P* value was ≤ 0.05, the primary was declared significant. 2. The secondary end points were to be tested only if the primary end point was declared significant, using the following approach for testing the two populations (i.e., TNF alpha-failure and overall): • If both *P* values for each of the analyses populations within each set were ≤ 0.05, both the TNF alpha-failure and the overall population were to be declared significant. • If one of the *P* values was ≤ 0.05, the other *P* value was to be tested at the 0.025 level and declared significant only if the *P* value was ≤ 0.025. 3. The remaining secondary end points were to be tested only if the comparison on the previous secondary end point was significant.[21]
Maintenance Phase	
GEMINI II	1. If both *P* values were ≤ 0.05, both dose regimens were to be declared significant. 2. If one of the *P* values for the two doses was ≤ 0.05, the other *P* value was to be tested at the 0.025 level and declared significant only if the *P* value was ≤ 0.025. 3. If neither dose was significant for the primary end point, no further testing was to be conducted. 4. If at least one of the dose regimens was significant, the sequential procedure was to be used to test the secondary end points.[15]

CRP = C-reactive protein; TNF alpha = tumour necrosis factor alpha antagonist.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

d) Analysis populations

The GEMINI II study included five analysis populations in the induction phase and eight populations in the maintenance phase.[15] Similarly, the GEMINI III induction study included six analysis populations.[21] The characteristics and application of the most relevant analysis populations are summarized below.

- Intention-to-treat (ITT): All randomized patients who received ≥ 1 dose of study drug. The ITT population was used for all primary efficacy end points and all proportion-based assessments.
- Modified ITT: All randomized patients who received ≥ 1 dose of study drug and had a baseline and ≥ 1 post-randomization measurement for the end point. The modified ITT population was used for all change from baseline end points.
- Per-protocol: All patients who met the following criteria:
  - Confirmed diagnosis of Crohn's disease of at least six months' duration and with a CDAI score of 210 to 490 at enrolment in GEMINI II, or confirmed diagnosis of Crohn's disease of at least three months' duration and a CDAI score of 210 to 410 in GEMINI III
  - Received the correct study medication as assigned
  - Completed end point assessments or met one or more of the following criteria for failure: received rescue medication or surgery for Crohn's disease due to lack of efficacy, drug-related withdrawal due to adverse event, or failed treatment in the opinion of the investigator (GEMINI II only)
  - Received all doses of study drug as assigned or demonstrated ≥ 1 of the criteria for failure

- Did not receive concomitant corticosteroid or other potentially effective medications (except as permitted per-protocol) for an unrelated condition
- Did not have the treatment assignment unblinded by the investigator.

The per-protocol population was used for sensitivity analyses for the primary and key secondary end points.

- Safety: All patients who received any amount of study drug. The safety population was used for all analyses of safety end points.

The following subgroup analyses were conducted in the induction phase of GEMINI II: age (< 35 or ≥ 35 years), gender, race, duration of Crohn's disease (< 1, ≥ 1 to < 3, ≥ 3 to < 7, or ≥ 7 years), CDAI at baseline (≤ 330 or > 330), baseline CRP (≤ 5 or > 5 mg/L), region, baseline fecal calprotectin (≤ 500 mcg/g or > 500 mcg/g), worst failure of prior therapy (TNF alpha antagonist[s], immunomodulators, or corticosteroids), and disease localization (ileal, colonic, or ileocolonic). In accordance with the CDR systematic review protocol, results of subgroup analyses were based on disease severity at baseline and previous therapy with a TNF alpha antagonist.

3.3 Patient Disposition

3.3.1 Induction studies

Patient disposition for the induction studies is summarized in Table 19. A total of 1,920 patients were screened for GEMINI II, and 1,116 patients were enrolled in the study (368 were enrolled in the double-blind cohort and 748 in the open-label cohort). All of the 368 patients in the double-blind cohort received at least one dose of the study treatments. A high proportion of patients in each treatment group completed the six-week induction phase (93% with placebo and with 90% vedolizumab). The reasons for discontinuation were similar between the treatment groups. Similar to the double-blind cohort, the majority of the patients who received open-label vedolizumab completed the six-week induction phase (90%). Among the reasons that led to premature discontinuation from the study, lack of efficacy was cited as the reason for 4% of the open-label vedolizumab patients. As noted in the outcomes section, the primary efficacy evaluation for GEMINI II was not scheduled until week 6; therefore, it is unclear what criteria were used to withdraw these patients from treatment.

A total of 660 patients were screened for GEMINI III, and 416 were randomized and treated. A high proportion of patients completed the week-10 assessments in both the vedolizumab and placebo treatment groups (93% with placebo and 94% with vedolizumab). Withdrawals due to adverse events were more common in the placebo group compared with the vedolizumab group (4% versus 2%), as were withdrawals due to a lack of efficacy (2% versus < 1%).

TABLE 19: PATIENT DISPOSITION FROM THE GEMINI II AND GEMINI III INDUCTION STUDIES

Disposition, n (%)	GEMINI II		GEMINI III	
	PLA	VDZ	PLA	VDZ
Randomized/assigned	148	220	207	209
Safety population	148 (100)	220 (100)	207 (100)	209 (100)
ITT population	148 (100)	220 (100)	207 (100)	209 (100)
PP population	141 (95)	205 (93)	194 (94)	192 (92)
Completed study	137 (93)	199 (90)	192 (93)	196 (94)
Discontinued	11 (7)	21 (10)	15 (7)	13 (6)
Adverse event	7 (5)	9 (4)	8 (4)	4 (2)
Protocol violation(s)	0	0	0	1 (< 1)
Lack of efficacy	1 (< 1)	3 (1)	5 (2)	1 (< 1)
Withdrawal of consent	3 (2)	9 (4)	2 (< 1)	4 (2)
Lost to follow-up	0	0	0	3 (1)
Other	0	0	0	0

ITT = intention-to-treat; PLA = placebo; PP = per-protocol; VDZ = vedolizumab.
Source: Common Technical Document, section 2.7.3.[34]

3.3.2 Maintenance study

Patient disposition for the maintenance study is summarized in Table 20. A total of 461 patients were randomized in the GEMINI II maintenance study, and all patients received at least one dose of the study treatments. The majority of patients in both the vedolizumab and placebo groups failed to complete the study. Discontinuation was more common in the placebo group (58%) compared with the vedolizumab group (53%). Lack of efficacy was cited as the primary reason for withdrawal in both of the treatment groups (42% with placebo and 38% with vedolizumab). Withdrawals due to adverse events were slightly more commonly reported in the placebo group (10%) compared with the vedolizumab group (8%).

TABLE 20: PATIENT DISPOSITION FROM THE GEMINI II MAINTENANCE STUDY

Disposition, n (%)	Maintenance Study	
	PLA	VDZ
Randomized	153	154
Safety population	153 (100)	154 (100)
ITT population	153 (100)	154 (100)
PP population	147 (96)	149 (97)
Completed study	64 (42)	73 (47)
Discontinued	89 (58)	81 (53)
Adverse event	15 (10)	12 (8)
Protocol violation(s)	1 (< 1)	2 (1)
Lack of efficacy	64 (42)	58 (38)
Withdrawal of consent	7 (5)	6 (4)
Lost to follow-up	1 (< 1)	3 (2)
Other	1 (< 1)	0
Enrolled into GEMINI-LTS	127 (83)	126 (82)

ITT = intention-to-treat; LTS = long-term study; PLA = placebo; PP = per-protocol; VDZ = vedolizumab.
Source: Common Technical Document, section 2.7.3.[34]

3.4 Exposure to Study Treatments

3.4.1 Study treatments

Exposure to the study treatments is summarized in Table 21. Nearly all patients in GEMINI II received two infusions (97% in both the placebo and vedolizumab groups), and nearly all patients in GEMINI III received three infusions (93% with placebo and 96% with vedolizumab).[15,21] The median days on study treatment reflected the different duration of the two induction trials (43 days in GEMINI II and 70 days in GEMINI III).[15,21] In the maintenance study, a greater proportion of vedolizumab-treated patients completed all 14 infusions compared with the placebo group (47% versus 39%). The median time of exposure was 336 days in the vedolizumab group and 297 days in the placebo group.[15]

TABLE 21: EXPOSURE TO STUDY TREATMENTS IN THE INDUCTION AND MAINTENANCE STUDIES

Exposure	GEMINI II		GEMINI III	
	PLA	VDZ	PLA	VDZ
Induction Studies				
Number of infusions, n (%)				
1 infusion	5 (3)	7 (3)	5 (2)	4 (2)
2 infusions	143 (97)	213 (97)	9 (4)	5 (2)
3 infusions	NA	NA	193 (93)	200 (96)
Exposure days, mean (SD)	40.7 (9.1)	40.2 (10.0)	69.5 (9.4)	69.7 (8.4)
Maintenance Study				
Number of infusions, n (%)			NA	
≥ 1 infusion[a]	153 (100)	154 (100)		
≥ 2 infusions[a]	153 (100)	154 (100)		
≥ 3 infusions	153 (100)	154 (100)		
≥ 4 infusions	148 (97)	146 (95)		
≥ 5 infusions	131 (86)	133 (86)		
≥ 6 infusions	120 (78)	112 (73)		
≥ 7 infusions	106 (69)	100 (65)		
≥ 8 infusions	98 (64)	91 (59)		
≥ 9 infusions	92 (60)	87 (56)		
≥ 10 infusions	87 (57)	84 (55)		
≥ 11 infusions	82 (54)	81 (53)		
≥ 12 infusions	78 (51)	79 (51)		
≥ 13 infusions	69 (45)	74 (48)		
≥ 14 infusions	60 (39)	72 (47)		
Exposure days, mean (SD)	260.6 (117.5)	257.6 (115.9)		

NA = not applicable; PLA = placebo; SD = standard deviation; VDZ = vedolizumab.
[a] The first 2 infusions were received during the induction phase of the study (i.e., weeks 0 and 2).
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

3.4.2 Concomitant medications

Concomitant IBD medications used in the induction and maintenance studies are summarized in Table 22. The majority of patients in the induction studies used at least one concomitant medication for Crohn's disease (79% in GEMINI II and 76% in GEMINI III). Corticosteroids were the most commonly used IBD medication in both of the induction studies. Use of 5-aminosalicylic acids was more common in

GEMINI II compared with GEMINI III (46% versus 31%) and a similar proportion of patients in both studies used immunomodulators (34% to 35%).

In the GEMINI II maintenance phase, the use of concomitant IBD medications was generally similar between the vedolizumab and placebo groups. Similar to the induction phase of the GEMINI II, corticosteroids were the most commonly used concomitant IBD medication; however, the overall proportion of patients using corticosteroids was greater in the maintenance phase than in the induction phase (i.e., approximately 60% at the beginning of the maintenance versus approximately 50% at the beginning of the induction phase).The proportion of patients using 5-aminosalicylic acids and immunomodulators was similar between the groups and across the induction and maintenance studies.[15]

TABLE 22: CONCOMITANT MEDICATIONS USED IN GEMINI II AND GEMINI III

Concomitant Medication, n (%)	GEMINI II		GEMINI III	
	PLA	VDZ	PLA	VDZ
Induction Studies				
≥ 1 IBD medication	121 (82)	170 (77)	157 (76)	159 (76)
Corticosteroids	73 (49)	106 (48)	115 (56)	111 (53)
Prednisone	37 (25)	42 (19)	75 (36)	66 (32)
Methylprednisolone	13 (9)	27 (12)	21 (10)	18 (9)
Prednisolone	16 (11)	23 (10)	6 (3)	8 (4)
Budesonide	11 (7)	18 (8)	17 (8)	21 (10)
Hydrocortisone	1 (< 1)	4 (2)	5 (2)	1 (< 1)
Triamcinolone	1 (< 1)	0	0	0
Beclomethasone	0	0	0	1 (< 1)
Dexamethasone	0	0	1 (< 1)	0
5-Aminosalicylic acids	67 (45)	101 (46)	61 (29)	68 (33)
Mesalazine	63 (43)	85 (39)	59 (29)	62 (30)
Sulfasalazine	4 (3)	15 (7)	1 (< 1)	6 (3)
Balsalazide	0	2 (< 1)	1 (< 1)	1 (< 1)
Immunomodulators	52 (35)	75 (34)	70 (34)	72 (34)
Azathioprine	43 (29)	62 (28)	44 (21)	51 (24)
Methotrexate	6 (4)	9 (4)	19 (9)	15 (7)
Mercaptopurine	3 (2)	5 (2)	7 (3)	6 (3)
Maintenance Study				
≥ 1 IBD medication	122 (80)	129 (84)	NA	
5-Aminosalicylic acids	66 (43)	64 (42)		
Mesalazine	58 (38)	59 (38)		
Sulfasalazine	7 (5)	3 (2)		
Balsalazide	1 (< 1)	2 (1)		
Olsalazine	0	1 (< 1)		
Immunomodulators	46 (30)	49 (32)		
Azathioprine	40 (26)	39 (25)		
Methotrexate	5 (3)	9 (6)		
Mercaptopurine	1 (< 1)	1 (< 1)		

Concomitant Medication, n (%)	GEMINI II		GEMINI III	
	PLA	VDZ	PLA	VDZ
Corticosteroids	90 (59)	89 (58)		
Prednisone	36 (24)	40 (26)		
Methylprednisolone	17 (11)	18 (12)		
Prednisolone	29 (19)	20 (13)		
Budesonide	12 (8)	15 (10)		
Hydrocortisone	2 (1)	3 (2)		
Triamcinolone	0	2 (1)		
Clobetasol	0	1 (< 1)		
Fluorometholone	0	1 (< 1)		
Beclomethasone	1 (< 1)	0		

IBD = inflammatory bowel disease; NA = not applicable; PLA = placebo; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

3.5 Critical Appraisal

3.5.1 Internal validity

Randomization was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., interactive voice response system). The variables used to stratify randomization were key prognostic factors for Crohn's disease (e.g., previous failure of TNF alpha antagonist and concomitant use of corticosteroids and/or immunomodulators). An additional stratification factor was used in the maintenance phase of GEMINI II based on the patients' previous enrolment in either the double-blind or open-label cohorts of the induction phase.

Patients were not specifically stratified according to their baseline level of disease activity (e.g., CDAI scores), contrary to recommendations from the European Medicines Agency (EMA); however, baseline disease severity was balanced across the placebo and vedolizumab groups. Overall, the baseline and demographic characteristics were balanced across the vedolizumab and placebo groups in the GEMINI II and GEMINI III induction studies.[35,41] There were some differences between the placebo and vedolizumab groups with respect to the disease locations (e.g., colon-only Crohn's disease in 28% in the placebo group versus 18% in the vedolizumab group) and the geographic location of enrolment (i.e., more patients in the vedolizumab groups were enrolled at sites in North America [38%] compared with the placebo group [24%], and more patients in the placebo group were enrolled at sites in Western and Northern Europe [35%] compared with the vedolizumab groups [19%]).[15] Regulatory authorities and the clinical expert consulted by CDR did not consider these imbalances to be a significant risk of bias. FDA reviewers noted that no single site contributed more than 5% of patients and, therefore, could not contribute disproportionately to the observed treatment effects. Results of pre-specified subgroup analyses demonstrated consistent treatment effects across the different geographic areas.[33]

The GEMINI II study used re-randomization at week 6 for vedolizumab patients who responded to induction therapy. The strength of this design is that it allows evaluation of whether the response is maintained in the absence or presence of continued vedolizumab therapy. The use of separate induction and maintenance studies in the design of GEMINI II is consistent with EMA guidance for the development of drugs for the treatment of Crohn's disease.[41,42] The use of the open-label cohort was noted by the EMA as a common enrichment strategy for maintenance trials conducted in patients with IBD and is identical to the strategy that was used in the pivotal study for vedolizumab in the treatment

of ulcerative colitis (GEMINI I).[43] Randomization in the maintenance phase was stratified by enrolment in the double-blind or open-label cohort in the induction phase.

Study treatments were administered in a double-blind manner in both the induction and maintenance studies. Covers were used to mask the contents of IV bags for the study drugs.[15,21] Given that the maintenance phase of the GEMINI II studies included two dosage regimens of vedolizumab (i.e., 300 mg every four weeks and 300 mg every eight weeks), patients who were randomized to receive vedolizumab every eight weeks received placebo infusions at every other study visit (i.e., weeks 10, 18, 26, 34, 42, and 50). The adverse event profile of vedolizumab was unlikely to compromise blinding of either the induction or maintenance studies, including the proportion of patients who experienced infusion-related reactions (Table 33).

The disposition of patients who were screened and enrolled in the pivotal trials was appropriately reported. A high proportion of patients completed the induction phase of GEMINI II and the GEMINI III study, with the overall proportion well balanced across the placebo and vedolizumab groups (i.e., more than 90%). The clinical expert consulted by CDR noted this is likely an accurate reflection of the proportion of patients who would complete induction dosing in routine clinical practice, particularly for patients who have exhausted all other pharmacotherapies for Crohn's disease.

A key limitation of the maintenance phase of GEMINI II is the large proportion of patients who prematurely discontinued treatment (i.e., 58% in the placebo group and 53% in the vedolizumab group). For all analyses related to clinical remission and clinical response, patients who discontinued for any reason were classified as treatment failures. This is a reasonable and common approach to handling missing data but may bias results in the case of differential withdrawal rates. Nevertheless, in the GEMINI II trial, the overall proportion of withdrawals and the reasons for discontinuation were generally similar between the placebo and vedolizumab groups. Lack of efficacy was the most commonly cited reason for discontinuation in both the placebo and vedolizumab groups (42% and 38%, respectively), suggesting that classifying discontinued patients as treatment failures is an accurate reflection for the majority of those who failed to complete the study. High rates of withdrawal are generally expected in a one-year trial for Crohn's disease and are consistent with the high rates of withdrawal (or early escape) reported in previous pivotal studies for TNF alpha antagonists in the maintenance treatment of Crohn's disease. FDA statisticians noted that the missing data were relatively consistent with similar trials conducted in Crohn's disease and that the distribution of the missing values was balanced across the treatment groups, supporting the manufacturer's approach for handling missing data (i.e., assumption of treatment failure).[33] The FDA reviewers noted that the primary analysis was supported by "extensive" sensitivity analyses to investigate the alternative approaches for imputing missing data (e.g., observed case, per-protocol, last observation carried forward, and multiple imputation). All of these analyses yielded results similar to the primary analysis.[33]

In accordance with EMA guidance,[42] the GEMINI II study protocol included a pre-specified regimen for tapering the dosage of corticosteroids for patients who have demonstrated clinical remission. The clinical expert consulted by CDR noted that the tapering regimen used in the GEMINI II trial was a reasonable reflection of clinical practice in Canada. Given that a greater proportion of vedolizumab-treated patients achieved clinical remission and initiated tapering of corticosteroids, the overall usage of corticosteroids was slightly higher in the placebo group compared with the vedolizumab group at 52 weeks (median 5.0 mg/day versus 4.0 mg/day).

3.5.2 External Validity

Inclusion and exclusion criteria for both the induction and maintenance studies were generally reflective of patients who would be considered candidates for treatment with vedolizumab in Canada. The Canadian Association of Gastroenterology stated in their clinical practice guidelines on the use of TNF alpha antagonists in the treatment of Crohn's disease that moderate to severe Crohn's disease should be defined as a CDAI score between 220 and 400.[44] This is consistent with the inclusion criteria of GEMINI III (where the thresholds were scores of 220 to 400) but not with either the pre- or post-amendment criteria used in GEMINI II (CDAI scores of 200 to 480 and 200 to 450, respectively). The clinical expert consulted by CDR indicated that, in clinical practice, some patients with Crohn's disease that is more moderate or more severe than the degree of severity covered by the Health Canada indication could be considered as candidates for vedolizumab provided they had failed to respond to alternative treatments (e.g., immunomodulators and TNF alpha antagonists). The efficacy of vedolizumab in these patient populations would be uncertain if the degree of severity was either unknown or outside the CDAI thresholds used in the clinical trials.

The study protocols for GEMINI II and GEMINI III specifically defined inclusion criteria for inadequate response, loss of response, or intolerance to a previous TNF alpha antagonist, immunomodulator, or corticosteroid. The protocols stated that a patient could be considered to have failed treatment with adalimumab after receiving one 80 mg dose followed by one 40 mg dose at least two weeks later. This is well below the dosage of adalimumab recommended in the Canadian product monograph for inducing remission (i.e., 160 mg at week 0 and 80 mg at week 2).[24] Similarly, a patient could be considered to have failed treatment with infliximab if they had received a dose of 5 mg/kg at least two weeks apart; however, the Canadian product monograph recommends three doses of 5 mg/kg for induction with infliximab (i.e., at weeks 0, 2, and 6).[13] Dosage recommendations in the Canadian Association of Gastroenterology guidelines on the use of TNF alpha antagonists in the treatment of Crohn's disease are consistent with those noted in the product monographs.[44] In addition, patients could be eligible for enrolment if they failed treatment with certolizumab pegol. Certolizumab has been approved for use in the treatment of Crohn's disease by the FDA,[45] but not by Health Canada[46] or the EMA.[47] The Canadian Association of Gastroenterology guidelines on the use of TNF alpha antagonists state that certolizumab has been shown to be clinically effective in the treatment of Crohn's disease.[44] However, the FDA and the Canadian Association of Gastroenterology recommend that certolizumab (400 mg subcutaneous) be administered at weeks 0, 2, and 4 for the induction of remission.[44,45] Similar to infliximab and adalimumab, patients enrolled in GEMINI II and GEMINI III could have been considered as having failed treatment with certolizumab after only doses (i.e., 400 mg subcutaneous, two doses at least two weeks apart). The clinical expert consulted by CDR noted that these thresholds for treatment failure are not reflective of clinical practice in Canada, where more aggressive dosage regimens are likely to be used prior to concluding that a patient is a nonresponder.

Given that the trials enrolled patients who were naive to treatment with TNF alpha antagonists, the lack of an active control group is a limitation of both the GEMINI II and GEMINI III studies. There are two other biologic drugs indicated for the treatment of Crohn's disease in Canada that could be considered to be relevant comparators: Infliximab and adalimumab. In the absence of a study directly comparing vedolizumab with infliximab and adalimumab, the manufacturer submitted an indirect comparison (Appendix 6); in addition, CDR identified three other indirect comparisons (see Appendix 7).

Study centres outside the US could have enrolled patients who have failed treatment only with corticosteroids (i.e., naive to both immunomodulators and TNF alpha inhibitors). These patients are captured within the Health Canada–approved indication for vedolizumab; however, the clinical expert

consulted by CDR indicated that the typical "step-up" treatment paradigm for Crohn's disease would involve treatment with one or more immunomodulators prior to initiating treatment with a biologic (though more aggressive treatment strategies could be used for patients with severe disease, particularly for patients who have been hospitalized). Overall, patients with corticosteroids as their worst treatment failure represented a small minority of the trial populations (17% in GEMINI II and 3% in GEMINI III)[15,21] and are unlikely to limit the generalizability of the results to patients who had failed treatment with immunomodulators and/or a TNF alpha inhibitor.

The CDAI has been validated within the Crohn's disease population (Appendix 4). The clinical expert consulted by CDR noted that CDAI scores are not calculated in clinical practice, although all of the various individual components of the scale are evaluated when assessing the status of a Crohn's disease patient. The definition of clinical remission (i.e., CDAI score < 150) is consistent with guidance from regulatory authorities[41,42] and with guidance from the Canadian Association of Gastroenterology.[44] Clinical remission was evaluated at six weeks in GEMINI II; however, the Canadian product monograph recommends that therapy with vedolizumab be discontinued in Crohn's disease patients who show no evidence of therapeutic benefit by 14 weeks (10 weeks for ulcerative colitis patients).[5] Therefore, the evaluation of patients at six weeks may not be reflective of the duration of follow-up that would be anticipated in Canadian clinical practice. In addition, the starting dosage regimen used in GEMINI II involved two infusions (at weeks 0 and 2), which is less than the three infusions (i.e., weeks 0, 2, and 6) recommended in the product monograph. As suggested by the results at the 10-week evaluation in GEMINI II, the results at six weeks reported in the induction studies therefore may have underestimated the clinical benefit of vedolizumab versus placebo.

The combined duration of the induction and maintenance studies was 52 weeks, which is consistent with guidance from regulatory authorities.[41,42] The duration of the pivotal studies may not have provided sufficient exposure to vedolizumab to allow adequate assessment of some more rare adverse events (e.g., malignancy, progressive multifocal leukoencephalopathy, and serious infections).[48] The manufacturer is currently conducting long-term prospective cohort studies to obtain additional safety information for vedolizumab.[4]

As is common in clinical trial settings, the patients enrolled in the GEMINI II and GEMINI III studies received extensive contact with health professionals, which would not be reflective of routine clinical practice in Canada. In addition, the Health Canada–approved dosage regimen for vedolizumab is 300 mg at weeks 0, 2, 6, and then once every eight weeks.[5] As noted above, in order to maintain blinding, all patients enrolled in the maintenance phase of GEMINI II received infusions of either the active drug or placebo every four weeks. This represents a significant increase in the number of clinic visits required for vedolizumab than would be anticipated in routine clinical practice (assuming that patients are treated in accordance with the frequency recommended in the product monograph). Hence, the treatment burden for patients in GEMINI II was potentially greater than would be expected in routine clinical practice, which may have resulted in underestimates of some improvements in the quality of life of patients.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (section 2.2, Table 7).

3.6.1 Induction treatment

a) Clinical remission

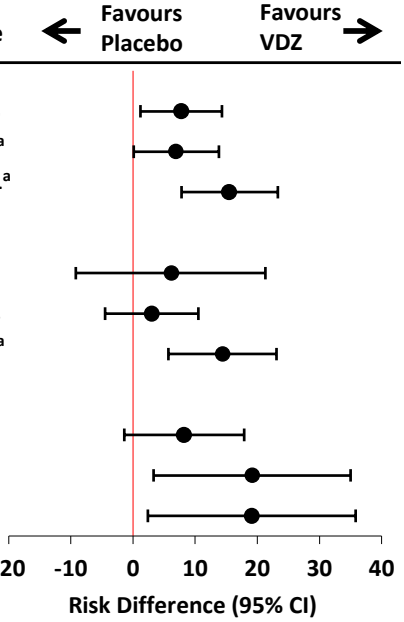
As shown in Figure 3, vedolizumab-treated patients (15.0% to 19.1%) were more likely to achieve clinical remission during the six-week induction phase than those treated with placebo (7% to 12.1%) in both

GEMINI II and GEMINI III. After six weeks of treatment, the adjusted RDs for vedolizumab versus placebo were 7.8% (95% CI, 1.2 to 14.3) in GEMINI II and 6.9% (95% CI, 0.1 to 13.8) in GEMINI III. The proportion of vedolizumab-treated patients with clinical remission further increased at the week-10 evaluation compared with placebo (28.7% versus 13.0%; RD 15.5%; 95% CI, 7.8 to 23.3). The difference between vedolizumab and placebo was statistically significant in GEMINI II (*P* = 0.0205), but not in GEMINI III (at either week 6 or week 10) due to failure of the statistical testing hierarchy at the primary end point (i.e., clinical remission in the TNF alpha antagonist-failure subpopulation).

In the TNF alpha antagonist-failure subpopulation, there was no statistically significant difference between vedolizumab and placebo for clinical remission (GEMINI II: RD = 6.2%; 95% CI, −9.2 to 21.3; and GEMINI III: RD 3.0; 95% CI, −4.5 to 10.5). This was the primary end point of GEMINI III; therefore, failure to demonstrate a statistically significant difference between vedolizumab and placebo stopped the statistical testing hierarchy at this end point. Similar to the evaluation conducted in the overall treatment population, the proportion of vedolizumab-treated patients with clinical remission increased at the 10-week evaluation compared with placebo (26.6% versus 12.1%; RD = 14.4%; 95% CI, 5.7 to 23.1). Subgroup analyses conducted for the TNF alpha antagonist-naive subpopulation demonstrated a numerical increase in the proportion of patients with clinical remission in the vedolizumab groups compared with the placebo groups (Figure 3; statistical testing was not conducted).

FIGURE 3: CLINICAL REMISSION IN THE INDUCTION STUDIES

Endpoint	Study	Remission; n (%) Placebo	Remission; n (%) VDZ	VDZ vs. Placebo RD (95% CI)	P value
Overall treatment population					
At 6 weeks	GEMINI-II	10 (7)	32 (15)	7.8 (1.2, 14.3)	0.0205
	GEMINI-III	25 (12.1)	40 (19.1)	6.9 (0.1, 13.8)	0.0478[a]
At 10 weeks	GEMINI-III	27 (13.0)	60 (28.7)	15.5 (7.8, 23.3)	<0.0001[a]
TNF-failure population					
At 6 weeks	GEMINI-II	3 (4.3)	11 (10.5)	6.2 (−9.2, 21.3)	NA
	GEMINI-III	19 (12.1)	24 (15.2)	3.0 (−4.5, 10.5)	0.4332
At 10 weeks	GEMINI-III	19 (12.1)	42 (26.6)	14.4 (5.7, 23.1)	0.0012[a]
TNF-naive population					
At 6 weeks	GEMINI-II	7 (9.2)	19 (17.4)	8.2 (−1.4, 17.9)	NA
	GEMINI-III	6 (12.0)	16 (31.4)	19.2 (3.3, 35.0)	NA
At 10 weeks	GEMINI-III	8 (16.0)	18 (35.3)	19.1 (2.4, 35.8)	NA



CI = confidence interval; NA = not applicable; RD = adjusted risk difference; TNF = tumour necrosis factor alpha; VDZ = vedolizumab; vs. = versus.
[a] *P* values are descriptive only.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

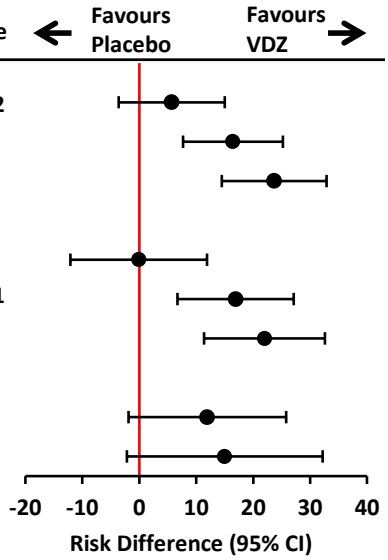
b) Enhanced clinical response

Enhanced clinical response at six weeks was one of the primary end points of the induction phase of GEMINI II, and there was no statistically significant difference between vedolizumab and placebo (31.4% versus 25.7%; RD = 5.7%; 95% CI, −3.6 to 15.0; *P* = 0.2322). In GEMINI III, there was a greater proportion of vedolizumab-treated patients with enhanced clinical response compared with placebo at both week 6

and week 10 (RD = 16.4%; 95% CI, 7.7 to 25.2; and RD 23.7; 95% CI, 14.5 to 32.9). Results in the TNF alpha antagonist-failure subgroup analyses were similar to those in the overall populations in both studies. The proportion of TNF alpha antagonist-failure patients with enhanced clinical response at six weeks was a secondary end point of GEMINI III and part of the pre-specified statistical testing hierarchy; therefore, the *P* value reported by the manufacturer (*P* = 0.0011) in relation to the difference between the vedolizumab and placebo groups is considered to be descriptive and not inferential.

FIGURE 4: ENHANCED CLINICAL RESPONSE IN THE GEMINI II AND GEMINI III INDUCTION STUDIES

Endpoint	Study	CL Response; n (%) Placebo	CL Response; n (%) VDZ	VDZ vs. Placebo RD (95% CI)	P value
Overall treatment population					
At 6 weeks	GEMINI-II	38 (25.7)	69 (31.4)	5.7 (−3.6, 15.0)	0.2322
	GEMINI-III	47 (22.7)	82 (39.2)	16.4 (7.7, 25.2)	NA
At 10 weeks	GEMINI-III	50 (24.2)	100 (47.8)	23.7 (14.5, 32.9)	NA
TNF-failure population					
At 6 weeks	GEMINI-II	15 (20.8)	23 (20.7)	−0.1 (−12.1, 11.9)	NA
	GEMINI-III	35 (22.3)	62 (39.2)	16.9 (6.7, 27.1)	0.0011
At 10 weeks	GEMINI-III	39 (24.8)	74 (46.8)	22.0 (11.4, 32.6)	NA
TNF-naive population					
At 6 weeks	GEMINI-II	23 (30.3)	46 (42.2)	11.9 (−1.9, 25.8)	NA
	GEMINI-III	12 (24.0)	20 (39.2)	15.0 (−2.2, 32.2)	NA



CI = confidence interval; CL = enhanced clinical response; NA = not applicable; RD = adjusted risk difference; TNF = tumour necrosis factor alpha; VDZ = vedolizumab; vs. = versus.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

c) Patient-reported outcomes

All patient-reported outcomes were considered exploratory by the manufacturer, and no statistical testing was performed.

Inflammatory Bowel Disease Questionnaire

As shown in Table 23, vedolizumab-treated patients demonstrated greater improvements from baseline in IBDQ in both GEMINI II and GEMINI III. Similar to the evaluation of clinical remission in GEMINI III, the improvement observed in the vedolizumab group compared with the placebo group was numerically greater at week 10 (mean difference [MD] 13.6; 95% CI, 7.3 to 19.9) compared with week 6 (MD 9.1; 95% CI, 3.1 to 15.1). Results in the TNF alpha antagonist-failure subgroup were similar to those in the overall population (Table 23).

TABLE 23: CHANGE FROM BASELINE IN IBDQ IN THE GEMINI II AND GEMINI III INDUCTION STUDIES

End Point	Statistic	GEMINI II		GEMINI III	
		Placebo	VDZ	Placebo	VDZ
Overall Population					
IBDQ score at week 6	Baseline mean (SE)	114.5 (2.54)	122.1 (2.20)	122.7 (2.18)	122.7 (2.46)
	Adjusted mean change (SE)	16.5 (2.75)	23.1 (2.28)	14.9 (2.16)	24.1 (2.14)
	Mean difference (95% CI)	6.5 (−0.5 to 13.6)		9.1 (3.1 to 15.1)	
IBDQ score at week 10	Baseline mean (SE)	–	–	122.5 (2.23)	124.3 (2.47)
	Adjusted mean change (SE)	–	–	15.0 (2.29)	28.6 (2.27)
	Mean difference (95% CI)	–		13.6 (7.3 to 19.9)	
TNF Alpha-Failure Subgroup					
IBDQ score at week 6	Baseline mean (SE)	–	–	121.2 (2.42)	122.1 (2.78)
	Adjusted mean change (SE)	–	–	14.6 (2.45)	24.0 (2.42)
	Mean difference (95% CI)	–		9.4 (2.6 to 16.2)	
IBDQ score at week 10	Baseline mean (SE)	–	–	120.7 (2.46)	122.4 (2.77)
	Adjusted mean change (SE)	–	–	15.4 (2.62)	28.3 (2.55)
	Mean difference (95% CI)	–		12.9 (5.7 to 20.1)	

CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; SE = standard error; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

Short Form (36) Health Survey

Results for the SF-36 PCS and SF-36 MCS are summarized in Table 24. The estimated treatment differences favour vedolizumab; however, the lower bound of the 95% CI crosses or falls on 0 for all of the evaluations at six weeks. As with the other end points of GEMINI III, the effect size for vedolizumab versus placebo was greater at the 10-week evaluation than at the six-week evaluation. The difference between vedolizumab and placebo in the SF-36 MCS at week 10 (MD 3.6; 95% CI, 1.6 to 5.7) exceeds the lower range of the MCID (2.5 to 5 points). Results in the TNF-failure subgroup were similar to those in the overall population (Table 24).

TABLE 24: CHANGE FROM BASELINE IN SF-36 IN THE GEMINI II AND GEMINI III INDUCTION STUDIES

End Point	Statistic	GEMINI II		GEMINI III	
		Placebo	VDZ	Placebo	VDZ
Overall Population					
SF-36 PCS at week 6	Baseline mean (SE)	35.7 (0.59)	36.4 (0.54)	36.4 (0.59)	36.7 (0.60)
	Adjusted mean change (SE)	2.4 (0.56)	3.5 (0.47)	2.2 (0.48)	3.3 (0.47)
	Mean difference (95% CI)	1.0 (−0.4 to 2.5)		1.1 (−0.2 to 2.4)	
SF-36 PCS at week 10	Baseline mean (SE)	–	–	36.5 (0.59)	37.0 (0.61)
	Adjusted mean change (SE)	–	–	3.3 (0.52)	4.7 (0.51)
	Mean difference (95% CI)	–		1.5 (0.0 to 2.9)	
SF-36 MCS at week 6	Baseline mean (SE)	35.0 (0.96)	36.4 (0.79)	36.6 (0.77)	37.4 (0.91)
	Adjusted mean change (SE)	2.4 (0.86)	4.6 (0.71)	3.3 (0.70)	3.9 (0.70)
	Mean difference (95% CI)	2.2 (0.0 to 4.4)		0.6 (−1.3 to 2.6)	
SF-36 MCS at week 10	Baseline mean (SE)	–	–	36.6 (0.79)	37.8 (0.91)
	Adjusted mean change (SE)	–	–	1.6 (0.73)	5.3 (0.72)
	Mean difference (95% CI)	–		3.6 (1.6 to 5.7)	

End Point	Statistic	GEMINI II		GEMINI III	
		Placebo	VDZ	Placebo	VDZ
TNF Alpha-Failure Subgroup					
SF-36 PCS at week 6	Baseline mean (SE)	–	–	35.7 (0.69)	36.4 (0.70)
	Adjusted mean change (SE)	–	–	2.2 (0.53)	3.3 (0.52)
	Mean difference (95% CI)	–		1.1 (−0.4 to 2.5)	
SF-36 PCS at week 10	Baseline mean (SE)	–	–	35.8 (0.70)	36.6 (0.70)
	Adjusted mean change (SE)	–	–	3.4 (0.59)	4.6 (0.58)
	Mean difference (95% CI)	–		1.2 (−0.4 to 2.8)	
SF-36 MCS at week 6	Baseline mean (SE)	–	–	36.6 (0.88)	37.8 (1.06)
	Adjusted mean change (SE)	–	–	3.0 (0.80)	4.1 (0.79)
	Mean difference (95% CI)	–		1.1 (−1.1 to 3.3)	
SF-36 MCS at week 10	Baseline mean (SE)	–	–	36.7 (0.88)	37.8 (1.06)
	Adjusted mean change (SE)	–	–	1.7 (0.83)	5.3 (0.81)
	Mean difference (95% CI)	–		3.5 (1.2 to 5.8)	

CI = confidence interval; MCS = mental component summary; PCS = physical component summary; SE = standard error; SF-36 = Short Form (36) Health Survey; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

EuroQol 5-Dimensions Questionnaire

As shown in Table 25, mean EQ-5D scores improved in both the vedolizumab and placebo groups at six weeks. As with the SF-36, the estimated treatment differences for the EQ-5D score favoured vedolizumab; however, the lower bound of the 95% CI crosses 0 in both GEMINI II and GEMINI III. After 10 weeks of treatment, vedolizumab-treated patients demonstrated improvements in EQ-5D relative to placebo-treated patients in GEMINI III (MD −0.5; 95% CI, −0.8 to −0.2). In GEMINI III, vedolizumab was associated with greater improvements in EQ-5D VAS scores at both week 6 (MD 4.8; 95% CI, 1.0 to 8.6) and week 10 (MD 9.2; 95% CI, 5.3 to 13.1). In GEMINI II, the improvements were similar between the two treatment groups (MD 1.5; 95% CI, −2.8 to 5.7) at six weeks. Results in the TNF alpha antagonist-failure subgroup were similar to those in the overall population (Table 25).

TABLE 25: CHANGE FROM BASELINE IN EQ-5D IN THE GEMINI II AND GEMINI III INDUCTION STUDIES

End Point	Statistic	GEMINI II		GEMINI III	
		Placebo	VDZ	Placebo	VDZ
Overall Population					
EQ-5D at week 6	Baseline mean (SE)	8.2 (0.14)	8.0 (0.11)	7.8 (0.11)	7.9 (0.11)
	Adjusted mean change (SE)	−0.3 (0.12)	−0.5 (0.10)	−0.2 (0.10)	−0.4 (0.10)
	Mean difference (95% CI)	−0.2 (−0.5 to 0.1)		−0.2 (−0.5 to 0.1)	
EQ-5D at week 10	Baseline mean (SE)	–	–	7.8 (0.10)	7.8 (0.11)
	Adjusted mean change (SE)	–	–	−0.1 (0.10)	−0.6 (0.10)
	Mean difference (95% CI)	–		−0.5 (−0.8 to −0.2)	
EQ-5D VAS at week 6	Baseline mean (SE)	46.6 (1.72)	48.8 (1.38)	51.3 (1.27)	50.3 (1.47)
	Adjusted mean change (SE)	5.4 (1.65)	6.9 (1.38)	4.8 (1.36)	9.6 (1.35)
	Mean difference (95% CI)	1.5 (−2.8 to 5.7)		4.8 (1.0 to 8.6)	
EQ-5D VAS at week 10	Baseline mean (SE)	–	–	52.0 (1.32)	51.1 (1.49)
	Adjusted mean change (SE)	–	–	3.8 (1.41)	13.0 (1.40)
	Mean difference (95% CI)	–		9.2 (5.3 to 13.1)	

End Point	Statistic	GEMINI II		GEMINI III	
		Placebo	VDZ	Placebo	VDZ
TNF Alpha-Failure Subgroup					
EQ-5D at week 6	Baseline mean (SE)	–	–	7.9 (0.12)	7.9 (0.13)
	Adjusted mean change (SE)	–	–	−0.1 (0.11)	−0.4 (0.11)
	Mean difference (95% CI)	–		−0.2 (−0.5 to 0.1)	
EQ-5D at week 10	Baseline mean (SE)	–	–	7.9 (0.11)	7.8 (0.13)
	Adjusted mean change (SE)	–	–	−0.1 (0.12)	−0.6 (0.12)
	Mean difference (95% CI)	–		−0.5 (−0.8 to −0.2)	
EQ-5D VAS at week 6	Baseline mean (SE)	–	–	51.1 (1.46)	50.0 (1.68)
	Adjusted mean change (SE)	–	–	3.9 (1.58)	9.7 (1.56)
	Mean difference (95% CI)	–		5.8 (1.4 to 10.2)	
EQ-5D VAS at week 10	Baseline mean (SE)	–	–	51.5 (1.53)	50.7 (1.70)
	Adjusted mean change (SE)	–	–	2.6 (1.62)	12.7 (1.59)
	Mean difference (95% CI)	–		10.1 (5.6 to 14.5)	

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions Questionnaire; SE = standard error; TNF alpha = tumour necrosis factor alpha; VAS = visual analogue scale; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II[15] and GEMINI III.[21]

3.6.2 Maintenance treatment

a) Clinical remission

There was a statistically significantly greater proportion of vedolizumab-treated patients who demonstrated clinical remission at 52 weeks compared with placebo (39.0% versus 21.6%; RD = 17.4%; 95% CI, 7.3 to 27.5; *P* = 0.0007). The results were similar when analyzed using the per-protocol data set (RD = 15.0%; 95% CI, 4.7 to 25.3).[15] The relative risk of achieving clinical remission was 1.8 (95% CI, 1.3 to 2.6).[15] The proportion of patients achieving clinical remission was reduced in the TNF alpha antagonist-failure subgroup (28.0% with vedolizumab and 12.8% with placebo); however, the adjusted RD between the two groups was similar to the analysis using the overall treatment population (RD 15.2; 95% CI, 3.0 to 27.5). Subgroup analyses based on disease severity at baseline demonstrated similar estimates of effect for patients with a baseline CDAI ≤ 330 (RD = 18.2%; 95% CI, 3.7 to 32.8) and those with a baseline CDAI greater than 330 (RD = 17.2%; 95% CI, 4.0 to 30.5).[15]

Durable clinical remission was defined as clinical remission in at least 80% of study visits, including the visit at week 52. There was no statistically significant difference between the vedolizumab and placebo groups (21.4% versus 14.4%; RD = 7.2; 95% CI, −1.5 to 16.0; *P* = 0.1036). Subgroup analyses were not reported for durable clinical remission.[15]

b) Enhanced clinical response

Enhanced clinical response was defined as a reduction in CDAI score of at least 100 from baseline. A statistically significantly greater proportion of vedolizumab-treated patients demonstrated enhanced clinical response at 52 weeks compared with placebo-treated patients (43.5% versus 30.1%; RD = 13.4%; 95% CI, 2.8 to 24.0; *P* = 0.0132). The relative risk for achieving enhanced clinical response was 1.4 (95% CI, 1.1 to 1.9).[15] The proportion of patients achieving enhanced clinical response was reduced in the TNF-failure subgroup, and the adjusted RD between the vedolizumab and placebo no longer excluded 0 (RD = 8.8%; 95% CI, −4.6 to 22.1). Subgroup analyses based on disease severity at baseline demonstrated similar estimates of effect for patients with a baseline CDAI ≤ 330 (RD = 12.4%; 95% CI, −2.5 to 27.3) and those with a baseline CDAI > 330 (RD = 16.0%; 95% CI, 0.7 to 31.2).[15]

c) Corticosteroid-free remission

Patients who were being treated with concomitant corticosteroids at the start of the maintenance phase and who achieved clinical remission were to begin having their dosage reduced according to the pre-specified tapering regimen. At the beginning of the maintenance phase, just more than half of the patients in the placebo (82 [54%]) and vedolizumab (82 [53%]) were receiving treatment with corticosteroids. As shown in Figure 5, a statistically significantly greater proportion of vedolizumab-treated patients achieved corticosteroid-free clinical remission at 52 weeks compared with the placebo group (31.7% versus 15.9%; RD = 15.9%; 95% CI, 3.0 to 28.7; *P* = 0.0154). In the TNF alpha antagonist-failure subgroup analysis, 24.4% of vedolizumab-treated patients achieved corticosteroid-free remission compared with no placebo-treated patients (RD = 24.4%; 95% CI, 2.4 to 45.1).

FIGURE 5: KEY EFFICACY END POINTS FROM THE GEMINI II MAINTENANCE STUDY

Endpoint	Achieved endpoint; n (%) Placebo	Achieved endpoint; n (%) VDZ	VDZ vs. Placebo RD (95% CI)	P value
Overall population				
Clinical remission	33 (21.6)	60 (39.0)	17.4 (7.3, 27.5)	0.0007
Enhanced clinical response	46 (30.1)	67 (43.5)	13.4 (2.8, 24.0)	0.0132
CS-free remission	13 (15.9)	26 (31.7)	15.9 (3.0, 28.7)	0.0154
Durable remission	22 (14.4)	33 (21.4)	7.2 (−1.5, 16.0)	0.1036
TNF-failure population				
Clinical remission	10 (12.8)	23 (28.0)	15.2 (3.0, 27.5)	NA
Enhanced clinical response	16 (20.5)	24 (29.3)	8.8 (−4.6, 22.1)	NA
CS-free clinical remission	0 (0)	10 (24.4)	24.4 (2.4, 45.1)	NA
TNF-naive population				
Clinical remission	19 (26.8)	34 (51.5)	24.8 (8.9, 40.6)	NA
Enhanced clinical response	27 (38.0)	40 (60.6)	22.6 (6.3, 38.9)	NA
CS-free clinical remission	11 (27.5)	15 (39.5)	12.0 (−8.8, 32.8)	NA

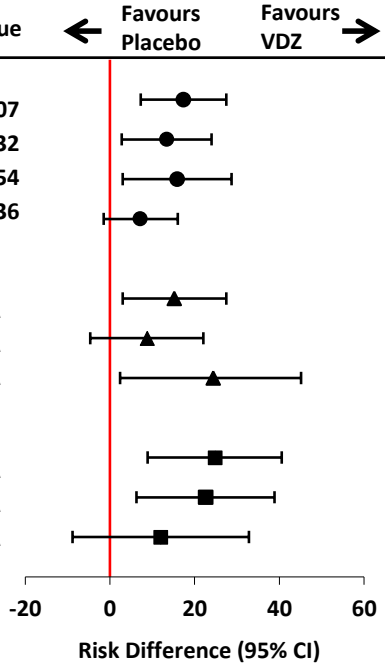


Figure shows adjusted RDs for vedolizumab versus placebo for maintenance phase end points in the overall population (●), TNF alpha antagonist-failure population (▲), and TNF alpha antagonist-naive population (■).
CI = confidence interval; CS = corticosteroid; RD = risk difference; RR = relative risk; VDZ = vedolizumab; vs. = versus.
Source: Clinical Study Reports for GEMINI II.[15]

d) Patient-reported outcomes

All patient-reported outcomes in the maintenance study were considered exploratory by the manufacturer, and no statistical testing was performed. Data for all patient-reported end points are summarized in Table 26.

Inflammatory Bowel Disease Questionnaire

After 52 weeks, IBDQ scores showed improvement from baseline in both the vedolizumab and placebo groups. Treatment with vedolizumab was associated with a greater improvement in IBDQ score compared with placebo (MD 15.1; 95% CI, 4.4 to 25.9).

Short Form (36) Health Survey

At week 52, scores for the SF-36 PCS and SF-36 MCS showed improvement from baseline in both the vedolizumab and placebo groups. The MDs between vedolizumab and placebo were 3.5 (95% CI, 1.1 to 5.9) for the SF-36 PCS and 3.0 (95% CI, −0.3 to 6.2) for the SF-36 MCS.[15]

EuroQol 5-Dimensions Questionnaire

Mean improvements from baseline to week 52 were greater with vedolizumab compared with placebo both the EQ-5D (MD −0.5; 95% CI, −0.9 to −0.1) and the EQ-5D VAS (MD 12.4; 95% CI, 7.0 to 17.8).

TABLE 26: PATIENT-REPORTED OUTCOMES IN THE GEMINI II MAINTENANCE PHASE

End Point		GEMINI II	
		Placebo	**VDZ**
IBDQ score at week 52	Baseline mean (SE)	122.6 (3.42)	126.6 (3.52)
	Adjusted mean change (SE)	35.5 (3.81)	50.7 (3.88)
	Mean difference (95% CI)	15.1 (4.4 to 25.9)	
SF-36 PCS at week 52	Baseline mean (SE)	37.5 (0.87)	37.9 (0.89)
	Adjusted mean change (SE)	5.9 (0.86)	9.4 (0.88)
	Mean difference (95% CI)	3.5 (1.1 to 5.9)	
SF-36 MCS at week 52	Baseline mean (SE)	36.7 (1.18)	36.7 (1.24)
	Adjusted mean change (SE)	7.8 (1.15)	10.7 (1.17)
	Mean difference (95% CI)	3.0 (−0.3 to 6.2)	
EQ-5D at week 52	Baseline mean (SE)	8.0 (0.18)	8.0 (0.17)
	Adjusted mean change (SE)	−1.0 (0.15)	−1.5 (0.15)
	Mean difference (95% CI)	−0.5 (−0.9 to −0.1)	
EQ-5D VAS at week 52	Baseline mean (SE)	51.4 (2.12)	51.5 (2.13)
	Adjusted mean change (SE)	14.2 (1.91)	26.6 (1.94)
	Mean difference (95% CI)	12.4 (7.0 to 17.8)	

CI = confidence interval; EQ-5D = EuroQol Five Dimensions Questionnaire; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mental Component Summary; PCS = Physical Component Summary; SE = standard error; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale; VDZ = vedolizumab.
Source: Clinical Study Reports for GEMINI II.[15]

e) Complications and surgeries for Crohn's disease

The manufacturer conducted an analysis of major Crohn's disease–related events (defined as a composite end point of Crohn's disease–related hospitalizations, Crohn's disease–related procedures, and bowel surgeries). As shown in Table 27, the proportions of patients who experienced major Crohn's disease–related events were similar between the vedolizumab (13.0%) and placebo group (11.8%), and no treatment differences were observed for the composite or individual study end points.[15]

TABLE 27: COMPLICATIONS AND SURGERIES FOR CROHN'S DISEASE IN GEMINI II

End Point	Patients With Event, n (%)		VDZ vs. PLA *P* value
	VDZ	PLA	
Major CD-related event[a]	20 (13.0)	18 (11.8)	0.9565
CD-related hospitalization	19 (12.3)	18 (11.8)	0.8328
CD-related procedure	3 (1.9)	5 (3.3)	0.4332
Bowel surgery	3 (1.9)	5 (3.3)	0.4332

CD = Crohn's disease; PLA = placebo; VDZ = vedolizumab; vs. = versus.
[a] Composite end point including CD-related hospitalizations, CD-related procedures, or bowel surgeries.
Source: Clinical Study Report for GEMINI II.[15]

3.7 Harms

Only those harms identified in the review protocol (see section 2.2, Table 7) are reported below. See Appendix 4 for detailed harms data.

The manufacturer conducted separate safety analyses for the induction phase and for the combined induction and maintenance phases (induction/maintenance).[22] Data from the induction phase of GEMINI III were pooled with data from the induction phase of GEMINI II to create the data set for the manufacturer's induction safety analysis. This analysis was based on the placebo and vedolizumab (at weeks 0, 2, and 6) treatment groups. Data from both phases of GEMINI II were used in the evaluation of safety in the induction/maintenance treatment population. As shown in Table 34, there were five treatment populations in the safety analysis. In accordance with the interventions of interest for the CDR systematic review protocol, only data for the following groups are summarized in this section of the report:

- Induction population: pooled results for the placebo group and the patients who received induction treatment with vedolizumab (double-blind or open-label) in GEMINI II (induction phase) and GEMINI III
- Induction/maintenance population: GEMINI II induction and maintenance phases for patients who responded to vedolizumab in the induction phase and were subsequently randomized to vedolizumab every eight weeks or placebo.

As shown in Table 28, a similar proportion of patients in the vedolizumab and placebo groups experienced at least one adverse event (57% and 60%, respectively) or serious adverse event (7% in each group), or withdrew as a result of an adverse event (3% and 5%, respectively) in the induction phase. The proportions of adverse events in the induction/maintenance phase were also similar in the vedolizumab and placebo groups, with adverse events (88% versus 84%, respectively) and serious adverse events (18% versus 15%, respectively) being slightly more common in the vedolizumab group and withdrawals due to adverse events being slightly more common in the placebo group (10% versus 8%, respectively). One death occurred during the induction phase in a patient who received two doses of vedolizumab (the cause [myocarditis] was not believed to be related to the drug).[15]

TABLE 28: SUMMARY OF ADVERSE EVENTS IN SAFETY POPULATIONS

AEs, n (%)	Induction (GEMINI II and GEMINI III)		Induction/Maintenance (GEMINI II)	
	VDZ (N = 1,176)	PLA (N = 355)	VDZ (N = 154)	PLA[a] (N = 153)
Any AE	668 (57)	212 (60)	135 (88)	128 (84)
WDAE	37 (3)	17 (5)	12 (8)	15 (10)
SAE	86 (7)	25 (7)	28 (18)	23 (15)
Serious infection	13 (1)	2 (< 1)	6 (4)	5 (3)
WDSAE	24 (2)	10 (3)	9 (6)	7 (5)
Deaths	1 (< 1)	0	1 (< 1)	0

AE = adverse event; PLA = placebo; SAE = serious adverse event; VDZ = vedolizumab; WDAE = withdrawal due to adverse event; WDSAE = withdrawal due to serious adverse event.
[a] Patients received VDZ during induction phase and were randomized to PLA for maintenance phase.
Source: Common Technical Document, section 2.7.4,[22] and Clinical Study Report for GEMINI II.[15]

3.7.1 Adverse events

A summary of commonly reported adverse events (i.e., those occurring in at least 3% of patients in the combined vedolizumab group) is provided in Table 29 for the induction population and in Table 30 for the induction/maintenance population. In the induction phase, a similar proportion of patients experienced at least one adverse event in the vedolizumab (57%) and placebo (60%) groups. Worsening Crohn's disease was the most commonly reported adverse event in the placebo group and occurred at greater frequency in the placebo group compared with the vedolizumab group (9% versus 5%). Fatigue was reported in 4% of vedolizumab-treated patients compared with 1% of placebo-treated patients. The relative frequency of the other common adverse events in the induction phase was similar between the vedolizumab and placebo groups.

Worsening Crohn's disease was the most common adverse event in the induction/maintenance population and was more commonly reported in the placebo group compared with the vedolizumab group (0.293 events per patient-year [PY] versus 0.230 events/PY). The next most commonly reported adverse events, arthralgia and pyrexia, were also more frequently reported in the placebo group (0.275 events/PY and 0.238 events/PY, respectively) compared with the vedolizumab group (0.193 events/PY and 0.166 events/PY, respectively). Nasopharyngitis (0.267 events/PY versus 0.165 events/PY), back pain (0.129 events/PY versus 0.064 events/PY), and fatigue (0.129 events/PY versus 0.101 events/PY) were more frequently reported in the vedolizumab group compared with the placebo group (respectively).

TABLE 29: ADVERSE EVENTS IN > 3% OF PATIENTS IN THE GEMINI II AND GEMINI III INDUCTION POPULATIONS

AEs, n (%)	Induction	
	VDZ (N = 1,176)	Placebo (N = 355)
At least 1 AE	668 (57)	212 (60)
Headache	84 (7)	27 (8)
Nausea	70 (6)	14 (4)
Crohn's disease	62 (5)	32 (9)
Pyrexia	56 (5)	15 (4)
Arthralgia	48 (4)	14 (4)

AEs, n (%)	Induction	
	VDZ (N = 1,176)	Placebo (N = 355)
Fatigue	44 (4)	5 (1)
Nasopharyngitis	40 (3)	12 (3)
Vomiting	39 (3)	8 (2)
Abdominal pain	35 (3)	10 (3)
URTI	33 (3)	10 (3)

AE = adverse event; URTI = upper respiratory tract infection; VDZ = vedolizumab.
Source: Common Technical Document, section 5.3.5.3.[9]

TABLE 30: ADVERSE EVENTS IN > 3% OF PATIENTS IN THE GEMINI II INDUCTION/MAINTENANCE POPULATION

Adverse Events	VDZ (N = 154, TPY = 108.6)		Placebo[a] (N = 153, TPY = 109.2)	
	n (%)	Event/PY	n (%)	Event/PY
Crohn's disease	25 (16)	0.230	29 (19)	0.293
Arthralgia	17 (11)	0.193	21 (14)	0.275
Pyrexia	18 (12)	0.166	23 (15)	0.238
Nasopharyngitis	23 (15)	0.267	14 (9)	0.165
Headache	20 (13)	0.230	28 (18)	0.495
Nausea	18 (12)	0.230	18 (12)	0.220
Abdominal pain	15 (10)	0.175	18 (12)	0.247
URTI	7 (5)	0.064	6 (4)	0.055
Fatigue	11 (7)	0.129	9 (6)	0.101
Vomiting	9 (6)	0.147	13 (8)	0.147
Back pain	14 (9)	0.129	7 (5)	0.064
UTI	7 (5)	0.092	4 (3)	0.037
Anemia	5 (3)	0.055	5 (3)	0.046
Cough	7 (5)	0.064	4 (3)	0.064
Bronchitis	5 (3)	0.046	4 (3)	0.046
Diarrhea	6 (4)	0.064	13 (8)	0.128
Influenza-like illness	7 (5)	0.074	7 (5)	0.082
Dizziness	8 (5)	0.074	6 (4)	0.073
Sinusitis	5 (3)	0.055	4 (3)	0.037
Anal abscess	1 (< 1)	0.009	3 (2)	0.027
Anal fistula	2 (1)	0.018	0	0.000
Pruritus	3 (2)	0.028	3 (2)	0.027

TPY = total patient-years; URTI = upper respiratory tract infection; UTI = urinary tract infection; VDZ = vedolizumab.
[a] Patients received VDZ during induction phase and were randomized to PLA for maintenance phase.
Source: Common Technical Document, section 5.3.5.3.[9]

3.7.2 Serious adverse events

A summary of serious adverse events is provided in Table 31 for the induction/maintenance population and in Table 36 for the induction population. In the induction phase, 7% of patients in both the vedolizumab and placebo groups experienced at least one serious adverse event. Worsening Crohn's disease was the only serious adverse event that occurred in at least 1% of patients in the induction

population and was more common in the placebo group compared with the vedolizumab group (5% versus 3%). In the induction/maintenance population, serious adverse events were slightly more common in the vedolizumab group compared with the placebo group (18% versus 15%). Nearly all of the serious adverse events in both the vedolizumab and placebo groups were classified as gastrointestinal disorders (12% in both groups) or infections and infestations (4% and 3%, respectively).

TABLE 31: SERIOUS ADVERSE EVENTS IN THE GEMINI II INDUCTION/MAINTENANCE POPULATION

SAEs, n (%)	VDZ (N = 154)	PLA (N = 153)
At least one SAE	28 (18)	23 (15)
Infections and infestations SOC	6 (4)	5 (3)
Anal abscess	1 (< 1)	0
Abdominal abscess	1 (< 1)	2 (1)
Gastroenteritis	1 (< 1)	1 (< 1)
Bacterial sepsis	1 (< 1)	0
Sepsis	1 (< 1)	0
Gastroenteritis viral	1 (< 1)	0
Device-related infection	0	1 (< 1)
Pelvic abscess	0	1 (< 1)
Wound infection	0	1 (< 1)
URTI	0	1 (< 1)
Influenza	1 (< 1)	0
GI disorders SOC	18 (12)	18 (12)
Crohn's disease	12 (8)	8 (5)
Enteritis	1 (< 1)	1 (< 1)
Small intestinal obstruction	1 (< 1)	1 (< 1)
Ileal stenosis	0	2 (1)
Small intestinal stenosis	0	1 (< 1)
Intestinal obstruction	2 (1)	0
Intestinal stenosis	1 (< 1)	1 (< 1)
Subileus	0	1 (< 1)
Ileus	0	1 (< 1)
Abdominal pain	0	2 (1)
Melena	0	1 (< 1)
Ileal perforation	0	1 (< 1)
Large intestine perforation	0	1 (< 1)
Pancreatitis	0	1 (< 1)
Peritonitis	0	1 (< 1)
Periproctitis	0	1 (< 1)
Rectal hemorrhage	1 (< 1)	0
Diarrhea	0	1 (< 1)

GI = gastrointestinal; PLA = placebo; SOC = system organ class; URTI = upper respiratory tract infection; VDZ = vedolizumab.
Source: Clinical Study Report for GEMINI II.[15]

3.7.3 Withdrawals due to adverse events

A summary of common withdrawals due to adverse events is provided in Table 32 for the induction/maintenance population and Table 37 for the induction population. In the induction phase, withdrawals due to adverse events were reported for 5% and 3% of patients in the placebo and vedolizumab groups, respectively. Worsening Crohn's disease was the most commonly cited adverse event leading to discontinuation in both the induction (4% of placebo-treated patients and 1% of vedolizumab-treated patients) and induction/maintenance populations (5% of placebo-treated patients and 4% of vedolizumab-treated patients). For the vedolizumab group, there were no other adverse events leading to discontinuation that were reported for more than one patient.

TABLE 32: WITHDRAWALS DUE TO ADVERSE EVENTS IN THE GEMINI II INDUCTION/MAINTENANCE POPULATION

WDAEs, n (%)	VDZ (N = 154)	PLA (N = 153)
WDAEs	12 (8)	15 (10)
Crohn's disease	6 (4)	8 (5)
Small intestinal obstruction	1 (< 1)	0
Abdominal pain	0	2 (1)
Ileus	0	1 (< 1)
Large intestine perforation	0	1 (< 1)
Rectal hemorrhage	1 (< 1)	0
Peritonitis	0	1 (< 1)
Abdominal abscess	1 (< 1)	1 (< 1)
Anal abscess	0	1 (< 1)
Rectal abscess	1 (< 1)	0
Bacterial sepsis	1 (< 1)	0
Clostridium difficile colitis	1 (< 1)	0
Back pain	0	1 (< 1)
Edema peripheral	1 (< 1)	0

PLA = placebo; VDZ = vedolizumab; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for GEMINI II.[15]

3.7.4 Notable Harms

a) Infusion-related reactions

As shown in Table 33, infusion-related adverse events were relatively rare in the induction/maintenance population. One vedolizumab-treated patient experienced an infusion-related adverse event that resulted in discontinuation from GEMINI II.[9]

TABLE 33: INFUSION-RELATED ADVERSE EVENTS IN THE GEMINI II INDUCTION/MAINTENANCE POPULATION

Infusion-Related Reactions, n (%)	VDZ (N = 154)	PLA[a] (N = 153)
At least 1 infusion-related adverse event	6 (4)	7 (5)
Nausea	2 (1)	4 (3)
Headache	1 (< 1)	1 (< 1)
Infusion-related reaction	1 (< 1)	0
Dizziness	1 (< 1)	0
Pruritus	0	1 (< 1)
Fatigue	2 (1)	1 (< 1)
Tension headache	0	1 (< 1)
Vomiting	0	1 (< 1)
Nasal congestion	1 (< 1)	0
Non-cardiac chest pain	1 (< 1)	0

PLA = placebo; VDZ = vedolizumab
[a] Patients received VDZ during induction phase and were randomized to PLA for maintenance phase.
Source: Clinical Study Report for GEMINI II.[15]

b) Malignancies

The manufacturer reported that there were no malignancies reported in GEMINI III. In GEMINI II, four patients (four of 815; 0.5%) in the combined vedolizumab group (i.e., both dosage groups of vedolizumab) were diagnosed with a malignancy. There were no malignancies reported for the placebo group.[9]

4. DISCUSSION

4.1 Summary of Available Evidence

The CDR systematic review included two pivotal, multi-centre, double-blind randomized controlled trials (GEMINI II and GEMINI III).[15,21] Both studies investigated the safety and efficacy of vedolizumab for inducing clinical remission in patients with moderate to severe Crohn's disease. The GEMINI II study also included a 46-week maintenance phase to investigate the efficacy and safety of vedolizumab as a maintenance treatment for patients who achieved clinical response with vedolizumab following an induction dosage regimen. Patients who completed the two pivotal trials were eligible to be enrolled in the GEMINI-LTS long-term extension study.[49] Evaluation of clinical remission and clinical response in GEMINI II and GEMINI III were based on changes in CDAI scores. Mucosal healing and reducing the need for Crohn's disease–related surgery were end points of interest in the CDR review protocol; however, neither GEMINI II nor GEMINI III was designed to evaluate these end points.

The vedolizumab induction dosage regimen differed between the two pivotal studies, with patients in GEMINI II receiving two infusions during the induction phase (i.e., 300 mg at weeks 0 and 2)[15] and those in GEMINI III receiving the recommended induction dosage regimen[a] of three infusions (i.e., 300 mg at weeks 0, 2, and 6).[21] The maintenance phase of GEMINI II included two vedolizumab groups (300 mg every eight weeks and 300 mg every four weeks);[15] however, the CDR review focused only on the Health Canada–approved dosage regimen of 300 mg every eight weeks.[5]

Both GEMINI II and GEMINI III enrolled patients with moderate to severe Crohn's disease who had failed treatment with one or more TNF alpha antagonists, immunomodulators, and/or corticosteroids. According to the clinical expert consulted by CDR, the trial populations were generally reflective of patients with moderate to severe Crohn's disease who are treated in Canadian clinical practice. Patients who had failed previous treatment with at least one TNF alpha antagonist comprised 75% of the GEMINI III study population and 50% of the GEMINI II population. The majority of patients in both studies had previous exposure to or were concomitantly receiving treatment with corticosteroids and/or immunomodulators. However, both studies included a minority of patients (17% in GEMINI II and 3% in GEMINI III)[15,21] with corticosteroids as their worst treatment failure (i.e., naive to both TNF alpha antagonists and immunomodulators). Although aligned with the Health Canada–approved indication for vedolizumab,[5] this is more liberal than the reimbursement criteria that are used in some of the CDR-participating drug plans for infliximab and adalimumab, which require demonstrated failure or intolerance to both corticosteroids and immunomodulators. The clinical expert consulted by CDR noted that ambulatory patients with moderate to severe Crohn's disease whose disease is inadequately controlled with corticosteroids (due to a lack of effectiveness or toxicity) or who have developed dependence on corticosteroids are likely to be treated using a "step-up" approach, where they would receive treatment with immunomodulators prior to initiating treatment with a biologic.

There were no studies identified in the CDR systematic review that compared vedolizumab against immunomodulators in patients for whom corticosteroids alone failed to adequately control their Crohn's disease. There were no head-to-head comparisons of vedolizumab against the TNF alpha antagonists that are approved for the treatment of Crohn's disease in Canada (i.e., infliximab and adalimumab); therefore, the CDR review considered the results of five indirect comparisons that have

[a] The Health Canada–approved product monograph for vedolizumab does not differentiate between induction and maintenance dosage regimens; however, the manufacturer's pharmacoeconomic evaluation states that the standard dose of vedolizumab is 300 mg at weeks 0, 2, 6 (induction), and every eight weeks thereafter (maintenance).

been conducted to evaluate the comparative efficacy of vedolizumab against infliximab and adalimumab.[50-53]

4.2 Interpretation of Results

4.2.1 Efficacy

Both GEMINI II and GEMINI III demonstrated that vedolizumab-treated patients were more likely to achieve clinical remission during the six-week induction phase than those treated with placebo. The adjusted RDs for vedolizumab versus placebo were 7.8% and 6.9% in GEMINI II and GEMINI III (respectively), suggesting that one in every 13 to 14 patients who are treated with vedolizumab would demonstrate clinical remission at six weeks following two induction doses (i.e., weeks 0 and 2). However, the standard induction dosage regimen for vedolizumab consists of three infusions (weeks 0, 2, and 6); therefore, the evaluation of clinical remission and response at six weeks is unlikely to be reflective of routine clinical practice. In the GEMINI III study, the manufacturer also evaluated clinical remission at 10 weeks (i.e., following three infusions), and the results demonstrated a relatively large increase in the number of vedolizumab-treated patients who achieved clinical remission (i.e., an increase from approximately 20% to 30% of vedolizumab-treated patients). In the evaluation at 10 weeks, the RD for achieving clinical remission improved to 15.5% (95% CI, 7.8 to 23.3), suggesting that one in every six patients treated with the complete induction dosage regimen of vedolizumab would achieve clinical remission. Although clinical remission at six weeks was the primary end point of GEMINI II and GEMINI III, the Canadian product monograph recommends that therapy with vedolizumab be discontinued in Crohn's disease patients who show no evidence of therapeutic benefit by 14 weeks.

Vedolizumab is indicated for use in the treatment of Crohn's disease patients with or without prior exposure to a TNF alpha antagonist. In the subpopulation of patients who had failed treatment with one or more TNF alpha antagonists, there was no statistically significant difference between the vedolizumab and placebo groups for achieving clinical remission at six weeks in GEMINI II or GEMINI III. Similar to the evaluation conducted in the overall treatment population, the proportion of vedolizumab-treated patients with clinical remission increased at the 10-week evaluation in the TNF alpha antagonist-failure subpopulation compared with placebo (26.6% versus 12.1%; RD 14.4%; 95% CI, 5.7 to 23.1). Because of failure of the statistical testing hierarchy at the six-week evaluation, statistical testing was not performed for the evaluation at 10 weeks; however, the CI excludes 0, suggesting a favourable treatment effect for vedolizumab.

The manufacturer suggested that the difference in responses at six weeks and 10 weeks was primarily attributable to patients with previous TNF alpha antagonist failure, where the proportion of vedolizumab-treated patients with clinical remission increased from 15.2% at 6 weeks to 26.6% at 10 weeks. In contrast, the proportion of TNF alpha antagonist-naive patients with a clinical response at 10 weeks (35.3%) was only marginally greater than the proportion at six weeks (31.4%; a difference of two additional patients).[21] A population of so-called delayed responders was also observed in a pivotal study for the use of adalimumab in the treatment of Crohn's disease (i.e., CLASSIC II).[24,44,54] The manufacturer[55] and regulators[35,41,56] noted that patients who have previously failed a TNF alpha antagonist may require an additional dose of vedolizumab and a longer duration of follow-up to demonstrate clinical remission compared with TNF alpha antagonist-naive patients. This is reflected in the Canadian product monograph, where the induction dosage regimen consists of three infusions (i.e., 300 mg at zero, two, and six weeks) and discontinuation is recommended for patients who fail to demonstrate a response by 14 weeks. Clinical remission at 14 weeks was not pre-specified as an end point in any of the controlled clinical trials; however, this time point would align with the first scheduled maintenance infusion (i.e., eight weeks after the final induction dosage at six weeks).

Long-term treatment with corticosteroids is associated with an increased risk of serious toxicities. At the beginning of the maintenance phase in the GEMINI II trial, just more than half of the patients were receiving concomitant treatment with corticosteroids. In accordance with the study protocol, these patients were to undergo a pre-specified corticosteroid-tapering regimen. A greater proportion of vedolizumab-treated patients achieved corticosteroid-free clinical remission at 52 weeks compared with the placebo group in both the overall population (31.7% versus 15.9%; *P* = 0.0154) and the TNF-failure subgroup analysis (24.4% versus 0%). The clinical expert consulted by CDR considered the tapering regimen used in GEMINI II to be consistent with routine clinical practice in Canada and the effect of vedolizumab to be clinically relevant for Crohn's disease patients who are dependent on corticosteroids.

In their input on the CDR review, the patient groups noted that they hope for additional non-surgical treatment options for Crohn's disease. They noted that surgery is associated with risks and should be considered the option of last resort. The clinical expert consulted by CDR also noted the importance of having additional non-surgical treatment options for patients with refractory Crohn's disease. Neither GEMINI II nor GEMINI III was designed to investigate the efficacy of vedolizumab for reducing the need for surgical intervention in Crohn's disease patients, and rates of bowel surgeries were low across all treatment groups.

According to the patient groups who provided input for the CDR review of vedolizumab (i.e., the Gastrointestinal Society and Crohn's and Colitis Canada), Crohn's disease has a profound negative impact on the quality of life of those living with the condition. Several instruments were used in the GEMINI II and GEMINI III trials to explore the effects of vedolizumab-treatment quality of life, including the EQ-5D, SF-36, and IBDQ. Statistical analyses were not conducted; however, vedolizumab was generally associated with a numerically greater improvement in these end points compared with placebo. At 52 weeks, the mean improvement in EQ-5D VAS exceeded the published MCID of 8.2,[38] whereas the mean improvement in SF-36 PCS was below the MCID of 4.2.[38] Although the difference between vedolizumab and placebo in the IBDQ (i.e., 13.6 and 15.1 at weeks 10 and 52, respectively) did not exceed the published MCID for the IBDQ (i.e., an improvement of ≥ 16),[7] the European product monograph for vedolizumab states that improvements in IBDQ were clinically meaningful.[8]

Health Canada concluded that the treatment effect observed in the induction studies was clinically meaningful for this patient population, who have history of being refractory to currently available treatment options, noting that the results may be particularly meaningful for patients with failure of one or more TNF alpha antagonists.[56] Similar conclusions were reached by EMA reviewers, who noted that there is an unmet need for Crohn's disease patients for whom TNF alpha antagonists have failed.[41] The clinical expert consulted by CDR also noted that the treatment effects of vedolizumab should be considered clinically relevant and that this treatment could potentially address the unmet need that currently exists in patients for whom TNF alpha antagonists have failed to control their disease. Clinical experts consulted by the National Institute for Health and Care Excellence (NICE) in the United Kingdom suggested that vedolizumab would primarily be used in patients who have failed treatment with one or more TNF alpha antagonists, due to the extensive experience with TNF alpha inhibitors in the clinical management of Crohn's disease.[20]

The EMA's Committee for Medicinal Products for Human Use noted that achieving a clinical response with vedolizumab requires a longer treatment period than with the approved TNF alpha antagonists (i.e., adalimumab and infliximab). As a result, they noted that the use of vedolizumab as the first biologic treatment option could require exposing nonresponders to a longer treatment with an ineffective drug before switching to a TNF alpha antagonist compared with the duration of exposure that would occur if

the TNF antagonist were used as the first-line biologic option.[41] It is unclear if this would be the case in Canadian practice, as the recommended time frame for discontinuing nonresponders is 14 weeks in the product monographs for both vedolizumab[5] and infliximab[13,14] and is only marginally lower with adalimumab (i.e., 12 weeks).[13]

The Canadian product monographs for both infliximab and adalimumab provide details about dose-escalation scenarios for patients who fail to respond or who lose response to those products.[13,14,24] In contrast, the controlled phases of the pivotal studies for vedolizumab did not evaluate dose escalation, and the current Canadian product monograph does not provide guidance regarding potential dose escalation scenarios. Dose escalation with vedolizumab was investigated in the GEMINI-LTS study, where a subset of patients (n = 57) who lost response while being treated with vedolizumab 300 mg every eight weeks during the maintenance phase of GEMINI II had their dosage increased to 300 mg every four weeks. At the 52-week evaluation in GEMINI-LTS, the manufacturer reported that 31.6% (18 of 57) and 47.4% (27 of 57) of these patients demonstrated clinical remission and clinical response, respectively.[57,58] Dose escalation of vedolizumab has also been reported outside a clinical trial setting. A small retrospective cohort study from a single US centre reported that patients who lost response to vedolizumab 300 mg every eight weeks responded favourably to an increased dosage frequency of once every four weeks (n = 10) or once every six weeks (n = 9).[59] Given the small number of patients evaluated and the absence of controlled studies examining dose escalation with vedolizumab, there is uncertainty regarding the overall clinical benefit and the comparative effectiveness of different dose escalation scenarios. However, increasing the dosage and frequency of administration would likely result in additional acquisition costs for publicly funded drug plans.

Although the Canadian[5] and US product monographs[60] do not comment on the efficacy and safety of dose escalation with vedolizumab, the European product monograph for vedolizumab states that Crohn's disease patients who have failed to respond after the induction dosage regimen may benefit from an additional dose at 10 weeks and that some patients who experienced a decrease in their response to vedolizumab may benefit from an increased dosing frequency to once every four weeks.[8] The European product monograph also states dosing once every four weeks could be considered for patients who undergo an interruption in vedolizumab treatment and subsequently need to restart treatment.[8] It is unclear if this regional variation in recommended dosing could influence utilization in Canada.

In the absence of head-to-head trials comparing vedolizumab against TNF alpha antagonists, CDR considered the results of five indirect comparisons.[50-53,61] The manufacturer submitted an indirect comparison of vedolizumab versus infliximab and adalimumab using the Bucher method, with placebo as the common comparator.[50] The manufacturer reported that vedolizumab was noninferior to infliximab for inducing and maintaining clinical remission but inferior for inducing and maintaining clinical response. The manufacturer also reported that, compared with adalimumab, vedolizumab was noninferior for inducing and maintaining clinical remission and corticosteroid-free clinical remission and for inducing clinical response. Vedolizumab was inferior to adalimumab for maintaining enhanced clinical response and clinical response. The manufacturer's claims of noninferiority and inferiority are limited by the absence of any pre-specified noninferiority margins or considerations of the statistical power required to make such conclusions. In addition, there is substantial heterogeneity in the study designs and patient characteristics across the studies included in the indirect comparison. CDR also considered the results of four published network meta-analyses (NMAs) that compared vedolizumab with biologic and non-biologic therapies for Crohn's disease (including one that was submitted to NICE by the manufacturer of vedolizumab).[51-53,61] Similar to the manufacturer's indirect comparison that was

submitted to CDR, there is substantial clinical and methodological heterogeneity across the various studies included in the published NMAs.

Overall, given the limitations of the available indirect comparisons and the heterogeneity across studies, the comparative efficacy of vedolizumab against infliximab and adalimumab is uncertain for both the induction and maintenance phases of treatment.

4.2.2 Harms

The proportion of patients who experienced at least one adverse event or serious adverse event or who discontinued due to an adverse event was similar between the vedolizumab and placebo groups across all of the included studies. Nasopharyngitis, back pain, and fatigue were more frequently reported in vedolizumab-treated patients compared with placebo-treated patients, but these did not lead to discontinuation of treatment. A subsequent pooled analysis[62] conducted by the manufacturer that included studies that were excluded from the CDR review (i.e., C13004 and GEMINI-LTS), in addition to data from GEMINI II and GEMINI III, suggested that back pain and fatigue were not more frequently reported with vedolizumab compared with placebo. However, this pooled analysis was a reflection of multiple vedolizumab dosage regimens (i.e., 2 mg/kg, 6 mg/kg, 300 mg every weeks, and 300 mg every four weeks) and different study designs (i.e., dose-finding study, induction studies, maintenance study, and a long-term extension study) and, therefore, may not be reflective of the adverse events that would be anticipated in routine clinical practice.

The combined duration of the induction and maintenance studies was 52 weeks, which may not have provided sufficient exposure to vedolizumab to allow adequate assessment of some more rare adverse events (e.g., malignancy, progressive multifocal leukoencephalopathy, and serious infections). FDA reviewers noted that the key safety issue associated with vedolizumab was the theoretical risk of progressive multifocal leukoencephalopathy.[35] No cases of progressive multifocal leukoencephalopathy have been reported in patients who have been treated with vedolizumab; however, the Canadian product monograph for vedolizumab contains a warning about this potential risk.[5] The potential risk of progressive multifocal leukoencephalopathy is due to the known increased risk that has been observed following treatment with natalizumab, another integrin antagonist. Natalizumab has been approved for use in the treatment of Crohn's disease by the United States[63] but not in Canada[64] or in the European Union.[65]

The manufacturer is currently completing a phase 3, open-label extension study to investigate the long-term safety and efficacy of vedolizumab in patients with ulcerative colitis and Crohn's disease (GEMINI-LTS; N = 2,243). The manufacturer has reported that, as of the third-interim analysis, the adverse event profile for vedolizumab is similar in GEMINI-LTS to that observed in the previous phase 3 studies (i.e., GEMINI I and GEMINI II). To evaluate the long-term safety of vedolizumab compared with other biologic drugs, the manufacturer is currently conducting prospective cohort studies (Entyvio PASS; N = 5,000 [estimated]), which is scheduled to be completed in 2021.[4]

Canadian product monographs for TNF alpha antagonists all contain black-box warnings regarding the risk of serious infections and malignancies.[13,14,24,46] The product monograph for vedolizumab does not currently contain such warnings;[5] however, there is less clinical experience with this product and it is possible that warnings could be added in the future. Given that vedolizumab is believed to have a gut-selective mechanism of action, it has been suggested that it may potentially be associated with a reduced risk of infectious adverse events compared with TNF alpha antagonists, which have a systemic mechanism of action.[66] The manufacturer has reported that vedolizumab is more tolerable than

infliximab and adalimumab;[66] however, the manufacturer's indirect comparison of safety end points demonstrated that vedolizumab was associated with an increased risk of serious adverse events compared with the TNF alpha antagonists and did not appear to be associated with fewer infectious adverse events.[50] These indirect comparisons were conducted with relatively short-term trials that were not individually powered to evaluate safety end points and were limited by substantial heterogeneity across the studies; therefore, the results may not be reflective of the comparative safety profile that would be observed in larger patient populations exposed for a greater duration of treatment.

The clinical expert consulted by CDR noted that vedolizumab may be associated with fewer infusion-related reactions compared with infliximab. An indirect comparison was not conducted for this end point; however, a naive comparison of rates from the maintenance studies suggests lower rates in GEMINI II (i.e., 4% with vedolizumab and 5% with placebo)[15] compared with the ACCENT I trial (23% with infliximab and 9% with placebo).[67] Further, the product monograph for Remicade states that 18% of patients who were treated with infliximab in phase 3 trials experienced an infusion reaction compared with 5% of placebo-treated patients,[13] whereas the pooled rates in the 52-week vedolizumab trials (i.e., GEMINI I and GEMINI II) were 4% with vedolizumab and 3% with placebo.[5] This is also lower than rate of injection-site reactions that were reported in the adalimumab clinical trials (13% with adalimumab and 7% with placebo).[24]

Patient groups expressed an understanding of the potential risks associated with biologic treatments and noted that those living with Crohn's disease are often willing to accept these risks rather than undergo surgery, which they consider to be a last resort.

4.3 Other Considerations

Vedolizumab and infliximab are currently available only as solutions for IV administration, whereas adalimumab can be administered via subcutaneous injection. The manufacturer for vedolizumab is currently enrolling patients in phase 3 randomized controlled trials to evaluate the efficacy of a subcutaneous formulation of vedolizumab for the maintenance treatment of patients with Crohn's disease[10] and ulcerative colitis[11] and is planning a longer-term safety study for the subcutaneous formulation.[12] Patient group input indicated that IV infusion was not considered to be a major issue for most patients, noting that IV administration is currently required for some currently available treatments (e.g., infliximab). It should be noted that the product monograph for vedolizumab recommends that the infusion occur over 30 minutes,[5] which is significantly less time than currently required for infliximab (i.e., not less than two hours).[13,14]

GEMINI II included a minority of patients with a draining fistula at baseline (n = 35), and the trial demonstrated that a greater proportion of vedolizumab-treated patients had closure of the fistula at week 52 (seven of 17, 47%) compared with placebo-treated patients (two of 18, 11.1%).[15] Vedolizumab is not currently indicated in the treatment of fistulizing Crohn's disease,[5] whereas infliximab is approved for use the treatment of fistulizing Crohn's disease.[13,14] The clinical expert consulted by CDR noted that, for patients who fail to respond to conventional therapy, a TNF alpha antagonist would likely be used, although vedolizumab would be considered as an alternative if treatment with a TNF alpha antagonist is considered to be inappropriate for safety reasons or has been shown to be ineffective. The manufacturer for vedolizumab is currently recruiting patients for a phase 4, double-blind randomized controlled trial to evaluate the use of vedolizumab in the treatment of fistulizing Crohn's disease (ENTERPRISE; N = 126 [estimated]).

The Australian Pharmaceutical Benefits Advisory Committee recommended the reimbursement of vedolizumab for the treatment of adults with severe Crohn's disease for patients who have failed to achieve an adequate response with or have demonstrated intolerance to corticosteroids and immunosuppressive therapy.[16-18] NICE and the Scottish Medicines Consortium have both accepted vedolizumab for use for the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a TNF alpha antagonist.[19,20]

4.4 Potential Place in Therapy

The information in this section is based on that provided in draft form by the clinical expert whom CDR reviewers consulted for the purpose of this review.

Patients with moderate to severe Crohn's disease require treatment with biologic therapies (specifically, the TNF alpha antagonists, infliximab and adalimumab) either immediately or following acute treatment with corticosteroids, antibiotics, and/or surgery. Biologic treatments are typically administered in combination with an immunosuppressant such as azathioprine or methotrexate. Patients who respond to this approach continue with biologic treatment for several years, and a large proportion of these patients demonstrate a sustained clinical response. However, some patients experience a reduction in response over time (e.g., due to the development of antibodies to a particular biologic drug) or become intolerant of biologic treatment (e.g., due to side effects such as an allergic reaction or other drug-related complications), which necessitates a change in the treatment regimen in order to maintain clinical responsiveness. At present, patients who experience a loss of response to either infliximab or adalimumab can be switched to the other TNF alpha antagonist, although this is often associated with a lower clinical response than in patients who have not been exposed previously to a TNF alpha antagonist. Therefore, there exists an unmet need for patients with moderate to severe Crohn's disease who are no longer responsive to or who are intolerant of TNF alpha antagonists.

Vedolizumab is a biologic agent that is an integrin inhibitor and therefore represents a different class of biologic compared with the TNF alpha antagonists. As vedolizumab appears to be an effective treatment for moderate to severe Crohn's disease,[5] this biologic agent represents an appropriate treatment for meeting the aforementioned unmet need for patients with moderate to severe disease who have failed other biologic treatments and for whom the only other option would likely be surgery. There are no barriers to identifying patients for whom vedolizumab treatment would be appropriate in a consistent manner, although specialized diagnostic tests are usually required to assess disease activity and severity for all patients who require biologic therapy, such as endoscopy, computed tomography scan, abdominal ultrasound, or magnetic resonance enterography, in accordance with standards of clinical practice.

5. CONCLUSIONS

Three phase 3, placebo-controlled, double-blind randomized controlled trials investigated the effects of vedolizumab on treatment induction (GEMINI II and GEMINI III) or maintenance (GEMINI II) in patients with moderate to severe Crohn's disease. Clinical remission was defined as a CDAI ≤ 150. Regulatory agencies and the clinical expert consulted by CDR noted that the definition of clinical remission was reflective of a clinically meaning improvement.

Patients who received vedolizumab were more likely to achieve clinical remission at six weeks than those who were treated with placebo in both GEMINI II and GEMINI III. The proportion of vedolizumab-treated patients who achieved clinical remission was greater at 10 weeks compared with that at six weeks in GEMINI III. In the subpopulation of patients who had previously failed treatment with at least one TNF alpha antagonist, treatment with vedolizumab was not associated with a statistically significant difference compared with placebo for inducing clinical remission at six weeks in either GEMINI II or GEMINI III, but a greater proportion of vedolizumab-treated patients in this subgroup did achieve clinical remission compared with placebo at 10 weeks in GEMINI III. The proportion of patients with an enhanced clinical response (defined as an improvement of at least 100 in CDAI) was greater at six and 10 weeks in GEMINI III, but there was no such difference versus placebo at six weeks in GEMINI II. In the maintenance phase of GEMINI II, a greater proportion of vedolizumab-treated patients demonstrated clinical remission and corticosteroid-free clinical remission at 52 weeks compared with placebo in both the overall population as well as the subpopulation of patients who had previously failed treatment with at least one TNF alpha antagonist. Compared with placebo-treated patients, a greater proportion of vedolizumab-treated patients demonstrated enhanced clinical response at 52 weeks in GEMINI II in the overall population, but not in the TNF alpha antagonist-failure population. Vedolizumab-treated patients demonstrated greater improvements from baseline in the IBDQ, SF-36, EQ-5D, and EQ-5D VAS, although it is not known whether these differences were statistically significant. The improvement in EQ-5D VAS exceeded the published MCID, whereas the improvements in SF-36 and IBDQ did not. The included studies were not designed to investigate the efficacy of vedolizumab for mucosal healing or reducing the need for surgical intervention and efficacy end points.

The proportion of patients who experienced at least one adverse event or serious adverse event or who discontinued due to an adverse event was similar between the vedolizumab and placebo groups across all of the included studies. Nasopharyngitis, back pain, and fatigue were more frequently reported in vedolizumab-treated patients compared with placebo-treated patients, but these did not lead to discontinuation of treatment. Infusion-related reactions were relatively rare and occurred at a similar frequency in the placebo and vedolizumab groups.

There were no studies in which vedolizumab has been compared directly against the TNF alpha antagonists, adalimumab and infliximab, for induction or maintenance treatment of Crohn's disease. Five indirect comparisons reviewed by CDR included comparisons of vedolizumab against other biologic treatment for Crohn's disease. However, each of these comparisons was limited by substantial heterogeneity associated with the study designs and patient characteristics of the studies included in the indirect comparisons, which precluded any definitive conclusions regarding the comparative efficacy and safety of vedolizumab compared with TNF alpha antagonists.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group(s) Supplying Input
Two patient groups representing people with inflammatory bowel disease (IBD) responded to the CADTH Common Drug Review (CDR) call for patient input.

The Gastrointestinal Society is a national organization providing evidence-based information relating to gastrointestinal tract and liver conditions. In addition to advocating for appropriate patient access to health care, the Society offers education and programs to both patients and health care professionals, as well as funding to support gastroenterology research. Funding was received from the following organizations: AbbVie Corporation, Actavis, AstraZeneca Canada Inc., Innovative Medicines Canada, Ferring Inc., Gilead Sciences Canada, Inc., GlaxoSmithKline Inc., Janssen Canada, Merck Canada Inc., Pfizer Canada Inc., Shire Canada Inc., and Takeda Canada Inc.

Crohn's and Colitis Canada is a volunteer-based national charity dedicated to investing in education, awareness, and research for Crohn's disease and ulcerative colitis. The charity has received funding from individual donors and various pharmaceutical companies. In the 2014-2015 fiscal year, Crohn's and Colitis Canada received less than 11% of its total revenue from pharmaceutical companies. Major supporters were AbbVie Corporation, Janssen Inc., The Leona M. and Harry B. Helmsley Charitable Trust, M&M Meat Shops, Takeda Canada Inc., and Vertex Pharmaceuticals (Canada) Inc.

Both the Gastrointestinal Society and Crohn's and Colitis Canada have declared no conflict of interest in the preparation of their submissions.

2. Condition-Related Information
The information in this section was collected through patient and caregiver interviews, a 2011 national survey conducted by Crohn's and Colitis Canada, a Canadian questionnaire conducted by the Gastrointestinal Society, patient roundtables, and a review of reports published by Crohn's and Colitis Canada.

Crohn's disease is a disabling, lifelong IBD that is characterized by inflammation of the digestive tract and can extend through the entire thickness of the bowel wall. According to the patient groups, Canada has the highest prevalence of Crohn's disease in the world, with approximately 129,000 diagnosed individuals. The disease can have a profound effect on a patient's physical, emotional, and social well-being. Within the patient input submissions, the groups expressed that having to face the uncertainty of where and when the next flare will occur may lead to anxiety and stress, and may limit the places patients can go and/or the activities they participate in (including work and school). "It makes it difficult to leave my house, play with my son, work, etc. when I am in a flare …" This is supported by the Crohn's and Colitis Canada 2011 survey that found that 43% of employed patients with IBD took some time off work, with an average of 7.2 missed days per year. Furthermore, 34% of respondents frequently missed out on playing sports, 22% missed school trips, 40% avoided parties, and 22% did not attend special events.

Although the most commonly reported symptoms of IBD include bloody diarrhea, bloating, abdominal pain, and fatigue, the patient groups also noted that Crohn's disease can lead to anemia, weight loss,

fever, arthritis, ulcers of the mouth or skin, tender and inflamed nodules on the shins, and delayed development in children. The groups also reported that some patients were concerned with the increased risk of colon cancer with long-standing Crohn's disease. The submissions noted two key concerns among patients with IBD. The first is the lack of control over bowel movements, including the urgent and frequent need of a bathroom. Crohn's and Colitis Canada's 2011 survey found that 73% of IBD patients reported five to 20 or even more bowel movements per day. As quoted by a patient, "When you have to go to the washroom 20 times a day, it impacts everything you do." The second major patient concern that emerged was a fear of flare-ups and the desire for sustained remission, which has been suggested to be more important than relieving any one symptom of IBD. Concerns about future flares and the uncertainty of their severity and occurrence were captured in numerous patient quotes: for example, "…when I'm not in an active flare I live in constant fear of when the next flare will occur" and "…The worst part is fearing the next big flare that will prevent me from being a mom to my 18-month-old."

3. Current Therapy–Related Information

Management of Crohn's disease is described as multi-faceted: It involves both symptom control and targeting of the underlying inflammation. Both submissions noted a lack of treatments available for Crohn's disease. First-line therapy is aminosalicylates (e.g., mesalamine) with steroids and, if remission is not achieved or if the condition worsens, immunomodulators (e.g., azathioprine), sometimes combined with corticosteroids (e.g., prednisone) and biologics, form the second-line therapy. Patients reported few side effects with aminosalicylates, but some patients reported liver problems with immunomodulators. On the contrary, the majority of patients reported side effects from steroids, the most common being mood swings, moon face, and weight gain. While these drugs may be effective in patients with mild to moderate disease, they often do not maintain remission in the long-term and are ineffective for moderate to severe disease. From patients' interviews, it was suggested that these treatments would help relieve some symptoms but would not offer control, as the need for constant and urgent washroom use remained. When the above-mentioned first-line and second-line therapies fail to provide symptom relief, biologics are often considered the last resort to avert surgery for patients with Crohn's disease. The large majority of surveyed patients said they would rather receive a biologic, despite its potential risks and side effects, than get a colectomy. As noted by one patient, "I have a strong desire to keep my body intact. The colon serves a myriad of beneficial functions."

According to the Gastrointestinal Society, surgical removal of the colon is not recommended by physicians in patients suffering from Crohn's disease, as the disease can affect the entire gastrointestinal tract and extend into the muscle wall. Patients further noted that surgery can be associated with its own complications — including soiling, poor pouch function, pouchitis, sexual dysfunction, and an increased risk of fertility loss among female patients — and should be considered only as a last resort. Patients expressed their concern with surgery and the lack of treatment options available to them: "Proposing surgery as a viable treatment option is inhumane and not fair. Surgery should be considered an option of last resort. It is a shame that there is nothing else to take."

Patient groups also reported an impact on caregivers, highlighting the inability of those who suffer from Crohn's disease to work and complete day-to-day tasks and the fatigue and stress associated with caring for those suffering from Crohn's disease.

4. Expectations About the Drug Being Reviewed

Information in this section was gathered from the product monograph, brochures, published reports, attending scientific sessions during Canadian Digestive Diseases Week, discussion with gastroenterologists, and patients with experience with vedolizumab.

Patients felt that more biologic options would be beneficial despite remarkable results observed with current biologics. Intestinal and extraintestinal symptom relief and remission were identified by patients as being most important when considering Crohn's disease treatment. Patients groups highlighted that each patient may respond differently to treatment, and where one patient may benefit, another may not. Within the submissions, it was noted that vedolizumab is a much-needed treatment option to provide choice and to address unmet needs with the currently available biologics. In addition, 98% of patients in the Gastrointestinal Society survey indicated that they would rather receive a biologic treatment than a surgical intervention despite the potential risks and side effects.

As part of the Crohn's and Colitis Canada submission, one-on-one telephone interviews were conducted with 10 Canadian patients who participated in a clinical trial and were still on vedolizumab. All reported an improvement in symptom relief, with remission achieved within the first four to six weeks of treatment. All patients were still in remission, with none experiencing any flare-ups since taking vedolizumab. One patient described his situation as follows: "Had I not found vedolizumab, surgery would have been my only option. […] With steroids, I was at 60% but with vedolizumab, I'm at 95%." No significant adverse effects were reported in these 10 patients. One interviewee further described the necessity of vedolizumab: "To me, vedolizumab is like insulin for diabetes."

Vedolizumab is administered by intravenous infusion. Most considered this a minor issue as the hassle of travelling to clinics is no different from what is done with some other biologics that are currently available. Patients raised concerns about the potential cost of the drug and the possibility that they may not be able to afford treatment without insurance coverage, as well as a concern with the proximity of infusion clinics. "I want this drug to get approved because for people like me, there is no coverage from work [in the construction field]. You have to look at the drug from the benefit it provides rather than the costs because when you are 100% you don't need to worry about being sick, feeling tired and wondering about who is going to take care of your kids."

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE Epub Ahead of Print, 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:	May 19, 2016
Alerts:	Biweekly search updates until September 21, 2016
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
Mh	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; MEDLINE Epub Ahead of Print, 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		
Line #	**Search strategy**	**Results**
1	(Entyvio* or vedolizumab* or LDP02 or "LDP 02" or MLN0002 or "MLN 0002" or MLN02 or "MLN 02" or 943609-66-3 or 9RV78Q2002).ti,ab,ot,kf,hw,rn,nm.	1076
2	1 use ppez	224
3	*vedolizumab/ or (vedolizumab* or LDP02 or "LDP 02" or MLN0002 or "MLN 0002" or MLN02 or "MLN 02" or 943609-66-3 or 9RV78Q2002).ti,ab,kw.	641
4	3 use oemezd	442
5	4 not conference abstract.pt.	246
6	2 or 5	470
7	remove duplicates from 6	301

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Keywords used: Entyvio/vedolizumab and Crohn's disease

Grey Literature

Dates for Search:	May 18-19, 2016
Keywords:	Entyvio, vedolizumab, Crohn's disease
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters), were searched:

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

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Takeda. Phase III study of MLN0002 (300 mg) in treatment of Crohn's Disease. 2014 Jan 15 [cited 2016 May 24; last updated: 2015 Aug 11]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000.[68]	Study results are not available
Amiot A, Grimaud JC, Peyrin-Biroulet L, Filippi J, Pariente B, Roblin X, et al. Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2016 Feb 22.[69]	Study design not of interest (i.e., not an RCT)

RCT = randomized controlled trial.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 34: SUMMARY OF SAFETY POPULATIONS

Population	Studies	Treatment Groups
Induction	Pooled GEMINI II (induction phase) and GEMINI III	• PLA • VDZ at weeks 0, 2, and 6[a]
Induction/ maintenance	GEMINI II induction and maintenance phases	**Randomized allocation:** • VDZ/PLA • VDZ/VDZ q4w • VDZ/VDZ q8w **Non-randomized allocation:** • PLA/PLA • VDZ Q4W (nonresponders)

PLA = placebo; PLA/PLA = PLA throughout both phases of the study; VDZ = vedolizumab; VDZ/PLA = VDZ in the induction phase and then PLA in the maintenance phase; VDZ/VDZ q4w = VDZ in the induction phase and then VDZ q4w in the maintenance phase; VDZ/VDZ q8w = VDZ in the induction phase and then VDZ q8w in the maintenance phase; VDZ q4w (nonresponders) = VDZ-treated patients who failed to respond in the induction phase and received VDZ Q4W in the maintenance phase.
[a] Week 6 induction dosage was used only in GEMINI III.
Source: Common Technical Document, section 2.7.4.[22]

TABLE 35: BASELINE AND DEMOGRAPHIC CHARACTERISTICS FOR TNF ALPHA-FAILURE SUBGROUPS IN GEMINI III

Characteristics	Placebo		300 mg VDZ	
	TNF Alpha-Failure	TNF Alpha-Naive	TNF Alpha-Failure	TNF Alpha-Naive
Women, n (%)	95 (61)	23 (46)	90 (57)	28 (55)
Age (y), median (range)	36.6 (19 to 77)	30.6 (19 to 60)	37.5 (20 to 69)	35.7 (20 to 64)
Body weight (kg), mean (range)	71.2 (41 to 125)	71.7 (43 to 147)	70.3 (40 to 144)	67.1 (40 to 99)
BMI (kg/m^2), median (range)	23.3 (15 to 48)	22.9 (17 to 43)	23.3 (15 to 43)	22.6 (16 to 33)
CD duration (y), median (range)	9.6 (1.0 to 42.9)	4.4 (0.3 to 24.8)	9.4 (0.5 to 41.8)	4.7 (0.3 to 40.8)
CDAI score, mean (SD)	306.1 (55.4)	286.1 (51.1)	316.1 (52.6)	307.3 (54.8)
CRP (mg/L), mean (SD)	18.8 (23.6)	17.7 (16.1)	20.7 (24.7)	13.9 (16.8)
Fecal calprotectin (mg/g), mean (SD)	1,459.5 (2,475.0)	1,321.0 (1,954.0)	1,249.2 (2,071.6)	836.9 (1,043.8)
Ileal CD, n (%)	20 (13)	9 (18)	21 (13)	12 (24)
Colonic CD, n (%)	40 (25)	12 (24)	40 (25)	8 (16)
Ileocolonic CD, n (%)	97 (62)	29 (58)	97 (61)	31 (61)
CD surgery, n (%)	80 (51)	9 (18)	73 (46)	19 (37)
Fistulizing disease, n (%)	67 (43)	10 (20)	57 (36)	14 (27)
Corticosteroid use, n (%)	85 (54)	23 (46)	86 (54)	24 (47)
Immunosuppressive use, n (%)	42 (27)	27 (54)	43 (27)	28 (55)
Mesalamine use, n (%)	29 (18)	32 (64)	37 (23)	31 (61)

Characteristics	Placebo		300 mg VDZ	
	TNF Alpha-Failure	TNF Alpha-Naive	TNF Alpha-Failure	TNF Alpha-Naive
Prior immunosuppressive use, n (%)	147 (94)	46 (92)	135 (85)	41 (80)
TNF alpha antagonist-failure, n (%)	157 (100)	NA	158 (100)	NA
1 TNF alpha antagonist, n (%)	43 (27)	NA	59 (37)	NA
2 TNF alpha antagonist, n (%)	90 (57)	NA	82 (52)	NA
3 TNF alpha antagonist, n (%)	21 (13)	NA	14 (9)	NA

BMI = body mass index; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; NA = not applicable; TNF = tumour necrosis factor; SD = standard deviation; VDZ = vedolizumab; y = years.
Source: Adapted from Sands et al., 2014.[31]

TABLE 36: SERIOUS ADVERSE EVENTS IN THE GEMINI II AND GEMINI III INDUCTION POPULATION

SAEs, n (%)	PLA (N = 355)	Combined VDZ (N = 1,176)
Patients with at least one SAE	25 (7)	86 (7)
Gastrointestinal disorders	19 (5)	61 (5)
Crohn's disease	16 (5)	41 (3)
Enteritis	0	1 (< 1)
Small intestinal obstruction	1 (< 1)	5 (< 1)
Abdominal pain	1 (< 1)	3 (< 1)
Abdominal pain lower	0	1 (< 1)
Pancreatitis	0	2 (< 1)
Enterovesical fistula	0	2 (< 1)
Diarrhea	0	1 (< 1)
Gastric ulcer	0	1 (< 1)
Gastritis	0	1 (< 1)
Subileus	0	1 (< 1)
Intestinal perforation	0	1 (< 1)
Colonic stenosis	0	1 (< 1)
Nausea	0	1 (< 1)
Vomiting	0	1 (< 1)
Peritonitis	0	1 (< 1)
Periproctitis	0	1 (< 1)
Anal fissure	1 (< 1)	0
Infections and infestations	2 (< 1)	13 (1)
Anal abscess	1 (< 1)	6 (< 1)
Abscess intestinal	0	1 (< 1)
Gastroenteritis	0	1 (< 1)
Influenza	0	1 (< 1)
Pneumonia	0	1 (< 1)
Staphylococcal bacteremia	0	1 (< 1)
Upper respiratory tract infection	0	1 (< 1)
Urinary tract infection	0	1 (< 1)
Device-related sepsis	1 (< 1)	0
Metabolism and nutrition disorders	1 (< 1)	4 (< 1)

SAEs, n (%)	PLA (N = 355)	Combined VDZ (N = 1,176)
Hypoalbuminemia	0	2 (< 1)
Dehydration	1 (< 1)	1 (< 1)
Iron deficiency	0	1 (< 1)
Hypokalemia	0	1 (< 1)
Hepatobiliary disorders	0	3 (< 1)
Cytolytic hepatitis	0	1 (< 1)
Hepatitis	0	1 (< 1)
Cholecystitis acute	0	1 (< 1)
General disorders and administration site conditions	1 (< 1)	2 (< 1)
Edema peripheral	0	1 (< 1)
Non-cardiac chest pain	0	1 (< 1)
General physical health deterioration	1 (< 1)	0
Blood and lymphatic system disorders	0	2 (< 1)
Anemia	0	2 (< 1)
Neoplasms benign, malignant, and unspecified	0	2 (< 1)
Breast cancer	0	1 (< 1)
Ependymoma	0	1 (< 1)
Renal and urinary disorders	0	2 (< 1)
Calculus ureteric	0	1 (< 1)
Renal colic	0	1 (< 1)
Investigations	1 (< 1)	1 (< 1)
Weight decreased	0	1 (< 1)
Clostridium test positive	1 (< 1)	0
Musculoskeletal and connective tissue disorders	1 (< 1)	1 (< 1)
Joint effusion	0	1 (< 1)
Polyarthritis	1 (< 1)	0
Cardiac disorders	0	1 (< 1)
Myocarditis	0	1 (< 1)
Eye disorders	0	1 (< 1)
Vision blurred	0	1 (< 1)
Injury, poisoning, and procedural complications	0	1 (< 1)
Infusion-related reaction	0	1 (< 1)
Respiratory, thoracic, and mediastinal disorders	0	1 (< 1)
Pulmonary embolism	0	1 (< 1)
Vascular disorders	0	1 (< 1)
Hypertension	0	1 (< 1)
Nervous system disorders	1 (< 1)	0
Demyelination	1 (< 1)	0
Pregnancy, puerperium, and perinatal conditions	1 (< 1)	0
Abortion spontaneous	1 (< 1)	0
Skin and subcutaneous tissue disorders	1 (< 1)	0
Urticaria	1 (< 1)	0

PLA = placebo; SAE = serious adverse event; VDZ = vedolizumab.
Source: Common Technical Document, section 5.3.5.3.[9]

TABLE 37: WITHDRAWALS DUE TO ADVERSE EVENTS IN THE GEMINI II AND GEMINI III INDUCTION POPULATION

WDAEs, n (%)	Combined VDZ (N = 1,176)	PLA (N = 355)
WDAE	37 (3)	17 (5)
Gastrointestinal disorders	24 (2)	15 (4)
Crohn's disease	16 (1)	14 (4)
Small intestinal obstruction	3 (< 1)	1 (< 1)
Nausea	2 (< 1)	0
Vomiting	1 (< 1)	0
Abdominal pain	1 (< 1)	0
Enterovesical fistula	1 (< 1)	0
Subileus	1 (< 1)	0
Infections and infestations, n (%)	5 (< 1)	0
Herpes zoster	1 (< 1)	0
Oral herpes	1 (< 1)	0
Anal abscess	1 (< 1)	0
Folliculitis	1 (< 1)	0
Pneumonia	1 (< 1)	0
General disorders and administration site conditions	2 (< 1)	0
Fatigue	1 (< 1)	0
Malaise	1 (< 1)	0
Pyrexia	1 (< 1)	0
Musculoskeletal and connective tissue disorders	2 (< 1)	0
Arthralgia	2 (< 1)	0
Neoplasms benign, malignant, and unspecified	2 (< 1)	0
Breast cancer	1 (< 1)	0
Ependymoma	1 (< 1)	0
Nervous system disorders	2 (< 1)	0
Dizziness	2 (< 1)	0
Paresthesia	2 (< 1)	0
Headache	1 (< 1)	0
Skin and subcutaneous tissue disorders	2 (< 1)	0
Eczema	1 (< 1)	0
Prurigo	1 (< 1)	0
Hepatobiliary disorders	1 (< 1)	0
Cytolytic hepatitis	1 (< 1)	0
Injury, poisoning, and procedural complications	1 (< 1)	0
Infusion-related reaction	1 (< 1)	0
Blood and lymphatic system disorders	0	2 (< 1)
Lymphopenia	0	2 (< 1)

PLA = placebo; VDZ = vedolizumab; WDAE = withdrawal due to adverse event.
Source: Common Technical Document, section 5.3.5.3.[9]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

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

Aim

To summarize the measurement properties (e.g., reliability, validity, minimal clinically important difference [MCID]) of the following outcome measures used in the GEMINI II and GEMINI III studies:

- Crohn's Disease Activity Index (CDAI)
- Inflammatory Bowel Disease Questionnaire (IBDQ)
- Short Form (36) Health Survey (SF-36)
- EuroQol 5-Dimensions Questionnaire (EQ-5D-3L)

Findings

1. Crohn's Disease Activity Index

The National Cooperative Crohn's Disease Study Group developed the CDAI using prospective data gathered from 187 visits of 112 patients suffering from Crohn's disease.[70] It is a disease-specific index and considered as the standard for assessing Crohn's disease activity. The CDAI consists of eight domains, which are used to evaluate overall disease severity. The overall score is based on the sum of the weighted value of each item and ranges from 0 to 600, where a score of 150 is defined as the threshold between remission and active disease. Scores ranging between 150 and 219 indicate mild to moderate Crohn's disease, scores ranging between 220 and 450 indicate moderate to severe Crohn's disease, whereas scores above 450 indicate very severe Crohn's disease.[71,72] Item scores are derived using patient diaries for the seven days preceding each visit. Generally, the CDAI is considered impractical for use in clinical practice, with no clear MCID clearly defined.[72,73] Originally, changes of 50 points in the CDAI were associated with physician evaluations of "slightly better" and/or "slightly worse" compared with baseline.[70,72,73] However, clinical trials have commonly used changes of 50, 60, 70, or 100 points in CDAI defined as clinical response.[72] More recently, the FDA and European Medicines Agency have suggested that a change of 100 points in CDAI is considered to be a more meaningful response (i.e., enhanced clinical response).[72]

Development of the Crohn's Disease Activity Index

Gastroenterologists considered 18 parameters to inform the CDAI, including the following Crohn's disease domains: subjective patient symptoms and need for symptomatic medications, objective clinical findings on physical examination, extraintestinal manifestations of Crohn's disease, complications of Crohn's disease (e.g., fistulas), radiologic and endoscopic examinations, and laboratory parameters. A global assessment score was also assessed at each visit by the gastroenterologist based on the following scheme: "very well" = 1, "fair to good" = 3, "poor" = 5, and "very poor" = 7.

Multiple regression and backwards stepwise deletions were utilized to assess the correlation between the 18 parameters and the physician global assessment score. Based on the results of the correlations, eight independent weighted variables (weighting ranges from 1 to 30) were included in the final CDAI formula.

TABLE 38: FINAL ITEMS INCLUDED IN THE CDAI AND THEIR WEIGHTS

Item (Daily Sum Per Week)	Weight
Number of liquid or very soft stools	2
Abdominal pain score in one week (rating: 0 to 3)	5
General well-being (rating: 0 to 4)	7
Sum of findings per week: • Arthritis/arthralgia • Mucocutaneous lesions (e.g., erythema nodosum aphthous ulcers) • Iritis/uveitis • Anal disease (fissure, fistula, etc.) • External fistula (enterocutaneous/vesicle/vaginal, etc.) • Fever > 37.8°C	20
Antidiarrheal use (e.g., diphenoxylate hydrochloride)	30
Abdominal mass (none = 0, equivocal = 2, present = 5)	10
47 minus hematocrit (males) or 42 minus hematocrit (females)	6
100 × (1 - [body weight divided by standard weight])	1

CDAI = Crohn's Disease Activity Index.
Source: Best et al.[70]

Reliability of the Crohn's Disease Activity Index

Reliability was not originally assessed during the development of the CDAI; however, the index did provide good to very good test–retest reliability evaluated based on two successive visits for 32 patients.[70,71] The CDAI was subsequently re-evaluated and re-derived using data collected from 1,058 patients and demonstrated little difference compared to the original formulation; therefore, the original version was recommended.[74]

Validity of the Crohn's Disease Activity Index

Construct validity: The items included in the CDAI were selected by gastroenterologists and are based on accepted features of Crohn's disease, thereby demonstrating construct validity.[71]

Content validity: The CDAI appears to be responsive as it allows detectable changes in Crohn's disease severity to be measured (i.e., the CDAI is able to differentiate levels of Crohn's disease severity). Additionally, the CDAI appears to be widely utilized in clinical trials and is an accepted measure by gastroenterologists as a primary end point to assess Crohn's disease activity. In contrast, the CDAI does not appear to be reflective of Crohn's disease activity for pediatric patients suffering from Crohn's disease, nor does the instrument address all aspects of Crohn's disease such as quality of life.[71]

Criterion validity: Selecting a gold standard measure for comparison is difficult when considering Crohn's disease, due to the heterogeneous nature of its manifestations. Generally, the CDAI does not demonstrate any significant correlation between the overall score and objective measurements such as mucosal healing; however, the lack of correlation may not be indicative of a lack of criterion validity due to the multi-faceted nature of Crohn's disease.[71] Predictability is another component of criterion validity. One study demonstrated that the CDAI scores increased two months preceding exacerbations of Crohn's disease and decreased one month following exacerbations of Crohn's disease, thereby demonstrating criterion validity.[71]

Limitations of the Crohn's Disease Activity Index

The CDAI scores appear to vary depending on the observer's review despite the evaluation of the same case histories.[75] In addition, the overall CDAI score is derived based on some subjective items such as "general well-being" and "intensity of abdominal pain" based on patient perception.

2. Inflammatory Bowel Disease Questionnaire

The IBDQ, developed by Guyatt et al.,[36,37] is a physician-administered questionnaire to assess health-related quality of life (HRQoL) in patients with IBD (e.g., ulcerative colitis and Crohn's disease).[76] It is a 32-item Likert-based questionnaire divided into four dimensions: bowel symptoms (10 items), systemic symptoms (five items), emotional function (12 items), and social function (five items). Patients are asked to recall symptoms and quality of life from the last two weeks with response graded on a 7-point Likert scale (1 being the worst situation, 7 being the best) with the total IBDQ score ranging between 32 and 224 (i.e., higher scores representing better quality of life). Scores of patients in remission typically range from 170 to 190.

This questionnaire has been validated in a variety of settings, countries, and languages.[76] A review[76] of nine validation studies on the IBDQ in patients with IBD reported that the IBDQ was able to differentiate clinically important differences between patients with disease remission and patients with disease relapse. In a randomized placebo-controlled trial on patients with ulcerative colitis, the IBDQ was found to be able discriminate changes in the social and emotional state of patients.[77] The IBDQ has high test–retest reliability in all four dimensional scores. Six studies evaluated IBDQ for sensitivity to change and all found that changes in HRQoL correlated to changes in clinical activity in patients with Crohn's disease.[76]

A study conducted by Gregor et al.[7] noted that a clinically meaningful improvement in quality of life would be an increase ≥ 16 points in the IBDQ total score or ≥ 0.5 points per question in patients with Crohn's disease.

3. Short Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. The SF-36 consists of eight domains: Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The SF-36 also provides two component summaries: The physical component summary (PCS) and the mental component summary (MCS), which are scores created by aggregating the eight domains. The SF-36-PCS, SF-36-MCS, and eight domains are each measured on a scale of 0 to 100, with an increase in score indicating improvement in health status. In general use of SF-36, a change of 2 to 4 points in each domain or 2 to 3 points in each component summary indicates a clinically meaningful improvement as determined by the patient.[78]

Validation work reports satisfactory reliability and discriminant ability for all SF-36 dimensions in patients with ulcerative colitis. As symptoms increase, HRQoL scores are statistically significantly reduced. In a population-based cohort in which patients were studied for 10 years, SF-36 scores of patients with ulcerative colitis were found to be comparable with those of a general population sample when adjusted for age, gender, and education. A study indicated that the individual domains may present with ceiling effects in patients with less severe ulcerative colitis. Individual domain scores were also found to have less responsiveness in patients with mild ulcerative colitis, although it is unclear if this can be generalized to the broader PCS and MCS scores.[79]

A study by Coteur et al.[38] explored MCID estimates within the Crohn's disease patient population using data from multinational, multi-centre, double-blind, placebo-controlled parallel group clinical trials in which clinical remission of Crohn's disease was assessed using the CDAI measure as the primary outcome. Secondary outcomes included the IBDQ and SF-36. All end points were measured at weeks 0, 6, 16, and 26 and used standardized procedures. A total of six estimates of MCID were evaluated for each SF-36 scale summary score to determine the most appropriate measure to use as the anchor: two analyses utilizing anchor-based methods and four analyses utilizing distribution-based methods. For the anchor-based estimates, a linear regression was performed using the two anchors, the CDAI and IBDQ. The MCID estimates for the SF-36 were then extracted from the regression equations using a change of 16 points for the IBDQ total score or a score change of 50 points for the CDAI score considered as meaningful. For distribution-based estimates, measures rely on the statistical distributions of HRQoL data and include effect size measures (effect sizes of 0.2 and 0.5 were used and suggested as small to moderate effect sizes), the standard error of measurement, and the standard error of the difference. Overall, the MCID for the SF-36 PCS and MCS summary scores ranged from 1.6 to 7.0 and 2.3 to 8.7, respectively, depending on the approach. Because score changes in the SF-36 showed greater correlations with score changes in the IBDQ than with the CDAI, the IBDQ was selected as the "best anchor," with corresponding MCID values of 4.1 and 3.9, respectively. The values derived by the IBDQ anchor-based method were similar to the values obtained by the distribution-based methods and were representative of small to moderate effect sizes.

4. EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic HRQoL instrument that may be applied to a wide range of health conditions and treatments.[39,40] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[39,40] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

1. A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. A population preference-weighted health index score based on the descriptive system
3. A self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the 3L version (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores < 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for the 3L version of the scale have ranged from 0.033 to 0.074.[80]

Studies are emerging supporting the validity of the EQ-5D in patients with IBD, including Crohn's disease. Both EQ-VAS and EQ-index scores were found to correlate well with disease activity indices and differed significantly between patients with active disease and remission. Test–retest reliability was high. EQ-VAS was more responsive to deterioration in health than improvement in health and tended to be more responsive than EQ-index scores.[81]

The study by Coteur et al.[38] explored MCID estimates within the Crohn's disease patient population using data from multinational, multi-centre, double-blind, placebo-controlled parallel group clinical trials in which clinical remission of Crohn's disease was assessed using the CDAI measure as the primary outcome. Secondary outcomes included the IBDQ and EQ-5D VAS scores. All end points were measured at weeks 0, 6, 16, and 26 and used standardized procedures. A total of six estimates of MCID were evaluated for the EQ-5D VAS score to determine the most appropriate measure to use as the anchor: Two analyses utilizing anchor-based methods and four analyses utilizing distribution-based methods. For the anchor-based estimates, a linear regression was performed using the two anchors, the CDAI and IBDQ. The MCID estimates for the EQ-5D VAS score were then extracted from the regression equations using a change of 16 points for the IBDQ total score or a score change of 50 points for the CDAI score considered as meaningful. For distribution-based estimates, measures rely on the statistical distributions of HRQoL data, and include effect size measures (effect sizes of 0.2 and 0.5 were used and suggested as small to moderate effect sizes), the standard error of measurement, and the standard error of the difference. Overall, the MCID for the EQ-5D VAS score ranged from 4.2 to 14.8, depending on the approach. Because score changes in the EQ-5D VAS score showed greater correlations with score changes in the IBDQ than with CDAI, the IBDQ was selected as the "best anchor" with a corresponding MCID value of 8.2. The values derived by the IBDQ anchor-based method were similar to the values obtained by the distribution-based methods and were representative of small to moderate effect sizes.

TABLE 39: SUMMARY OF OUTCOMES MEASURES

Measure	Definition	Evidence of Validity	MCID	Reference
CDAI	Physician-evaluated 8-item CD-specific index used to assess CD severity	Yes	NA	Best et al.[70]
IBDQ	Physician-administered 32-item questionnaire used to assess HRQoL in patients with IBD	Yes	16	Gregor et al.[7]
SF-36	Patient-reported generic QoL instrument	Yes	PCS 4.1 MCS 3.9	Coteur et al.[38]
EQ-5D	Patient-reported generic QoL instrument	Yes	VAS 8.2	Coteur et al.[38]

CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; HRQoL = health-related quality of life; IBD = Inflammatory Bowel Disease; IBDQ = Inflammatory Bowel Disease Questionnaire; MCID = minimal clinically important difference; MCS = mental component summary; NA = not applicable; PCS = physical component summary; QoL = quality of life; SF-36 = Short Form (36) Health Survey; VAS = visual analogue scale.

Conclusion

The CDAI, IBDQ, SF-36, and EQ-5D have all been validated within the Crohn's disease population. Although a definition of an MCID change in the CDAI, IBDQ, SF-36, and EQ-5D instruments has not been established, some regulatory agencies rely on a reduction of 100 points in the CDAI as meaningful change, while other studies suggest MCIDs of 16, 4.1, 3.9, and 8.2 for the IBDQ, SF-36-PCS, SF-36-MCS, and EQ-5D, respectively.

APPENDIX 6: SUMMARY OF MANUFACTURER'S INDIRECT COMPARISON

Introduction

Background

Given the absence of head-to-head studies that have compared vedolizumab against other relevant biologics for moderate to severe Crohn's disease in this CDR review, the objective of this Appendix is to summarize and critically appraise the evidence available regarding the comparative efficacy and safety of vedolizumab versus infliximab and adalimumab through indirect comparison (IDC). Both induction and maintenance treatment in adult patients with moderate to severely active Crohn's disease are evaluated in the review.

Methods for Manufacturer's Indirect Comparison

Study eligibility and selection process

The manufacturer reported that the IDC is based on a systematic literature review; however, its methodology was poorly reported. There is limited information about the methods used for the literature search, study selection, data extraction, and risk of bias assessment. The methods for the literature search were missing information regarding the search terms, electronic search strategy, dates associated with the original and updated literature searches (it was noted that the current review was conducted as an updated), and any limitations or filters applied in the search. It can be inferred from the results section that the literature search included the following: Embase, MEDLINE, the Cochrane Library, the manufacturer's internal database, clinical trial registries (e.g., clinicaltrials.gov), and manual searching based on reference lists of retrieved articles.

The inclusion criteria for the systematic review are summarized in Table 40. The eligibility criteria for the systemic review were reported only at a high level in the introduction and are absent from the methods section. CADTH reviewers extracted information from the results section of the report to populate the summary provided in Table 40.

TABLE 40: INCLUSION CRITERIA FOR THE MANUFACTURER'S INDIRECT COMPARISON

	MANUFACTURER'S INDIRECT COMPARISON

Patient Population	• Moderate to severe CD
	  ○ TNF alpha antagonist-naive
	  ○ TNF alpha antagonist-failure

Intervention	• Vedolizumab (300 mg)
Comparators	• Infliximab • Adalimumab
Outcomes	**Efficacy outcomes:** • Clinical remission • Clinical response • Enhanced clinical response • Durable clinical remission • Corticosteroid-free clinical remission **Harms outcomes:** • Adverse events • Discontinuation due to adverse events • Serious adverse events

	MANUFACTURER'S INDIRECT COMPARISON
	• Infectious adverse events • Serious infectious adverse events • Death
Study Design	Placebo-controlled RCTs (induction and maintenance studies)

CD = Crohn's disease; RCT = randomized controlled trial; TNF = tumour necrosis factor.
Source: Manufacturer's Indirect Comparison Report.[50]

In general, inclusion was limited to placebo-controlled trials investigating one or more of the following: vedolizumab, infliximab, or adalimumab. The Methods section lacks any description about how any of the following characteristics were considered in the study selection process: Definitions for moderate to severe Crohn's disease, dosage regimens of adalimumab and infliximab, study durations, and previous exposure to pharmacotherapy in the management of Crohn's disease. However, an examination of the reasons for study exclusion suggests that studies were excluded if they were perceived to lack comparability with the vedolizumab pivotal studies with regard to patient characteristics (e.g., fistulizing Crohn's disease or recent respective surgery) or trial end points (e.g., absence of induction phase outcome or recurrence of Crohn's disease following surgery). In addition, at least one study was excluded for using an infliximab dosing regimen that exceeds the recommended induction dosage in Canada (i.e., 10 mg/kg rather than 5 mg/kg). Studies were also excluded if they investigated combination usage of a tumour necrosis factor (TNF) alpha antagonist with other agents (e.g., azathioprine).

Quality assessment of included studies

Quality assessment of the individual included studies was performed, but the specific instrument used was not identified in the methods section. Based on the results section, the following characteristics were considered in the manufacturer's quality assessment: Allocation concealment, blinding, withdrawals, and the use of an intention-to-treat (ITT) analysis.

Indirect comparison methods

The manufacturer conducted IDCs of vedolizumab versus infliximab and adalimumab using the Bucher method, with placebo as the common comparator. All of the outcomes that were evaluated in the IDC were dichotomous outcomes, and differences between treatments were reported as relative risks (RRs). In instances where there are data from multiple clinical studies (e.g., GEMINI II and GEMINI III), the results from the individual studies were pooled using a random-effects model. The pooled estimate was subsequently used in the Bucher calculations. Analyses were conducted using the overall study populations, and subgroup analyses were conducted for patients who were TNF alpha antagonist-naive and those who had experienced failure with or intolerance to one or more TNF alpha antagonists. A summary of the IDCs conducted by the manufacturer is provided in Table 41 for the induction studies and in Table 42 for the maintenance studies.

TABLE 41: OUTCOMES AND POPULATIONS EVALUATED IN INDIRECT COMPARISON FOR INDUCTION STUDIES

Outcome	Definition	Drug	Trial	Time Point	Study Population		
					ITT	TNF Alpha-Naive	TNF Alpha-Failure
Vedolizumab vs. Infliximab							
Clinical remission	CDAI ≤ 150	VDZ	GEMINI II GEMINI III	Week 6	Yes	Yes	Yes
		IFX	T16	Week 4	Yes	Yes	No
Clinical response	Reduction in CDAI ≥ 70	VDZ	GEMINI II GEMINI III	Week 6	Yes	Yes	Yes
		IFX	T16	Week 4	Yes	Yes	No
Vedolizumab vs. Adalimumab							
Clinical remission	CDAI ≤ 150	VDZ	GEMINI II GEMINI III	Week 6	Yes	Yes	Yes
		ADA	CLASSIC I	Week 4	Yes	Yes	Yes
			Watanabe GAIN		Yes	No	Yes
Enhanced clinical response	Reduction in CDAI ≥ 100	VDZ	GEMINI II GEMINI III	Week 6	Yes	Yes	Yes
		ADA	CLASSIC I	Week 4	Yes	Yes	No
			GAIN		Yes	No	Yes
			Watanabe		Yes	Yes	No
Clinical response	Reduction in CDAI ≥ 70	VDZ	GEMINI II GEMINI III	Week 6	Yes	Yes	Yes
			CLASSIC I	Week 4	Yes	Yes	No
			GAIN		Yes	No	Yes
			Watanabe		Yes	Yes	Yes

ADA = adalimumab; CDAI = Crohn's Disease Activity Index; IFX = infliximab; ITT = intention-to-treat; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab; vs. = versus.
Source: Manufacturer's Indirect Comparison Report.[50]

TABLE 42: OUTCOMES AND POPULATIONS EVALUATED IN INDIRECT COMPARISON FOR MAINTENANCE STUDIES

Outcome	Definition	Drug	Trial	Time Point	Study Population		
					ITT	TNF Alpha-Naive	TNF Alpha-Failure
Vedolizumab vs. Infliximab							
Clinical remission	CDAI ≤ 150	VDZ	GEMINI II	Week 52	Yes	Yes	Yes
		IFX	ACCENT I	Week 54	Yes	Yes	No
Clinical response	Reduction in CDAI ≥ 70 and ≥ 25% from baseline	VDZ	GEMINI II	Week 52	Yes	Yes	Yes
		IFX	ACCENT I	Week 54	Yes	Yes	No
Durable clinical remission	Clinical remission at > 80% of visits, including week 52	VDZ	GEMINI II	Week 52	Yes	Yes	Yes

Outcome	Definition	Drug	Trial	Time Point	Study Population		
					ITT	TNF Alpha-Naive	TNF Alpha-Failure
	Clinical remission at every visit from week 14 to week 54	IFX	ACCENT I	Week 54	Yes	Yes	No
Vedolizumab vs. Adalimumab							
Clinical remission	CDAI ≤ 150	VDZ	GEMINI II	Week 52	Yes	Yes	Yes
		ADA	CHARM	Week 56	Yes	Yes	Yes
			Watanabe		Yes	No	Yes
Enhanced clinical response	Reduction in CDAI ≥ 100	VDZ	GEMINI II	Week 52	Yes	Yes	Yes
		ADA	CHARM	Week 56	Yes	Yes	Yes
			Watanabe		Yes	No	No
Clinical response	Reduction in CDAI ≥ 70	VDZ	GEMINI II	Week 52	Yes	No	No
		ADA	CHARM	Week 56	Yes	No	No
			Watanabe				
CS-free clinical remission	Discontinuation of CS and clinical remission	VDZ	GEMINI II	Week 52	Yes	No	No
		ADA	CHARM	Week 56			
			Watanabe				

ADA = adalimumab; CDAI = Crohn's Disease Activity Index; CS = corticosteroid; IFX = infliximab; ITT = intention-to-treat; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab; vs. = versus.
Source: Manufacturer's Indirect Comparison Report.[50]

Results

Study and patient characteristics

In total, nine unique placebo-controlled randomized controlled trials were included in the manufacturer's IDC. The following studies were included in the manufacturer's evaluation of induction phase end points: Two studies of vedolizumab (GEMINI II and GEMINI III), one study of infliximab (T16),[82] and three studies of adalimumab (CLASSIC-I,[83] GAIN,[84] and Watanabe et al.[85]). The following studies were included in the manufacturer's evaluation of maintenance phase end points: one study of vedolizumab (GEMINI II), one study of infliximab (ACCENT I[67]), and three studies of adalimumab (CLASSIC II,[54] CHARM,[86] and Watanabe et al.[85]). Study characteristics of the randomized controlled trials included in the IDC are summarized in Table 43. The vedolizumab trials (GEMINI II and GEMINI III) have already been detailed in this review. All of the included studies were used in the IDCs for the efficacy end points, with the exception of the CLASSIC II maintenance study, which was excluded due to the requirement for demonstrating clinical response twice for inclusion in the maintenance phase (i.e., at weeks 4 and 8). However, CLASSIC II was included in the IDC for safety end points.

TABLE 43: SELECT STUDY CHARACTERISTICS INCLUDED IN THE INDIRECT COMPARISON

Drug	Study	Treatment Group Included in IDC (n)[a]	Primary End Point	Mean CDAI (SD)	Prior Anti-TNF Alpha (%)	Concomitant Medications	
						CS	IM
Induction Studies							
VDZ	GEMINI II	• VDZ 300 mg weeks 0, 2 (220) • PLA (148)	Clinical remission (week 6) Enhanced clinical response (week 6)	VDZ: 327 (71) PLA: 325 (78)	VDZ: 50% PLA: 49%	PLA: 71 (48) VDZ: 105 (48)	PLA: 51 (34) VDZ: 75 (34)
	GEMINI III	• VDZ 300 mg weeks 0, 2, 6 (209) • PLA (207)	Clinical remission (week 6)	VDZ: 314 (53) PLA: 301 (55)	VDZ: 76% PLA: 76%	PLA: 108 (52) VDZ: 110 (53)	PLA: 69 (33) VDZ: 71 (34)
ADA	CLASSIC I	• ADA 160 mg week 0, 80 mg week 2 (76) • PLA (74)	Clinical remission (week 4)	ADA: 295 (52) PLA: 296 (60)	ADA: 0% PLA: 0%	PLA: 25 (34) ADA: 24 (32)	PLA: 22 (30) ADA: 22 (29)
	GAIN	• ADA 160 mg week 0, 80 mg week 2 (159) • PLA (166)	Clinical remission (week 4)	ADA: 313 (58) PLA: 313 (66)	ADA: 100% PLA: 100%	PLA: 73 (44) ADA: 55 (35)	PLA: 85 (51) ADA: 73 (46)
	Watanabe	• ADA 160 mg week 0, 80 mg week 2 (33) • PLA (23)	Clinical remission (week 4)	ADA: 301 (67) PLA: 308 (64)	ADA: 58% PLA: 57%	PLA: 5 (22) ADA: 8 (24)	PLA: 8 (35) ADA: 10 (30)
IFX	T16	• IFX 5 mg/kg week 0 (27) • PLA (25)	Clinical response (week 4)	PLA: 288 (54) IFX: 312 (56)	PLA: 0% IFX: 0%	PLA: 16 (64) IFX: 15 (56)	PLA: 11 (44) IFX: 9 (33)
Maintenance Studies							
VDZ	GEMINI II	• VDZ 300 mg q8w (154) • PLA (153)	Clinical remission (week 52)	VDZ: 326 (69) PLA: 325 (66)	PLA: 82 (54) VDZ: 87 (56)	PLA: 82 (54) VDZ: 82 (53)	PLA: 49 (32) VDZ: 50 (32)
ADA	CLASSIC II	• ADA 40 mg q2w (19) • PLA (18)	Clinical remission (week 60)	ADA: 106 (33) PLA: 107 (62)	PLA: 0 ADA: 0	PLA: 10 (56) ADA: 8 (47)	PLA: 3 (17) ADA: 4 (21)
	CHARM	• ADA 40 mg q2w (172) • PLA (170)	Clinical remission (week 26) Clinical remission (week 56)	ADA: 316 (62) PLA: 321 (67)	PLA: 81 (48) ADA: 86 (50)	All: 499 (42)	PLA: 83 (49) ADA: 77 (45)
	Watanabe	• ADA 40 mg q2w (25) • PLA (25)	Clinical remission (week 56)	ADA: 326 (62) PLA: 297 (65)	PLA: 14 (56) ADA: 13 (52)	PLA: 5 (20) ADA: 3 (12)	PLA: 7 (28) ADA: 11 (44)
IFX	ACCENT I	• IFX 5 mg/kg q8w (193)	Clinical remission (week 30)	All (median	IFX: 0	All: 175 (52)	All: 91 (27)

Drug	Study	Treatment Group Included in	Primary End Point	Mean CDAI	Prior	Concomitant Medications	
		• PLA (188)	Time to loss of response (week 54)	[IQR]): 299 (264, 342)	PLA: 0		

ADA = adalimumab; CDAI = Crohn's Disease Activity Index; CS = corticosteroid; IDC = indirect comparison; IFX = infliximab; IM = immunomodulators; IQR = interquartile range; ITT = intention-to-treat; PLA = placebo; q2w = every two weeks; q8w = every eight weeks; SD = standard deviation; TNF alpha = tumour necrosis factor alpha; VDZ = vedolizumab.

[a] Treatment groups with a lower-than-recommended dosage regimen were not included in the IDC and, for brevity, are not summarized in the table.

Source: Adapted from the manufacturer's Indirect Comparison Report.[50]

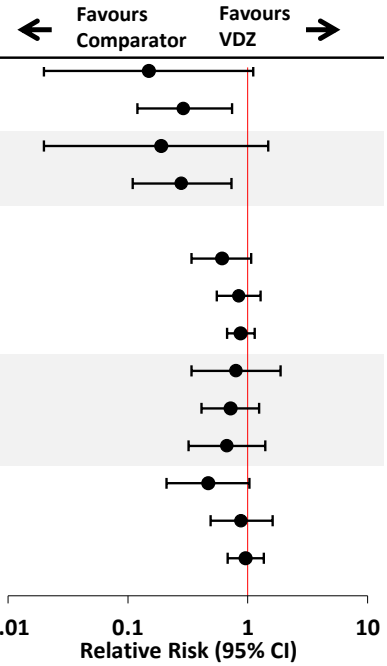
Induction therapy

The results of the IDCs for induction therapy are summarized in Figure 6. In the overall treatment population, the manufacturer's IDC of vedolizumab versus infliximab provided estimates of effect favouring treatment with infliximab for inducing clinical remission (RR 0.15; 95% confidence interval [CI], 0.02 to 1.11) and clinical response (RR 0.29; 95% CI, 0.12 to 0.74). Similar results were reported for the TNF-failure subgroup analyses, with RRs of 0.19 (95% CI, 0.02 to 1.48) and 0.28 (95% CI, 0.11 to 0.73) for inducing clinical remission and clinical response, respectively. The manufacturer reported that vedolizumab was noninferior to infliximab for the induction of clinical remission in both the overall and TNF-naive populations and inferior for clinical remission in both populations.

Similar to the comparison against infliximab, the indirect estimate effect for clinical remission favoured adalimumab over vedolizumab (RR 0.61; 95% CI, 0.34 to 1.08), although the upper bound of the CI did not exclude unity. The indirect estimates for enhanced clinical response (RR 0.84; 95% CI, 0.55 to 1.28) and clinical response (RR 0.87; 95% CI, 0.67 to 1.14) were closer to unity. Results were similar in the TNF-failure subgroups. For all comparisons in the induction phase, the manufacturer reported that vedolizumab was noninferior to adalimumab.

FIGURE 6: RESULTS FROM THE INDIRECT COMPARISON OF INDUCTION STUDIES

Comparison	Population	Endpoint	RR (95% CI)
VDZ vs. IFX	ITT	Clinical remission	0.15 (0.02, 1.11)
		Clinical response	0.29 (0.12, 0.74)
	TNF-naïve	Clinical remission	0.19 (0.02, 1.48)
		Clinical response	0.28 (0.11, 0.73)
VDZ vs. ADA	ITT	Clinical remission	0.61 (0.34, 1.07)
		Enhanced clinical response	0.84 (0.55, 1.28)
		Clinical response	0.87 (0.67, 1.14)
	TNF-naïve	Clinical remission	0.80 (0.34, 1.88)
		Enhanced clinical response	0.72 (0.41, 1.24)
		Clinical response	0.67 (0.32, 1.40)
	TNF-experienced	Clinical remission	0.47 (0.21, 1.03)
		Enhanced clinical response	0.88 (0.49, 1.61)
		Clinical response	0.96 (0.68, 1.36)



ADA = adalimumab; CI = confidence interval; IFX = infliximab; ITT = intention-to-treat; RR = relative risk; TNF = tumour necrosis factor alpha antagonist; VDZ = vedolizumab; vs. = versus.
Source: Manufacturer's Indirect Comparison Report.[50]

Maintenance therapy

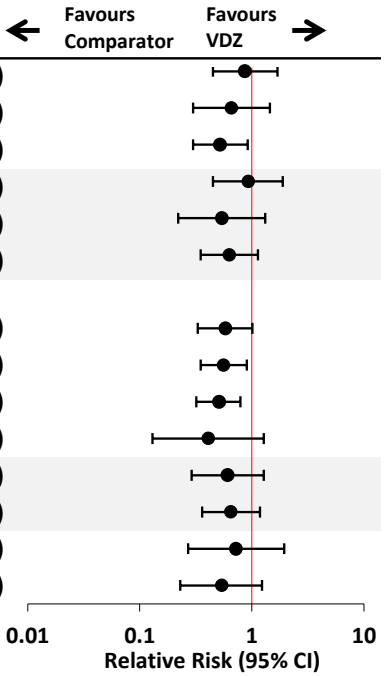
The results of the IDCs for maintenance therapy are summarized in Figure 7. The manufacturer reported that vedolizumab was noninferior to infliximab for maintenance of clinical remission (RR 0.87; 95% CI, 0.49 to 1.69) and durable clinical remission (RR 0.66; 95% CI, 0.30 to 1.45). In contrast, the manufacturer reported that vedolizumab was inferior to infliximab for maintaining clinical response (RR 0.52; 95% CI, 0.30 to 0.92). Results were similar for the TNF-naive subgroup; however, the indirect estimate for

maintaining clinical response did not exclude unity, and therefore, the manufacturer claimed that vedolizumab was noninferior to infliximab.

The indirect estimate of effect for maintaining clinical remission favoured adalimumab compared with vedolizumab; however, the CI does not exclude unity (RR 0.58; 95% CI, 0.37 to 1.01). Therefore, the manufacturer reported that vedolizumab was noninferior to adalimumab for the maintenance of the clinical remission. The manufacturer reported that vedolizumab was inferior to adalimumab for enhanced clinical response (RR 0.56; 95% CI, 0.35 to 0.90) and clinical response (RR 0.51; 95% CI, 0.32 to 0.79) and noninferior to adalimumab for corticosteroid-free clinical remission (RR 0.41; 95% CI, 0.13 to 1.28). For the TNF-failure subpopulation, the manufacturer reported that vedolizumab was noninferior to adalimumab for both clinical remission and enhanced clinical response.

FIGURE 7: RESULTS FROM THE INDIRECT COMPARISON OF MAINTENANCE STUDIES

Comparison	Population	Endpoint	RR (95% CI)
VDZ vs. IFX	ITT	Clinical remission	0.87 (0.45, 1.69)
		Durable clinical remission	0.66 (0.30, 1.45)
		Clinical response	0.52 (0.30, 0.92)
	TNF-naïve	Clinical remission	0.93 (0.45, 1.89)
		Durable clinical remission	0.54 (0.22, 1.32)
		Clinical response	0.63 (0.35, 1.13)
VDZ vs. ADA	ITT	Clinical remission	0.58 (0.33, 1.01)
		Enhanced clinical response	0.56 (0.35, 0.90)
		Clinical response	0.51 (0.32, 0.79)
		CS-free clinical remission	0.41 (0.13, 1.28)
	TNF-naïve	Clinical remission	0.61 (0.29, 1.28)
		Enhanced clinical response	0.65 (0.36, 1.18)
	TNF-experienced	Clinical remission	0.72 (0.27, 1.94)
		Enhanced clinical response	0.54 (0.23, 1.23)

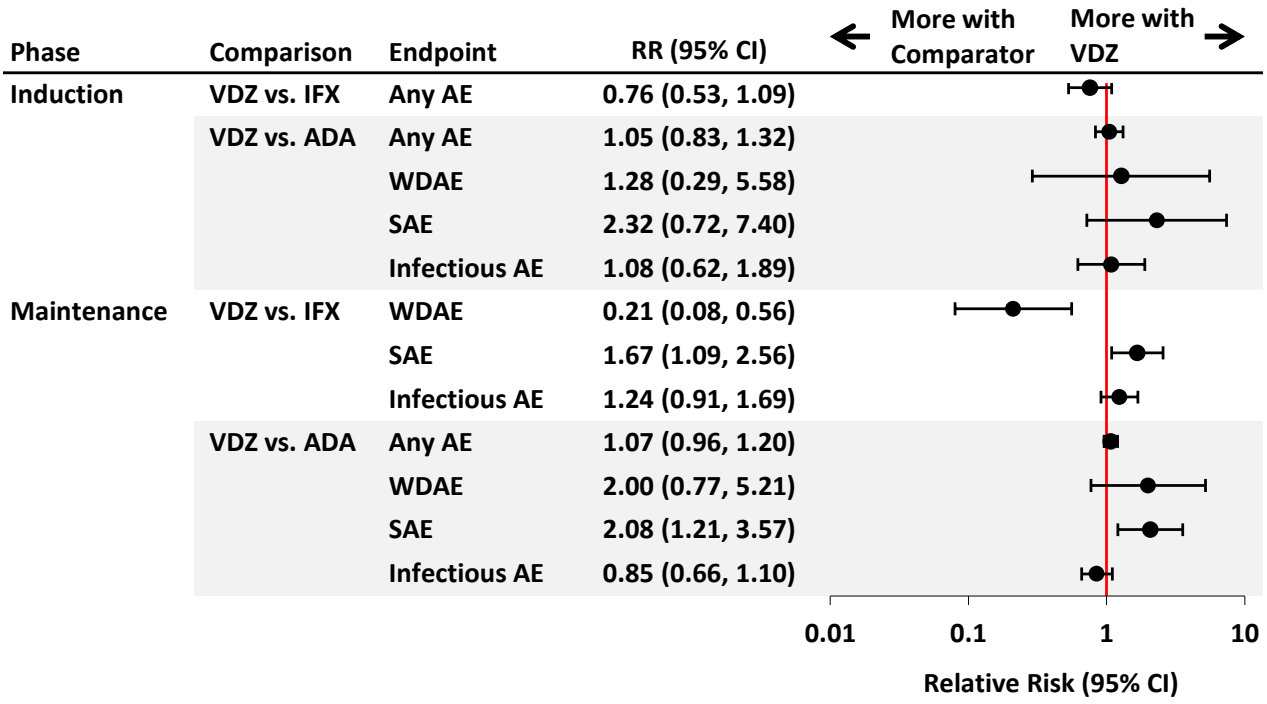


ADA = adalimumab; CI = confidence interval; IFX = infliximab; ITT = intention-to-treat; RR = relative risk; TNF = tumour necrosis factor alpha antagonist; VDZ = vedolizumab; vs. = versus.
Source: Manufacturer's Indirect Comparison Report.[50]

Harms

The manufacturer conducted a number of IDCs for safety end points in both the induction and maintenance phases. RRs for the IDCs are summarized in Figure 8. The manufacturer reported that vedolizumab was noninferior to the comparators for all safety end points with the exception of being associated with a reduced risk of withdrawals due to adverse events compared with infliximab in the maintenance phase and a greater risk of serious adverse events compared with infliximab and adalimumab in the maintenance phase.

FIGURE 8: RESULTS FROM THE INDIRECT COMPARISON OF HARMS FROM THE INDUCTION AND MAINTENANCE STUDIES



ADA = adalimumab; AE = adverse event; CI = confidence interval; IFX = infliximab; RR = relative risk; SAE = serious adverse event; VDZ = vedolizumab; vs. = versus; WDAE = withdrawal due to adverse event.
Source: Manufacturer's Indirect Comparison Report.[50]

Critical Appraisal of Manufacturer's Indirect Comparison

The quality of data reported in the manufacturer's IDC was assessed according to the recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[87] A summary of heterogeneity is provided in Table 44 for the induction studies and Table 45 for the maintenance studies. The manufacturer's rationale for conducting the IDC (i.e., absence of head-to-head studies) and the objectives of the IDC (i.e., comparisons of vedolizumab against infliximab and adalimumab) are clearly reported in the manufacturer's submission. However, the manufacturer did not provide a rationale for electing to submit an IDC using the Bucher method, as opposed to the network meta-analysis (NMA) that was submitted to NICE (National Institute for Health and Care Excellence) and the Scottish Medicines Consortium for the same indication.

Study characteristics

The GEMINI II and GEMINI III studies (concluded in 2012) were conducted later than trials for the comparators, particularly for infliximab (T16 concluded in 1996;[82] ACCENT I concluded in 2001[67]). It is possible that the clinical management of Crohn's disease has evolved over the period since the introduction of the first biologic, introducing heterogeneity between the included studies.

The only study included in the induction phase IDC for infliximab (i.e., T16) evaluated the efficacy end points after a single 5 mg/kg induction dose of infliximab.[82] This is not reflective of the induction dosage regimen recommended in the Canadian product monograph (i.e., 5 mg/kg at weeks 0, 2, and 6).[13,14] In contrast, vedolizumab was administered multiple times prior to the evaluation of efficacy end points

(i.e., at weeks 0 and 2 in GEMINI II and 0, 2, and 6 in GEMINI III).[15,21] These additional dosages of active treatment may bias the study results in favour of vedolizumab. The ACCENT I maintenance study that was used for the IDC comparing vedolizumab with infliximab used a maintenance dose of 5 mg/kg every eight weeks, which is consistent with recommendations in the Canadian product monograph;[13,14] however, clinical response in the induction phase was evaluated at two weeks, after a single 5 mg/kg infusion at week 0.[67] Patients who demonstrated a clinical response at week 2 were subsequently randomized to receive infusions of either infliximab or placebo at weeks 2 and 6, followed by every eight weeks. Therefore, patients in the placebo group of ACCENT I received only a single infusion of active treatment (i.e., at week 0) compared with the two infusions of active treatment in the GEMINI II trial (i.e., at weeks 0 and 2).[15] This difference in exposure to the active treatments within the placebo groups is a significant source of heterogeneity between the vedolizumab and infliximab trials and could contribute to the reduced placebo-response rates reported in ACCENT I compared with those reported in GEMINI II.

The induction phase trials[83-85] that were included in the IDC for adalimumab each had one treatment group that used induction doses that were consistent with recommendations in the Canadian product monograph (i.e., 160 mg at week 0 and 80 mg at week 2).[24] Dosing in at least one treatment group of the maintenance phase of the adalimumab trials was also consistent with recommendations in the Canadian product monograph (i.e., 40 mg every two weeks); however, the doses provided in the induction phase of the maintenance trials were below the recommended doses: All patients in CHARM received adalimumab at doses of 80 mg at week 0 and 40 mg at week 2,[86] and patients in Watanabe could have received 160 mg/80 mg or 80 mg/40 mg at weeks 0 and 2 (respectively).[85] Similar to the infliximab comparison, these differences in exposure to active treatment within the placebo groups is a significant source of heterogeneity between the vedolizumab and adalimumab trials and could contribute to the reduced placebo-response rates reported in the CHARM and Watanabe trials compared with those reported in GEMINI II. Patients in CLASSIC II also received induction doses below those recommended in Canada (i.e., 80 mg at week 0 and 40 mg at week 2).[54] As noted previously, this study was not used in the IDC for efficacy evaluations due to the requirement for demonstrating clinical response twice for inclusion in the maintenance phase (i.e., at both week 4 and week 8); however, it was included in the pairwise frequentist meta-analyses used to calculate the pooled relatives of the various safety end points. For all safety comparisons, using less than the recommended doses of infliximab and adalimumab could underestimate the comparative harms associated with these treatments (with the exception of those associated with disease exacerbation).

As shown in Table 43, induction of clinical remission was evaluated at four weeks in the adalimumab and infliximab trials and six weeks in the vedolizumab trials. The Australian Pharmaceutical Benefits Advisory Committee noted that this difference could potentially favour vedolizumab.[16] In the maintenance trials, there were also differences in the timing used to evaluate response to induction treatment prior to enrolment in the maintenance phase. All of the maintenance trials used in the IDC efficacy evaluations used clinical response (i.e., a reduction of at least 70 in CDAI score) as the threshold for inclusion; however, this was assessed at week 6 in the vedolizumab trial (GEMINI II), week 4 in the adalimumab trials (CHARM and Watanabe),[85,86] and week 2 in the infliximab trial (ACCENT I).[67] In addition, the efficacy end points in the maintenance phase studies were also evaluated at different time points (46 weeks with vedolizumab, 52 weeks with infliximab, and 52 to 56 weeks with adalimumab). Given that patients who failed to complete the trials were considered to be nonresponders in all of the included studies and that the proportion of patients who withdrew for any reason (including loss of efficacy and patients who were lost to follow-up) increased with time, having an earlier end point evaluation in the maintenance phase could favour vedolizumab treatment compared with the alternatives.

Study populations

The population of interest for the current CDR submission is patients with moderately to severely active Crohn's disease who have had an inadequate response to alternative therapies (as per the indication under review for vedolizumab). Mean baseline CDAI scores for the induction phase studies were all within the moderate to severe range and were generally similar across the different studies. However, there is substantial heterogeneity in the characteristics of the different study populations, including clinically relevant parameters such as prior exposure to TNF antagonists and concomitant use of corticosteroids.

Patients were enrolled in the maintenance phase studies only if they had demonstrated a response to the active treatment in the induction phase. This introduces variation within the placebo groups across the studies, as the patients who were randomized to receive placebo in the maintenance phase had been previously treated with a different biologic therapy (i.e., vedolizumab, adalimumab, or infliximab). There were also differences in the placebo-response rates for maintaining clinical remission across the studies (12% and 9% in the adalimumab trials; 14% in the infliximab trial; and 22% in the vedolizumab trial). The reason for these differences in the baseline risk for inducing and maintaining clinical remission is unclear; however, the manufacturer of vedolizumab has suggested that the differences in the maintenance phase could be attributed to the longer-lasting effect of vedolizumab compared with the TNF alpha antagonists (i.e., remission induced as a result of vedolizumab treatment is maintained longer than remission induced with the TNF alpha antagonists following removal of active treatment). Overall, these differences are an important source of between-study heterogeneity, and the implications on the results of the IDC are unclear.

The placebo-response rate for inducing clinical remission was lower in the infliximab trial (4%) compared with the trials for vedolizumab (7% to 12%) and adalimumab (7% to 13%). Similar to the maintenance phase analyses, the reasons for the differences in placebo-response rates are unclear for the induction phase, and the analyses were not adjusted for differences in the placebo-response rates.

As infliximab was the first biologic to be approved for use in the treatment of Crohn's disease, all patients enrolled in the infliximab trials were naive to biologic therapy for Crohn's disease. In contrast, the study populations of GEMINI II and GEMINI III studies were composed of 50% and 75% patients, respectively, who had previously failed at least one TNF alpha antagonist. In addition, as shown in Table 12, a significant proportion of the patients in the vedolizumab trials had failed treatment with two TNF alpha antagonists (approximately 20% in GEMINI II and 40% in GEMINI III) or three TNF alpha antagonists (5% in GEMINI II and 8% in GEMINI III). Some of the adalimumab trials included patients with prior exposure to TNF antagonists, although few would have failed multiple TNF alpha antagonists as those patients enrolled in the vedolizumab trials. These differences in prior exposure to biologic therapy for Crohn's disease may be clinically relevant and may be an indication that the study populations of GEMINI II and GEMINI III trials are composed of patients with Crohn's disease that is more refractory to treatment.

There were differences between the induction studies in the proportion of patients using corticosteroids at baseline. Usage of corticosteroids was reported for 60% of patients in the infliximab trial,[82] approximately 50% in the vedolizumab trials, and ranged from 23% to 39% in the adalimumab trials. The clinical expert consulted by CDR indicated that dependence on corticosteroids was more common in Crohn's disease patients before the introduction of TNF alpha antagonists. Hence, the greater usage of corticosteroids in the T16 infliximab trial may be a reflection of clinical practice at that time (i.e., 1996),[82] when there were fewer alternative treatments for patients with refractory Crohn's disease. The use of

corticosteroids in the maintenance phase was similar in the vedolizumab trial (GEMINI II, 53%),[15] the infliximab trial (ACCENT I, 52%),[67] and the smallest of the adalimumab trials (CLASSIC II, 49%).[54] For the remaining adalimumab studies, corticosteroid usage was slightly lower in CHARM (42%)[86] and substantially lower in Watanabe (16%).[85] As noted previously, the manufacturer conducted pairwise frequentist meta-analyses to calculate the differences for adalimumab versus placebo. As expected, given the differences in sample size, the results from CHARM contributed to more than 90% of the estimated treatment effect for all efficacy end points for adalimumab.[50] This weighting of the response may help mitigate the potential impact of the large disparity in corticosteroid usage between Watanabe and the other trials. Overall, there is insufficient evidence to evaluate whether or not these across-trial imbalances in corticosteroid usage could influence the results of the IDCs, particularly in the induction phase analyses where the differences were most pronounced.

Systematic review methods

The methods for the literature search were incomplete, with inadequate reporting of the following information: Electronic search strategy, search terms, dates associated with the original and updated literature searches, and the limitations used in the search. Overall, eligibility criteria for the IDC were poorly reported. The report contains a general PICO (population, intervention, comparison, outcomes) statement in the objective section, but provides no details in the methods section. However, the relevant information can be inferred based on the study inclusions and the exclusion reasons provided for the individual studies. Definitive statements about the following criteria are absent from the report: definitions for moderate to severe Crohn's disease, acceptable dosage regimens of interventions and comparators, and the minimum study durations. The end points of interest for the review are identified only as "key efficacy and safety outcomes" in the methods section; however, the end points that were evaluated are adequately described in the IDC report.

Methods for the systematic review are poorly reported, with just a statement indicating that "relevant methods suitable for determining the evidence base that can be included in a health technology assessment (HTA) submission" were used. There is no description of methodology used for study selection, data extraction, or critical appraisal. Quality assessment of individual studies was performed, but the specific instrument that was used was not identified in the methods section. Based on the results section, the following characteristics were included in the quality assessment: Allocation concealment, blinding, follow-up, and use of an ITT analysis.

Analysis methods

The methodological description of the Bucher analyses was adequately reported, and both direct (placebo comparisons) and indirect (active comparisons) estimates of effect are presented in the report (as applicable). The results of the IDCs for both efficacy and safety end points were adequately reported in summary tables, as RRs with 95% CIs. Study-level results and direct pairwise meta-analyses were also presented.

There was no description or justification for the manufacturer's noninferiority assessments, which were reported for all efficacy and safety end points. There is no discussion of the noninferior margin that was used (though it appears that any indirect estimates where the upper bound of the CI did not exclude unity were considered to be noninferior by the manufacturer). It is unclear if the manufacturer's IDCs were adequately powered to evaluate noninferiority for any of the outcomes that were assessed. Similar concerns were noted by the Australian Pharmaceutical Benefits Advisory Committee, who appraised the same indirect comparative data.[16] In addition, all of these analyses were conducted using the ITT analysis populations from the included trials; however, per-protocol data sets are typically

considered to be more conservative when establishing the noninferiority of two treatments. The individual trials included in the manufacturer's IDC were relatively short-term studies that were not powered or designed to conduct robust statistical evaluations of adverse events. Therefore, it is unclear if the IDCs that were calculated using the effect sizes derived from the individual studies had sufficient statistical power to support the manufacturer's claims of noninferiority.

Subgroup analyses were conducted based on whether or not the patients were treatment-experienced or treatment-naive with TNF alpha antagonists, which are relevant patient characteristics. The manufacturer provides a description of some potential sources of bias in the IDC (e.g., differences in placebo-response rates); however, there were no sensitivity analyses conducted to investigate the potential effects of such bias (though the limited number of studies that were considered to be comparable would likely preclude the conduct of these analyses).

Conclusion

The manufacturer submitted an IDC of vedolizumab versus infliximab and adalimumab using the Bucher method, with placebo as the common comparator. The manufacturer reported that vedolizumab was noninferior to infliximab for inducing and maintaining clinical remission, but inferior for inducing and maintaining clinical response. The manufacturer also reported that, compared with adalimumab, vedolizumab was noninferior for inducing and maintaining clinical remission and corticosteroid-free clinical remission and inducing clinical response. Vedolizumab was inferior to adalimumab for maintaining enhanced clinical response and clinical response.

The manufacturer's claims of noninferiority are limited by the absence of any pre-specified noninferiority margins or considerations of the statistical power required to make such conclusions. In addition, there is substantial heterogeneity in the study designs and patient characteristics across the studies included in the IDC. Overall, given the limitations of the manufacturer's analysis and the heterogeneity across studies, the comparative efficacy of these agents is uncertain in both the induction and maintenance phases of treatment. Therefore, there is uncertainty with the manufacturer's conclusions about the noninferiority or inferiority of vedolizumab compared with infliximab and adalimumab.

TABLE 44: HETEROGENEITY IN THE INDUCTION STUDIES INCLUDED IN THE MANUFACTURER'S INDIRECT COMPARISON

Characteristics	Drug	Details	Potential Heterogeneity
Dosing of comparators	IFX	Administered as one 5 mg/kg dose, which is not reflective of the induction dosage regimen recommended in the PM (i.e., 5 mg/kg at weeks 0, 2, and 6).[13,14]	Below-recommended dose of IFX could bias efficacy end points in favour of VDZ and harms end points in favour of IFX. CLASSIC II included only safety comparisons; however, using less than the recommended dose could bias harms in favour of ADA.
	ADA	Administered at a dose consistent with recommendations in the PM (i.e., 160 mg at week 0 and 80 mg at week 2)[24] with the exception of CLASSIC II (i.e., 80 mg at week 0 and 40 mg at week 2).	
	VDZ	Administered multiple times prior to the evaluation of efficacy end points (i.e., at weeks 0 and 2 in GEMINI II and weeks 0, 2, and 6 in GEMINI III).	
Disease severity	IFX	Mean CDAI was 312 with IFX group and 288 with PLA.	Mean baseline CDAI scores for the induction phase studies were all within the moderate to severe range and were generally similar across the different studies.
	ADA	Mean CDAI ranged from 295 to 313 with ADA and 296 to 313 with PLA.	
	VDZ	Mean CDAI ranged from 314 to 327 with VDZ and 301 to 325 with PLA.	
Concomitant CS	IFX	CSs were used by 60% of patients in the IFX trial.[82]	There were differences between the studies in the use of CS at baseline. The clinical expert consulted by CDR indicted that dependence on CS was more common in CD patients before the introduction of TNF inhibitors. Hence, the greater usage of CS in the IFX trial may be a reflection of clinical practice at a time when there were fewer treatments for patients with refractory CD. Overall, there is insufficient evidence to evaluate whether or not these imbalances in CS usage could influence the results of the indirect comparisons.
	ADA	CSs were used by approximately 50% in the VDZ trials.	
	VDZ	CS usage ranged from 23% to 39% in the ADA trials.	
TNF exposure	IFX	All patients were naive to TNF antagonists.	All patients in the IFX trial were naive to biologic therapy for CD. In contrast, some of the ADA trials included patients with prior exposure to TNF antagonists, though few would have failed multiple TNF antagonists (as many of those enrolled in the VDZ trials). These differences in prior exposure to TNF inhibitors may be an indication that the study populations of the VDZ trials were composed of patients with CD that is more refractory to treatment.
	ADA	All patients in CLASSIC I were naive to TNF antagonists. All patients in GAIN had prior exposure to a TNF antagonist, and the majority of patients in Watanabe had prior exposure to a TNF antagonist (58%).	
	VDZ	50% and 75% of patients in the VDZ trials had previously failed ≥ 1 TNF antagonist. A significant proportion of the patients had failed treatment with 2 or 3 TNF antagonists (20% to 40% and 5% to 8%,	

Characteristics	Drug	Details	Potential Heterogeneity
		respectively).	
Definition and timing of end point evaluation	IFX	• Clinical remission (CDAI ≤ 150) measured at week 4. • Clinical response (reduction in CDAI ≥ 70) measured at week 4.	Induction of clinical remission and clinical response were evaluated at 4 weeks in the ADA and IFX trials and 6 weeks in the VDZ trials. This difference could potentially bias efficacy results in favour of VDZ.
	ADA	• Clinical remission (CDAI ≤ 150) measured at week 4. • Clinical response (reduction in CDAI ≥ 70) measured at week 4. • Enhanced clinical response (reduction in CDAI ≥ 100) measured at week 4.	
	VDZ	• Clinical remission (CDAI ≤ 150) measured at week 6. • Clinical response (reduction in CDAI ≥ 70) measured at week 6.	
Placebo-response rates for inducing remission	IFX	Placebo-response rate was 4% in the IFX induction study.	The placebo-response rate for inducing clinical remission was lower in the IFX trial (4%) compared with the trials for VDZ (7% to 12%) and ADA (7% to 13%). The reasons for the differences are unclear and the analyses were not adjusted for differences in the placebo-response rates.
	ADA	Placebo-response rates ranged from 7% to 13% in the ADA induction studies.	
	VDZ	Placebo-response rates ranged from 7% to 12% in the VDZ induction studies.	

ADA = adalimumab; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDR = CADTH Common Drug Review; CS = corticosteroid; IFX = infliximab; PM = product monograph; TNF = tumour necrosis factor; VDZ = vedolizumab.

TABLE 45: HETEROGENEITY IN THE MAINTENANCE STUDIES INCLUDED IN THE MANUFACTURER'S INDIRECT COMPARISON

Characteristics	Drug	Details	Potential Heterogeneity
Dosing of comparators	IFX	Administered at dose of 5 mg/kg q8w in the maintenance phase, which is consistent with recommendations in the PM;[13,14] however, induction phase dosing consisted of only a single 5 mg/kg infusion at week 0.[67]	Dosing in the maintenance phase was consistent with recommendations in the PM. Induction phase dosing for the maintenance trials was not consistent with recommendations; this creates inequalities in the exposure to active treatment within the placebo groups.
	ADA	Dosing in at least one treatment group of the maintenance phase was consistent with recommendations in the PM (i.e., 40 mg q2w); however, the doses provided in the induction phase of the maintenance trials were below the recommended doses.	
	VDZ	Administered at dose of 300 mg q8w,which is consistent with recommendations in the Canadian PM.[13,14]	
Exposure to active treatment in the placebo group	IFX	Patients in the placebo group of ACCENT I received only a single infusion of active treatment (i.e., at week 0).	The patients in the placebo groups of ACCENT I, CHARM, and Watanabe received induction doses of active treatment that were below those recommended in the Canadian PMs for IFX and ADA. This could contribute to the reduced placebo-response rates reported in the IFX and ADA trials compared with those reported in GEMINI II.
	ADA	Patients in the placebo group received two infusions of active treatment (i.e., at week 0 and 2); however, the doses were below those recommended in the PM: all patients in CHARM received 80 mg at week 0 and 40 mg week 2;[86] and patients in Watanabe could have received 160 mg/80 mg or 80 mg/40 mg at weeks 0 and 2, respectively.[85]	
	VDZ	Patients in the placebo group received two infusions of active treatment (i.e., 300 mg at week 0 and 2).	
Placebo-response rates for maintaining clinical remission	IFX	Placebo-response rate was 14% in the IFX maintenance trial.	There were differences in the placebo-response rates for maintaining clinical remission across the studies (12% and 9% in the ADA trials; 14% in the IFX trial; and 22% in the VDZ trial). The reasons for these differences are unclear; however, the manufacturer of VDZ has suggested that the differences could be attributed to the longer-lasting effective of VDZ compared with the TNF inhibitors. As noted previously, there was variation in exposure to active treatment across the placebo groups.
	ADA	Placebo-response rates ranged from 9% to 12% in the ADA maintenance trials.	
	VDZ	Placebo-response rate was 22% in the VDZ maintenance trial.	
Concomitant CS	IFX	CSs were used by 52% of patients in the IFX trial.	The use of CSs in the maintenance phase was similar in the VDZ (GEMINI II, 53%),[15] the IFX (ACCENT I, 52%),[67] and the smallest of the ADA trials (CLASSIC II, 49%).[54] For the remaining ADA studies, CS usage was slightly lower in CHARM
	ADA	CSs were used by approximately 53% of patients in the VDZ trial.	

Characteristics	Drug	Details	Potential Heterogeneity
	VDZ	CSs were used by 49% of patients in CLASSIC II, 42% of patients in CHARM, and 16% of patients in Watanabe (16%).	(42%)[86] and substantially lower in Watanabe (16%).[85] Overall, there is insufficient evidence to evaluate whether or not these across-trial imbalances in CS usage could influence the results of the indirect comparisons.
TNF exposure	IFX	All patients were naive to TNF antagonists.	All patients in the IFX trial were naive to biologic therapy for CD. In contrast, some of the ADA trials included patients with prior exposure to TNF antagonists, though few would have failed multiple TNF antagonists as those enrolled in the VDZ trials. These differences in prior exposure to biologic therapy for CD may be clinically relevant and may be an indication that the study populations of the VDZ trials were composed of patients with CD that is more refractory to treatment.
	ADA	All patients in CLASSIC II were naive to TNF antagonists. Approximately 50% of patients in CHARM and Watanabe had previously failed ≥ 1 TNF antagonist.	
	VDZ	Approximately 50% of patients in the VDZ trial had previously failed ≥ 1 TNF antagonist.	
Definition and timing of end point evaluation	IFX	• Clinical remission (CDAI ≤ 150) measured at week 54. • Clinical response (reduction in CDAI ≥ 70 and ≥ 25% from baseline) measured at week 54. • Durable clinical remission (remission at every visit from week 14 to 54).	All of the maintenance trials used clinical response as the threshold for inclusion; however, this was assessed at week 6 in the VDZ trial, week 4 in the ADA trials, and week 2 in the IFX trial. In addition, the efficacy end points in the maintenance phase were evaluated at different time points (46 weeks with VDZ, 52 weeks with IFX, and 52 to 56 weeks with ADA). Given that patients who failed to complete the trials were considered to be nonresponders and that the proportion of patients who withdraw for any reason increases with time, having an earlier end point evaluation in the maintenance phase could bias results in favour of VDZ for both efficacy and safety evaluations.
	ADA	• Clinical remission (CDAI ≤ 150) measured at week 56. • Clinical response (reduction in CDAI ≥ 70) measured at week 56. • Enhanced clinical response (reduction in CDAI ≥ 100) measured at week 56. • CS-free clinical remission (discontinuation of CS and remission).	
	VDZ	• Clinical remission (CDAI ≤ 150) measured at week 52. • Clinical response (reduction in CDAI ≥ 70) measured at week 52. • Enhanced clinical response (reduction in CDAI ≥ 100) measured at week 52. • Durable clinical remission (remission at > 80% of visits, including week 52). • CS-free clinical remission (discontinuation of CS and clinical remission).	

ADA = adalimumab; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDR = CADTH Common Drug Review; CS = corticosteroid; IFX = infliximab; PM = product monograph; q8w = every 8 weeks; TNF = tumour necrosis factor; VDZ = vedolizumab.

APPENDIX 7: SUMMARY OF PUBLISHED INDIRECT COMPARISONS

Background

To summarize and critically appraise the comparative efficacy and safety of the available treatments for moderate to severe Crohn's disease in adults through indirect comparisons (IDCs). A literature search was completed using MEDLINE, Embase, and PubMed. After screening the results, three IDCs[51,52,61] comparing the efficacy and safety of the available treatments for moderate to severe Crohn's disease in adults were identified. In addition, the publicly available IDC submitted by the manufacturer to NICE was also included in this review.[88]

Results

Study eligibility and selection process

The IDCs were all conducted using systematic literature reviews. Detailed information concerning the literature search strategies are presented in Table 46, and the inclusion and exclusion criteria of the included trials are presented in Table 47. The methods section in the NMA by Hazelwood et al. and the IDC by Miligkos et al. did not provide any information about whether the systematic review followed a standardized tool for reporting. The majority of the included trials were placebo-controlled and investigated one or more of the following biologics: vedolizumab, adalimumab, infliximab, certolizumab, ustekinumab, and natalizumab. The methods sections in the NMA submitted to NICE, the IDC conducted by Miligkos et al., and the NMA conducted by Hazelwood et al. lack any description about how definitions of moderate to severe Crohn's disease were considered in the study selection process. The NMA submitted to NICE did not provide a description of whether or how study durations were considered in the study selection process

Quality assessment of included studies

Quality assessment of the individual included studies was performed using a variety of methods. Two investigators independently rated the quality of the included studies based on the criteria established by the Evidence-Based Gastroenterology Steering Group,[89] which considers concealed random allocation, patient and caregiver blinding, interventions between treatment arms, follow-up, and use of an ITT analysis, in the NMA conducted by Singh et al., in contrast to one investigator in the IDC conducted by Miligkos et al., while the NMA by Hazelwood et al. and the NMA submitted to NICE were conducted used the Cochrane Risk of Bias tool and the assessment criteria recommended by NICE, respectively.

TABLE 46: SYSTEMATIC REVIEW STRATEGIES

	Singh et al.	Hazelwood et al.	NICE IDC	Miligkos et al.
Reporting Strategy	PRISMA	NR	Cochrane methodology, NICE recommendation, PRISMA	NR
Sources of Information	• MEDLINE, In-Process & Other Non-Indexed Citation, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science, and Scopus • Manual searching based on bibliographies of included trials and systematic reviews • Conference abstracts	• MEDLINE, Embase, Cochrane Central Register of Controlled Trials • Manual searching based on bibliographies of a technical report from the American Gastroenterology Association and Cochrane Database of Systematic Reviews • Clinical trial registries (e.g., clinicaltrials.gov) • Conference abstracts	• MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness • Manual searching based on bibliographies of included trials and systematic reviews • Clinical trial registries (e.g., clinicaltrials.gov, World Health Organization's International Clinical Trials Registry)	• MEDLINE, Cochrane Central Register of Controlled Trials
Search Dates	• Database search between January 1, 1985, and September 30, 2013 • Relevant conference abstracts search between 2005 and 2013	• Vedolizumab search only between 1966 and June 2014 • Database and conference abstract search between 2007 and June 2014	• No time horizons	• Since inception to July 2015
Search Terms Strategy	No language restrictions with controlled vocabulary for RCTs of biologic therapies in patients with IBD	Controlled vocabulary for RCTs of biologic and immunosuppressant therapies in patients with CD	No language restrictions with controlled vocabulary for CD trials	Controlled vocabulary for RCTs of biologic therapies in patients with CD published in English
Screening	• Two investigators screened the trials identified in the systematic literature search, first by the titles and abstracts, and then followed by the full texts. • Disagreements between investigators were settled by consultation between the investigators and a third investigator.			• Two investigators screened the trials identified in the systematic literature search, first by the titles and abstracts, and then followed by

	Singh et al.	Hazelwood et al.	NICE IDC	Miligkos et al.
				the full texts. • Any disagreements between investigators were settled by consensus.
Quality Assessment	Two investigators independently rated the quality of the included studies based on the criteria established by the Evidence-Based Gastroenterology Steering Group, which considers concealed random allocation, patient and caregiver blinding, interventions between treatment arms, follow-up, and ITT analysis.	Qualitative assessment was conducted on each of the included studies based on the Cochrane Risk of Bias tool.	Qualitative assessment was conducted on each of the included studies based on the assessment criteria recommended by NICE.	One investigator rated the quality of the included studies based on the criteria established by Evidence-Based Gastroenterology Steering Group, which considers concealed random allocation, patient and caregiver blinding, interventions between treatment arms, follow-up, and ITT analysis.

CD = Crohn's disease; IBD = inflammatory bowel disease; IDC = indirect comparison; ITT = intention-to-treat; NICE = National Institute for Health and Care Excellence; NR = not reported; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.
Source: Singh et al.,[51] Hazelwood et al.,[52] NICE IDC,[88] and Miligkos et al.[61]

TABLE 47: INCLUSION AND EXCLUSION CRITERIA OF THE INCLUDED TRIALS USED IN THE INDIRECT COMPARISONS

	Singh et al.	Hazelwood et al.	NICE IDC	Miligkos et al.
Patient Population	Moderate to severe CD defined as CDAI between 220 and 450 • Biologic-naive	Moderate to severe CD • TNF alpha antagonist-naive • TNF alpha antagonist-failure/experienced	Moderate to severe CD • TNF alpha antagonist-naive • TNF alpha antagonist-failure/experienced	Moderate to severe CD • TNF alpha antagonist-naive • TNF alpha antagonist-failure/experienced
Intervention	Vedolizumab	Vedolizumab	Vedolizumab	Vedolizumab
Comparators	• Infliximab • Adalimumab • Certolizumab pegol • Ustekinumab • Natalizumab	• Infliximab • Adalimumab • Certolizumab • Azathioprine/6-mercaptopurine • Methotrexate • Sulfasalazine • Prednisone • Infliximab + azathioprine • Infliximab + methotrexate	• Infliximab • Adalimumab	• Infliximab • Adalimumab • Certolizumab pegol • Natalizumab
Outcomes	**Primary:** Clinical remission defined as CDAI < 150 or enhanced clinical response or clinical response defined as a reduction of 100 or 70 points from baseline in the CDAI, respectively	**Primary:** Clinical remission defined as CDAI < 150 or remission criteria as defined in the included trials **Secondary:** Total withdrawals, WDAEs	**Primary:** Clinical remission defined as CDAI < 150 or enhanced clinical response or clinical response defined as a reduction of 100 or 70 points from baseline in the CDAI, respectively	**Primary:** Clinical remission defined as CDAI < 150 or enhanced clinical response or clinical response defined as a reduction of 100 or 70 points from baseline in the CDAI, respectively **Secondary:** AEs, SAEs, WDAEs
Study Design	RCT	RCT	RCT	RCT
Other Inclusion Criteria	• Minimum treatment duration of 14 days in the induction phase • Minimum treatment duration of 22 weeks in the maintenance phase	• All trials including azathioprine/6-mercatopurine, methotrexate, and combination therapies • Follow-up for induction phase between 12 and 17 weeks for immunosuppressants • Follow-up for induction phase between 4 and 17 weeks for biologics	• None	• Minimum treatment duration of 2 weeks

	Singh et al.	Hazelwood et al.	NICE IDC	Miligkos et al.
		• Follow-up for maintenance phase at least 24 weeks		
Other Exclusion Criteria	• Biologics not used in clinical practice • Pediatric studies • Studies including biologic-experienced participants that did not report subgroup analyses according to biologic experience	• Natalizumab studies • Pediatric studies • Post-operative studies • Non-fixed treatment studies • Randomized withdrawal design • Cross-over design • Studies including participants with fistulizing CD only • Trials not reporting remission as an outcome	• Certolizumab trials • Natalizumab trials • IBD studies that did not report separate outcomes for UC or CD	• None

AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IBD = inflammatory bowel disease; IDC = indirect comparison; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial; SAE = serious adverse events; TNF alpha = tumour necrosis factor alpha; UC = ulcerative colitis; WDAE = withdrawals due to adverse events.
Source: Singh et al.,[51] Hazelwood et al.,[52] NICE IDC,[88] Miligkos et al.[61]

Indirect comparison methods

The NMAs all used Bayesian methods with placebo as the common comparator, with the exception of the IDC by Miligkos et al., which conducted IDCs of vedolizumab using the Bucher method with placebo as the common comparator. All of the outcomes that were evaluated in the NMAs were dichotomous outcomes, and differences between treatments were reported as RRs or odds ratios (ORs) with 95% credible intervals (CrIs), with the exception of the IDC conducted by Miligkos et al., which reported ORs with 95% CIs. In instances where there were data from multiple clinical studies, the results from the individual studies were pooled across studies using random-effects models, with the exception of the withdrawals due to adverse events data from the NMA by Hazelwood et al., which used a fixed-effect model (authors claim a fixed-effect model is more appropriate given the rarity of adverse events). Summaries of the trial characteristics included in the NMAs are provided in Table 48, Table 49, and Table 50.

TABLE 48: STUDY CHARACTERISTICS INCLUDED IN THE NETWORK META-ANALYSIS BY SINGH ET AL.

Drug	Study	Treatment Group Included in IDC	Primary End Point	Concomitant CD Treatment (%)				
				CS	AZA	6-MP	5-ASA	IS
Induction Studies								
VDZ	Feagan 2008	• VDZ 0.5 or 2.0 mg/kg at weeks 0 and 4 • PLA	Clinical remission CDAI < 150 (week 8)	PLA: 64 VDZ: 58	PLA: 28 VDZ: 20	PLA: 16 VDZ: 14	PLA: 68 VDZ: 57	NR
	GEMINI II 2012	• VDZ 300 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 6)	PLA: 48 VDZ: 48	NR	NR	NR	PLA: 17 VDZ: 24
ADA	CLASSIC I 2006	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 34 ADA: 37	PLA: 18 ADA: 13	PLA: 11 ADA: 13	PLA: 50 ADA: 52	NR
	Watanabe 2012	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 22 ADA: 21	NR	NR	PLA: 100 ADA: 88	PLA: 35 ADA: 31
IFX	T16 1996	• IFX 5, 10 or 20 mg/kg at week 0 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 64 IFX: 58	PLA: 28 IFX: 20	PLA: 16 IFX: 14	PLA: 68 IFX: 57	NR
	Lémann 2006	• IFX 5 mg/kg at weeks 0, 2, and 6 • PLA	Clinical remission CDAI < 150 (week 12)	PLA: 100 IFX: 100	PLA: 100 IFX: 100	PLA: 100 IFX: 100	NR	NR
CRT	PRECISE I 2007	• CRT 400 mg at weeks 0, 2, and 4 • PLA	Clinical remission CDAI −100 (week 6)	PLA: 29 CRT: 39	NR	NR	NR	PLA: 38 CRT: 37
	Sandborn 2011	• CRT 400 mg at weeks 0, 2, and 4 • PLA	Clinical remission CDAI ≤ 150 (week 6)	PLA: 46 CRT: 44	NR	NR	NR	PLA: 31 CRT: 35
UTK	Sandborn 2008	• UTK SC 90 mg at weeks 0, 1, 2, and 3 or IV 4.5 mg/kg at week 0 • PLA	Clinical remission CDAI – 70 (week 8)	PLA: 30 UTK: 33	NR	NR	PLA: 51 UTK: 37	PLA: 38 UTK: 29
NAT	Ghosh 2003	• NAT 3 or 6 mg/kg at weeks 0 and 4 • PLA	Clinical remission CDAI < 150 (week 6)	PLA: 49 NAT: 59	NR	NR	PLA: 48 NAT: 61	PLA: 35 NAT: 22
	Sandborn 2005	• NAT 300 mg at weeks 0, 4, and 8 • PLA	Clinical remission CDAI < 150 (week 10)	PLA: 39 NAT: 37	PLA: 44 NAT: 47	PLA: 4 NAT: 7	PLA: 21 NAT: 23	NR
Maintenance Studies								
VDZ	GEMINI II 2012	• VDZ 300 mg every 4 or 8 weeks • PLA	Clinical remission CDAI < 150 (week 52)	PLA: 54 VDZ: 53	NR	NR	NR	PLA: 32 VDZ: 33
ADA	CLASSIC II 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 60)	PLA: 56 ADA: 46	PLA: 6 ADA: 16	PLA: 0 ADA: 8	PLA: 40 ADA: 70	NR

Drug	Study	Treatment Group Included in IDC	Primary End Point	Concomitant CD Treatment (%)				
				CS	AZA	6-MP	5-ASA	IS
	CHARM[a] 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 56)	42	33	8	41	NR
	Watanabe 2012	• ADA 40 mg every other week • PLA	Clinical remission CDAI < 150 (week 56)	PLA: 20 ADA: 12			PLA: 76 ADA: 100	PLA: 28 ADA: 44
IFX	ACCENT I[a] 2001	• IFX 5 or 10 mg/kg at weeks 2, 6, and every 8 weeks • PLA	Clinical remission CDAI < 150 (week 30)	52	24		47	NR
	Rutgeerts1999	• IFX 10 mg/kg every 8 weeks • PLA	Clinical remission CDAI < 150 (week 36)	NR	NR	NR	NR	NR
CRT	PRECISE II 2007	• CRT 400 mg every 4 weeks • PLA	Clinical remission CDAI < 150 (week 26)	PLA: 40 CRT: 35	NR	NR	NR	PLA: 41 CRT: 37
UTK	Sandborn 2012	• UTK 90 mg at weeks 8 and 16 • PLA	Clinical remission CDAI < 150 (week 22)	NR	NR	NR	NR	NR
NAT	Sandborn 2005	• NAT 300 mg every 4 weeks • PLA	Clinical remission CDAI < 150 (week 70)	PLA: 44 NAT: 38	PLA: 26 NAT: 25	PLA: 4 NAT: 7	PLA: 54 NAT: 45	NR

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; ADA = adalimumab; AZA = azathioprine; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRT = certolizumab; CS = corticosteroid; IDC = indirect comparison; IFX = infliximab; IS = immunosuppressant; IV = intravenous; NAT = natalizumab; NR = not reported; PLA = placebo; SC = subcutaneous; SD = standard deviation; UTK = ustekinumab; VDZ = vedolizumab.

[a] Concomitant CD treatment data available only for the overall cohort (i.e., combines active and control group concomitant CD treatment data).

Source: Singh et al.[51]

TABLE 49: STUDY CHARACTERISTICS INCLUDED IN THE NETWORK META-ANALYSIS BY HAZELWOOD ET AL.

Drug	Study	Treatment Group Included in IDC	Primary End Point	Baseline CD Severity	Prior Anti-TNF Alpha (%)	Concomitant CD Treatment (%)	
						CS	IS
Induction Studies							
VDZ	Feagan 2008	• VDZ 0.5 or 2.0 mg/kg at weeks 0 and 4 • PLA	Clinical remission CDAI < 150 (week 8)	CDAI (220 to 450)	0	33	29
	GEMINI II 2012	• VDZ 300 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 6)	CDAI (220 to 450)	62	34	17
	GEMINI III 2012	• VDZ 300 mg at weeks 0, 2, and 6 • PLA	Clinical remission CDAI < 150 (week 6)	CDAI (220 to 450)	76	54	34
ADA	CLASSIC I 2006	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	CDAI (220 to 450)	0	33	29
	GAIN 2007	• ADA 160/80 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	CDAI (220 to 450)	100	39	49
	Watanabe 2012	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	CDAI (220 to 450)	58	21	32
IFX	T16 1996	IFX 5, 10 or 20 mg/kg at week 0 • PLA	Clinical remission CDAI < 150 (week 4)	CDAI (220 to 400)	0	59	37
CRT	Sandborn 2011	• CRT 400 mg at weeks 0, 2, and 4 • PLA	Clinical remission CDAI ≤ 150 (week 6)	CDAI (220 to 450)	0	45	33
	Schreiber 2005	• CRT 100, 200 or 400 mg at weeks 0, 4, and 8 • PLA	Clinical remission CDAI ≤ 150 (week 12)	CDAI (220 to 450)	22	36	37
	Winter 2004	• CRT 5, 10 or 20 mg/kg at week 0 • PLA	Clinical remission CDAI ≤ 150 (week 4)	CDAI (220 to 450)	24	28	45
Maintenance Studies							
VDZ	GEMINI II 2012	• VDZ 300 mg every 4 or 8 weeks • PLA	Clinical remission CDAI < 150 (week 52)	CDAI < 150 after induction therapy	54	36	17
ADA	EXTEND 2012	• ADA 40 mg every other week • PLA	Mucosal healing (week 52)	70-point decrease in baseline CDAI (220 to 450) after induction therapy	52	26	41
	CHARM 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 56)	70-point decrease in baseline CDAI (220 to 450) after induction therapy	50	44	47

Drug	Study	Treatment Group Included in IDC	Primary End Point	Baseline CD Severity	Prior Anti-TNF Alpha (%)	Concomitant CD Treatment (%)	
						CS	IS
	CLASSIC II 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 60)	CDAI < 150 after induction therapy	0	49	22
	Watanabe 2012	• ADA 40 mg every other week • PLA	Clinical remission CDAI < 150 (week 56)	70-point decrease in baseline CDAI (220 to 450) after induction therapy	54	16	36
IFX	ACCENT I 2001	• IFX 5 or 10 mg/kg at weeks 2, 6, and every 8 weeks • PLA	Clinical remission CDAI < 150 (week 30)	70-point decrease in baseline CDAI (220 to 400) after induction therapy	0	52	27
	Rutgeerts 1999	• IFX 10 mg/kg every 8 weeks • PLA	Clinical remission CDAI < 150 (week 44)	70-point decrease in baseline CDAI (220 to 400) after induction therapy	0	NR	NR
CRT	PRECISE II 2007	• CRT 400 mg every 4 weeks • PLA	Clinical remission CDAI < 150 (week 26)	100-point decrease in baseline CDAI (220 to 450) after induction therapy	24	36	40
	PRECISE I 2007	• CRT 400 mg at weeks 0, 2, and 4 • PLA	Clinical remission CDAI ≤ 150 (week 26)	CDAI (220 to 450)	28	39	37

ADA = adalimumab; anti-TNF = anti–tumour necrosis factor; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRT = certolizumab; CS = corticosteroid; IDC = indirect comparison; IFX = infliximab; IS = immunosuppressant; NR = not reported; PLA = placebo; TNF = tumour necrosis factor; VDZ = vedolizumab.
Source: Hazelwood et al.[52]

TABLE 50: STUDY CHARACTERISTICS INCLUDED IN THE NETWORK META-ANALYSIS SUBMITTED TO NICE

Drug	Study	Treatment Group Included in IDC[a]	Primary End Point	Mean Baseline CD Severity (CDAI)	Prior Anti-TNF Alpha Experience (%)
Induction Studies					
VDZ	GEMINI II 2012	• VDZ 300 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 6)	PLA: 324.6 VDZ: 327.3	PLA: 49 VDZ: 50
	GEMINI III 2012	• VDZ 300 mg at weeks 0, 2, and 6 • PLA	Clinical remission CDAI < 150 (week 10)	PLA: 297.4 VDZ: 311.4	PLA: 76 VDZ: 76
ADA	CLASSIC I 2006	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 296 ADA: 295 to 301	PLA: 0 ADA: 0
	EXTEND 2012	• ADA 40/20 mg[a] • PLA	Mucosal healing (week 12)	PLA: 321.1 ADA: 318.7	PLA: 66.9 ADA: 46.9
	GAIN 2007	• ADA 160/80 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 313 ADA: 313	PLA: 100 ADA: 100
	Watanabe 2012	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 308.1 ADA: 300.5 to 302.7	PLA: 56.5 ADA: 57.6 to 58.8
IFX	T16 1996	• IFX 5, 10 or 20 mg/kg at week 0 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 288 IFX: 307 to 312	PLA: 0 IFX: 0
Maintenance Studies					
VDZ	GEMINI II 2012	• VDZ 300 mg every 4 or 8 weeks • PLA	Clinical remission CDAI < 150 (week 52)	PLA: 325.2 VDZ: 317 to 325.5	PLA: 54 VDZ: 54 to 57
ADA	EXTEND 2012	• ADA 40 mg every other week • PLA	Mucosal healing (week 52)	PLA: 321.1 ADA: 318.7	PLA: 56.9 ADA: 46.9
	CHARM 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 56)	PLA: 316.6 ADA: 316.6	PLA: 50.4 ADA: 50.4
	CLASSIC II 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 56)	PLA: 107 ADA: 88 to 106	PLA: 0 ADA: 0
	Watanabe 2012	• ADA 40 mg every other week • PLA	Clinical remission CDAI < 150 (week 52)	PLA: 296.7 ADA: 325.5	PLA: 56 ADA: 52
IFX	ACCENT I 2001	• IFX 5 or 10 mg/kg • PLA	Clinical remission CDAI < 150 (week 54)	PLA: 299 IFX: 299	PLA: 0 IFX: 0

ADA = adalimumab; anti-TNF = anti–tumour necrosis factor; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IDC = indirect comparison; IFX = infliximab; NICE = National Institute for Health and Care Excellence; PLA = placebo; TNF = tumour necrosis factor; VDZ = vedolizumab.

[a] Limited or no dosing information provided in the IDC submitted to NICE.

Source: NICE IDC.[88]

TABLE 51: STUDY CHARACTERISTICS INCLUDED IN THE NETWORK META-ANALYSIS BY MILIGKOS ET AL.

Drug	Study	Treatment Group Included in IDC	Primary End Point	Prior Anti-TNF Alpha (%)	Concomitant CD Treatment (%)	
					CS	IS
Induction Studies						
VDZ	Feagan 2008	• VDZ 0.5 or 2.0 mg/kg at weeks 0 and 4 • PLA	Clinical remission CDAI < 150 (week 8)	PLA: 0 VDZ: 0	NR	NR
	GEMINI II 2012	• VDZ 300 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 6)	PLA: 49 VDZ: 51	PLA: 31 VDZ: 39	PLA: 17 VDZ: 29
	GEMINI III 2012	• VDZ 300 mg at weeks 0, 2, and 6 • PLA	Clinical remission CDAI < 150 (week 6)	PLA: 76 VDZ: 76	PLA: 52 VDZ: 53	PLA: 33 VDZ: 34
ADA	CLASSIC I 2006	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 0 ADA: 0	PLA: 23 to 43 ADA: 24	PLA: 28 to 31 ADA: 100
	GAIN 2007	• ADA 160/80 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 100 ADA: 100	PLA: 44 ADA: 35	PLA: 51 ADA: 46
	Watanabe 2012	• ADA 160/80 mg or 80/40 mg at weeks 0 and 2 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 56 ADA: 58	PLA: 22 ADA: 18 to 24	PLA: 35 ADA: 30 to 33
IFX	T16 1996	• IFX 5, 10 or 20 mg/kg at week 0 • PLA	Clinical remission CDAI < 150 (week 4)	PLA: 0 IFX: 0	PLA: 64 IFX: 56 to 61	PLA: 44 IFX: 28 to 43
	Lémann 2006	• IFX 5 mg/kg at weeks 0, 2, and 6 • PLA	Clinical remission CDAI < 150 (week 12)	PLA: 0 IFX: 0	PLA: 100 IFX: 100	PLA: 100 IFX: 100
	Colombel 2010	• IFX 5 mg/kg at weeks 0, 2, and 6 • PLA	NR	PLA: 0 IFX: 0	PLA: 24 IFX: 28	PLA: 100 IFX: 100
CRT	Sandborn 2007	• CRT 400 mg at weeks 0, 2, and 4 • PLA	NR	PLA: 26 CRT: 30	PLA: 23 CRT: 22	PLA: 20 CRT: 21
	Sandborn 2011	• CRT 400 mg at weeks 0, 2, and 4 • PLA	Clinical remission CDAI ≤ 150 (week 6)	PLA: 0 CRT: 0	PLA: 46 CRT: 44	PLA: 31 CRT: 35
	Schreiber 2005	• CRT 100, 200 or 400 mg at weeks 0, 4, and 8 • PLA	Clinical remission CDAI ≤ 150 (week 12)	PLA: 22 CRT: 17 to 24	PLA: 40 CRT: 31 to 40	PLA: 36 CRT: 35 to 40
	Winter 2004	• CRT 5, 10 or 20 mg/kg at week 0 • PLA	Clinical remission CDAI ≤ 150 (week 4)	PLA: 13 CRT: 28	PLA: 28 CRT: 24 to 35	PLA: 44 CRT: 44 to 53
NAT	Ghosh 2003	• NAT 3 or 6 mg/kg at weeks 0 and 4 • PLA	Clinical remission CDAI < 150 (week 6)	PLA: 0 NAT: 0	PLA: 49 NAT: 59	PLA: 35 NAT: 22
	Sandborn	• NAT 300 mg at weeks 0, 4, and 8	Clinical remission CDAI	PLA: 38	PLA: 39	PLA: 29

Drug	Study	Treatment Group Included in IDC	Primary End Point	Prior Anti-TNF Alpha (%)	Concomitant CD Treatment (%)	
					CS	IS
	2005	• PLA	< 150 (week 10)	NAT: 40	NAT: 37	NAT: 34
	Targan 2007	• NAT 400 mg at weeks 0, 4, and 8 • PLA	NR	PLA: 45 NAT: 50	PLA: 38 NAT: 42	PLA: 38 NAT: 37
Maintenance Studies						
VDZ	GEMINI II 2012	• VDZ 300 mg every 4 or 8 weeks • PLA	Clinical remission CDAI < 150 (week 52)	PLA: 54 VDZ: 57	PLA: 37 VDZ: 38	PLA: 15 VDZ: 18
ADA	EXTEND 2012	• ADA 40 mg every other week • PLA	Mucosal healing (week 52)	PLA: 57 ADA: 47	PLA: 39 ADA: 14	PLA: 39 ADA: 44
	CHARM 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 56)	PLA: 10 ADA: 30	PLA: NR ADA: 42	PLA: NR ADA: 48
	CLASSIC II 2007	• ADA 40 mg every week or every other week • PLA	Clinical remission CDAI < 150 (week 60)	PLA: 0 ADA: 0	PLA: 56 ADA: 47 to 50	PLA: 17 ADA: 21 to 28
	Watanabe 2012	• ADA 40 mg every other week • PLA	Clinical remission CDAI < 150 (week 56)	PLA: 56 ADA: 52	PLA: 22 ADA: 18 to 24	PLA: 35 ADA: 30 to 33
IFX	ACCENT I 2001	• IFX 5 or 10 mg/kg at weeks 2, 6, and every 8 weeks • PLA	Clinical remission CDAI < 150 (week 30)	PLA: 0 IFX: 0	PLA: NR IFX: 52	PLA: NR IFX: 27
	Rutgeerts 1999	• IFX 10 mg/kg every 8 weeks • PLA	Clinical remission CDAI < 150 (week 44)	PLA: 0 IFX: 0	NR	NR
CRT	PRECISE II 2007	• CRT 400 mg every 4 weeks • PLA	Clinical remission CDAI < 150 (week 26)	PLA: 24 CRT: 24	PLA: 21 CRT: 22	PLA: 25 CRT: 27
NAT	Sandborn 2005	• NAT 300 mg at weeks 0, 4, and 8 • PLA	Clinical remission CDAI < 150 (week 70)	PLA: 40 NAT: 33	PLA: 44 NAT: 37	PLA: 35 NAT: 38

ADA = adalimumab; anti-TNF = anti–tumour necrosis factor; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRT = certolizumab; CS = corticosteroid; IC = indirect comparison; IFX = infliximab; IS = immunosuppressant; NAT = natalizumab; NR = not reported; PLA = placebo; TNF = tumour necrosis factor; VDZ = vedolizumab.
Source: Miligkos et al.[61]

Efficacy

Induction therapy

The results of the NMAs for induction therapy are summarized in Table 52 and Table 53. The NMA conducted by Singh et al. included a biologic-naive population only and suggests no significant difference between vedolizumab and adalimumab, with an RR of 0.47 (95% CrI, 0.13 to 1.75), for inducing clinical remission in the induction phase. However, the NMA conducted by Singh et al. does provide estimates of effect favouring treatment with infliximab over vedolizumab for inducing clinical remission in the induction phase, with an RR of 0.23 (95% CrI, 0.06 to 0.78). Furthermore, the NMA conducted by Hazelwood et al. included a mixed population of participants with and without prior experience with TNF alpha antagonists and suggests no significant difference between vedolizumab and adalimumab or infliximab for inducing clinical remission, with an OR of 0.67 (95% CrI, 0.33 to 1.5) and 0.70 (95% CrI, 0.25 to 1.5), respectively.

The IDC conducted by Miligkos et al. included a mixed population of participants with and without prior experience with TNF alpha antagonists and suggests no significant difference between adalimumab and vedolizumab, with an OR of 1.27 (95% CI, 0.69 to 2.33), for inducing clinical response in the induction phase. However, the IDC conducted by Miligkos et al. does provide estimates of effect favouring treatment with infliximab over vedolizumab for inducing clinical response in the induction phase, with an of 2.81 (95% CI, 1.10 to 7.20). With regard to clinical remission in the induction phase, the IDC conducted by Miligkos et al. suggests no significant differences between both infliximab and adalimumab compared with vedolizumab, with ORs of 1.41 (95% CI, 0.74 to 2.67) and 1.09 (95% CI, 0.60 to 1.98), respectively.

The NMA submitted to NICE provided only ORs versus placebo and did not present any data indirectly comparing active treatments to vedolizumab. In the anti-TNF-naive population, the NMA submitted to NICE did provide estimates of effect favouring treatment with vedolizumab, adalimumab, and infliximab when compared with placebo for inducing clinical remission in the induction phase, with ORs of 0.29 (95% CrI, 1.5 to 6.0), 4.1 (95% CrI, 1.8 to 10) and 26 (95% CrI, 4.0 to 425), respectively. Similarly, estimates of effect favouring treatment with vedolizumab, adalimumab, and infliximab when compared with placebo were observed for both enhanced clinical response and clinical response in the induction phase.

The NMA submitted to NICE also provided results based on an anti-TNF–experienced/failure population. The results for this population suggest no significant difference between vedolizumab and placebo for inducing clinical remission in the induction phase (OR 1.4; 95% CrI, 0.8 to 2.6). However, the IDC submitted to NICE does provide estimates of effect favouring treatment with adalimumab over placebo for inducing clinical remission in the induction phase with an OR of 3.6 (95% CrI, 1.8 to 7.1). Similar to the anti-TNF-naive treatment population, estimates of effect favouring treatment with vedolizumab and adalimumab when compared with placebo were observed for both enhanced clinical response and clinical response in the induction phase for the anti-TNF–experienced/failure population.

The NMA submitted to NICE provided no information with respect to infliximab in the induction phase for the anti-TNF–experienced/failure population.

TABLE 52: CLINICAL REMISSION OR RESPONSE IN THE INDUCTION PHASE

Comparator	Singh et al.	Hazelwood et al.	Miligkos et al.[a]	
	Vedolizumab (RR 95% CrI)	Vedolizumab (OR 95% CrI)	Vedolizumab (OR 95% CI)	Vedolizumab (OR 95% CI)
	Clinical Remission			Clinical Response
PLA	1.40 (0.63 to 3.28)	2.0 (1.2 to 3.3)	NR	NR
IFX	0.23 (0.06 to 0.78)	0.70 (0.25 to 1.5)	1.41 (0.74 to 2.67)	2.81 (1.10 to 7.20)
ADA	0.47 (0.13 to 1.75)	0.67 (0.33 to 1.5)	1.09 (0.60 to 1.98)	1.27 (0.69 to 2.33)
CRT	0.95 (0.34 to 2.79)	1.4 (0.77 to 2.7)	0.50 (0.32 to 0.78)	0.75 (0.43 to 1.32)
UTK	NR[a]	NA	NR	NR
NAT	1.03 (0.35 to 3.08)	NA	0.60 (0.39 to 0.93)	1.03 (0.54 to 1.98)
AZA/6-MP	NA	1.6 (0.78 to 3.2)	NA	NA
MTX	NA	1.3 (0.53 to 3.2)	NA	NA
IFX + AZA	NA	0.47 (0.18 to 1.1)	NA	NA
IFC + MTX	NA	0.75 (0.17 to 2.7)	NA	NA

6-MP = 6-mercaptopurine; ADA = adalimumab; AZA = azathioprine; CI = confidence interval; CrI = credible interval; CRT = certolizumab; IFX = infliximab; MTX = methotrexate; NA = not available; NAT = natalizumab; NMA = network meta-analysis; NR = not reported; OR = odds ratio; PLA = placebo; RR = relative risk; UTK = ustekinumab.

[a] ORs reported in the NMA conducted by Miligkos et al. are presented as the OR of the comparator versus vedolizumab.

[b] Relative risk was reported only for ustekinumab compared with vedolizumab (RR 0.43; 95% CrI, 0.09 to 2.23).

Source: Singh et al.,[51] Hazelwood et al.,[52] Miligkos et al.[61]

TABLE 53: INDUCTION PHASE EFFICACY END POINTS IN THE NETWORK META-ANALYSIS SUBMITTED TO NICE

Outcome	Follow-Up for Outcome	OR vs. Placebo (95% CrI)		
		VDZ (300 mg)	ADA (160/80 mg)	IFX (5 mg)
Anti-TNF–Naive Population				
Clinical remission CDAI < 150	Week 6	2.9 (1.5 to 6.0)	4.1 (1.8 to 10.0)	26.0 (4.0 to 425.0)
	Week 6 T16[a]	3.0 (1.6 to 6.2)	4.1 (1.9 to 10.0)	NA
	Week 10	2.7 (1.4 to 5.4)	4.1 (1.8 to 10.0)	25.0 (4.1 to 451.0)
Enhanced clinical response Decrease of 100 points from baseline in CDAI	Week 6	1.9 (1.1 to 3.1)	2.9 (1.4 to 5.9)	NA
	Week 10	2.3 (1.4 to 3.8)	2.9 (1.4 to 5.9)	NA
Clinical response Decrease of 70 points from baseline in CDAI	Week 6	1.8 (1.1 to 3.0)	2.6 (1.3 to 4.8)	25.0 (6.2 to 128.0)
	Week 6 T16[a]	1.8 (1.1 to 3.0)	2.5 (1.3 to 5.0)	NA
	Week 10	1.9 (1.2 to 3.1)	2.5 (1.4 to 4.9)	25.0 (6.3 to 118.0)
Anti-TNF–Experienced/Failure Population				
Clinical remission CDAI < 150	Week 6	1.4 (0.8 to 2.6)	3.6 (1.8 to 7.1)	NA
	Week 10	2.5 (1.5 to 4.3)	3.5 (1.8 to 7.4)	
Enhanced clinical response Decrease of 100 points from baseline in CDAI	Week 6	1.7 (1.2 to 2.6)	1.9 (1.2 to 3.1)	
	Week 10	2.0 (1.3 to 3.0)	1.9 (1.2 to 3.1)	
Clinical response Decrease of 70 points from baseline in CDAI	Week 6	1.9 (1.3 to 2.8)	2.1 (1.4 to 3.3)	
	Week 10	1.9 (1.3 to 2.8)	2.1 (1.4 to 3.3)	

ADA = adalimumab; anti-TNF = anti–tumour necrosis factor; CDAI = Crohn's Disease Activity Index; CrI = credible interval; IFX = infliximab; NA = not available; NICE = National Institute for Health and Care Excellence; OR = odds ratio; VDZ = vedolizumab; vs. = versus.

[a] Analysis does not include the T16 trial.

Source: NICE Indirect Comparison.[88]

Maintenance therapy

The results of the NMAs for maintenance therapy are summarized in Table 54 and Table 55. The NMA conducted by Singh et al. included a biologic-naive population only and suggests no significant difference between vedolizumab and adalimumab or infliximab for maintaining clinical remission in the maintenance phase, with RRs of 0.43 (95% CrI, 0.05 to 3.36) and 0.67 (95% CrI, 0.06 to 5.64), respectively. Furthermore, the NMA conducted by Hazelwood et al. included a mixed population including participants with and without prior experience with anti-TNF treatments and suggests no significant difference between vedolizumab and infliximab for maintaining clinical remission in the maintenance phase, with ORs of 0.77 (95% CrI, 0.39 to 1.5) and 0.70 (95% CrI, 0.25 to 1.5), respectively. However, the NMA conducted by Hazelwood et al. does provide estimates of effect favouring treatment with adalimumab over vedolizumab for maintaining clinical remission in the maintenance phase, with an odds ratio of 0.42 (95% CrI, 0.22 to 0.85).

The IDC conducted by Miligkos et al. included a mixed population of participants with and without prior experience with TNF alpha antagonists and suggests estimates of effect favouring treatment with infliximab and adalimumab over vedolizumab for maintaining clinical response in the maintenance phase, with ORs of 1.95 (95% CI, 1.03 to 3.70) and 2.23 (95% CI, 1.26 to 3.93), respectively. With regard to clinical remission in the maintenance phase, the IDC conducted by Miligkos et al. suggests no significant differences between infliximab compared with vedolizumab, with an OR of 1.61 (95% CI, 0.80

to 3.22). However, the IDC conducted by Miligkos et al. does provide estimates of effect favouring treatment with adalimumab over vedolizumab for maintaining clinical remission in the maintenance phase, with an odds ratio of 2.22 (95% CI, 1.20 to 4.09).

The NMA submitted to NICE provided only ORs versus placebo and did not present any data indirectly comparing active treatments to vedolizumab. In the anti-TNF–naive population, the NMA submitted to NICE did provide estimates of effect favouring treatment with vedolizumab and infliximab when compared with placebo for maintaining clinical remission in the maintenance phase, with ORs of 2.9 (95% CrI, 1.4 to 6.1) and 2.5 (95% CrI, 1.3 to 5.2), respectively. Similarly, estimates of effect favouring treatment with vedolizumab and infliximab were observed for maintaining clinical response in the maintenance phase when compared with placebo.

The NMA submitted to NICE provided no information with respect to adalimumab in the maintenance phase for the anti-TNF–naive population nor did it provide any information with respect to the maintenance phase for any biologics in the anti-TNF–experienced/failure population.

TABLE 54: CLINICAL REMISSION OR RESPONSE IN THE MAINTENANCE PHASE

Comparator	Singh et al.	Hazelwood et al.	Miligkos et al.[a]	
	Vedolizumab (RR 95% CrI)	Vedolizumab (OR 95% CrI)	Vedolizumab (OR 95% CI)	Vedolizumab (OR 95% CI)
	Clinical Remission			Clinical Response
PLA	2.20 (0.37 to 13.54)	2.2 (1.3 to 3.7)	NR	NR
IFX	0.67 (0.06 to 5.64)	0.77 (0.39 to 1.5)	1.61 (0.80 to 3.22)	1.95 (1.03 to 3.70)
ADA	0.43 (0.05 to 3.36)	0.42 (0.22 to 0.85)	2.22 (1.20 to 4.09)	2.23 (1.26 to 3.93)
CRT	0.97 (0.08 to 12.54)	1.1 (0.57 to 2.1)	1.02 (0.56 to 1.87)	1.60 (0.90 to 2.82)
UTK	NR[b]	NA	NR	NR
NAT	0.52 (0.04 to 6.62)	NA	1.98 (1.03 to 3.81)	2.15 (1.15 to 4.00)
AZA/6-MP	NA	1.3 (0.65 to 2.3)	NA	NA
MTX	NA	0.91 (0.39 to 2.3)	NA	NA
IFX + AZA	NA	0.42 (0.17 to 0.92)	NA	NA
IFC + MTX	NA	0.85 (0.29 to 2.5)	NA	NA

6-MP = 6-mercaptopurine; ADA = adalimumab; AZA = azathioprine; CI = confidence interval; CrI = credible interval; CRT = certolizumab; IFX = infliximab; MTX = methotrexate; NA = not available; NAT = natalizumab; NMA = network meta-analysis; NR = not reported; OR = odds ratio; PLA = placebo; RR = relative risk; UTK = ustekinumab.
[a] ORs reported in the NMA conducted by Miligkos et al. are presented as the OR of the comparator versus vedolizumab.
[b] Relative risk was reported only for ustekinumab compared with vedolizumab (RR 0.87; 95% CrI, 0.07 to 11.36).
Source: Singh et al.,[51] Hazelwood et al.,[52] Miligkos et al.[61]

TABLE 55: MAINTENANCE PHASE EFFICACY END POINTS IN THE NETWORK META-ANALYSIS SUBMITTED TO NICE

Population	Outcome	OR vs. Placebo (95% CrI)	
		VDZ (300 mg)	IFX (5 mg)
Anti-TNF–naive population	Clinical remission CDAI < 150	2.9 (1.4 to 6.1)	2.5 (1.3 to 5.2)
	Clinical response Decrease of 70 points from baseline in CDAI	2.6 (1.3 to 5.0)	3.4 (1.9 to 6.5)

anti-TNF = anti–tumour necrosis factor; CDAI = Crohn's Disease Activity Index; CrI = credible interval; IFX = infliximab; NICE = National Institute for Health and Care Excellence; OR = odds ratio; VDZ = vedolizumab; vs. = versus.
Source: NICE Indirect Comparison.[88]

Safety

The results of the IDCs for safety are summarized in Table 56 and Table 57. The IDC conducted by Hazelwood et al. included a mixed population including participants with and without prior experience with anti-TNF treatments and suggests no significant difference between vedolizumab and adalimumab or infliximab in total withdrawals, with ORs of 2.1 (95% CrI, 1.0 to 4.6) and 1.3 (95% CrI, 0.57 to 2.9), respectively. When considering withdrawals due to adverse events, the NMA conducted by Hazelwood et al. suggests no significant difference between vedolizumab and adalimumab, with an odds ratio of 1.4 (95% CrI, 0.72 to 2.8). However, the NMA conducted by Hazelwood et al. does suggest a significant difference favouring treatment with vedolizumab over infliximab with respect to withdrawals due to adverse events, with an odds ratio of 0.24 (95% CrI, 0.12 to 0.51).

The IDC conducted by Miligkos et al. included a mixed population including participants with and without prior experience with anti-TNF treatments and suggests no significant difference between vedolizumab and infliximab or adalimumab with respect to adverse events, with ORs of 1.46 (95% CI, 0.75 to 2.84) and 0.75 (95% CI, 0.44 to 1.28) in the induction phase, and 0.83 (95% CI, 0.35 to 1.96) and 1.04 (95% CI, 0.54 to 2.04) in the maintenance phase, respectively.

The NMA submitted to NICE provided only ORs versus placebo and did not present any data indirectly comparing active treatments to vedolizumab. In the anti-TNF–naive population, the NMA submitted to NICE did provide significant estimates of effect favouring treatment with adalimumab when compared with placebo when considering withdrawals due to adverse events in the induction phase, with an OR of 0.0 (95% CrI, 0.0 to 0.7); however, vedolizumab was not associated with a significant difference with an OR of 1.4 (95% CrI, 0.3 to 7.4). In contrast, when considering the anti-TNF–experienced/failure population, the NMA submitted to NICE did provide estimates of effect favouring treatment with vedolizumab but not adalimumab when compared with placebo when considering withdrawals due to adverse events in the induction phase, with ORs of 0.4 (95% CrI, 0.1 to 0.9) and 0.5 (95% CrI, 0.1 to 2.4), respectively.

The NMA submitted to NICE also provided results based on an anti-TNF–naive population during the maintenance phase. The results for this population provide no significant estimates of effect for treatment with vedolizumab when compared to placebo when considering withdrawals due to adverse events in the maintenance phase with an OR of 0.8 (95% CrI, 0.3 to 2.7); however, infliximab was associated with a significant increase with an OR of 3.4 (95% CrI, 1.3 to 10.0).

TABLE 56: TOTAL WITHDRAWALS AND WITHDRAWALS DUE TO ADVERSE EVENTS IN HAZELWOOD ET AL.

End Point	Comparator	Hazelwood et al.
		Vedolizumab (OR 95% CrI)
Total withdrawals	PLA	0.89 (0.51 to 1.6)
	AZA/6-MP	1.3 (0.65 to 2.9)
	MTX	0.93 (0.38 to 2.3)
	CRT	1.0 (0.50 to 2.1)
	IFX	1.3 (0.57 to 2.9)
	ADA	2.1 (1.0 to 4.6)
	IFX + AZA	3.3 (1.1 to 12)
	IFC + MTX	1.2 (0.28 to 5.1)
WDAE	PLA	0.68 (0.40 to 1.1)
	AZA/6-MP	0.17 (0.09 to 0.35)
	MTX	0.05 (0.01 to 0.23)
	CRT	0.77 (0.41 to 1.4)
	IFX	0.24 (0.12 to 0.51)
	ADA	1.4 (0.72 to 2.8)
	IFX + AZA	0.21 (0.21 to 0.50)
	IFC + MTX	0.10 (0.00 to 1.5)

6-MP = 6-mercaptopurine; ADA = adalimumab; AZA = azathioprine; CrI = credible interval; CRT = certolizumab; IFX = infliximab; MTX = methotrexate; OR = odds ratio; PLA = placebo; WDAE = withdrawal due to adverse event.
Source: Hazelwood et al.[52]

TABLE 57: WITHDRAWALS DUE TO ADVERSE EVENTS IN THE NETWORK META-ANALYSIS SUBMITTED TO NICE

Treatment Phase	Population	OR vs. Placebo (95% CrI)		
		VDZ	ADA	IFX
Induction phase	Anti-TNF–naive	1.4 (0.3 to 7.4)	0.0 (0.0 to 0.7)	NA
	Anti-TNF–experienced/failure	0.4 (0.1 to 0.9)	0.5 (0.1 to 2.4)	NA
Maintenance phase	Anti-TNF–naive	0.8 (0.3 to 2.7)	NA	3.4 (1.3 to 10.0)

ADA = adalimumab; anti-TNF = anti–tumour necrosis factor; CrI = credible interval; IFX = infliximab; NA = not available; NICE = National Institute for Health and Care Excellence; OR = odds ratio; VDZ = vedolizumab; vs. = versus.
Source: NICE Indirect Comparison.[88]

TABLE 58: ADVERSE EVENTS IN THE INDUCTION AND MAINTENANCE PHASES

Adverse Events	Miligkos et al.
	Vedolizumab (OR 95% CI)
Induction Phase	
IFX	1.46 (0.75 to 2.84)
ADA	0.75 (0.44 to 1.28)
CRT	1.28 (0.85 to 1.92)
Maintenance Phase	
IFX	0.83 (0.35 to 1.96)
ADA	1.04 (0.54 to 2.04))
CRT	0.85 (0.46 to 1.55)

ADA = adalimumab; CI = confidence interval; CRT = certolizumab; IFX = infliximab; OR = odds ratio.
Source: Miligkos et al.[61]

Critical appraisal of the indirect cmparisons
Summaries of the limitations and heterogeneities of the included NMAs are presented in Table 59 and Table 60.

Study characteristics
The majority of trials for vedolizumab were conducted later than the trials for the comparators, particularly for infliximab (T16 concluded in 1996;[82] ACCENT I concluded in 2001[67]). It is possible that the clinical management of Crohn's disease has evolved over the period since the introduction of the first biologic, introducing heterogeneity between the included studies.

Some of the studies included in the induction phase NMAs for infliximab, adalimumab, and vedolizumab utilized doses that are not reflective of the induction dosage regimens recommended in the Canadian product monographs (e.g., T16[82]). These below-recommended dosages of active treatment may bias the study results in favour of vedolizumab for efficacy end points and against vedolizumab for safety end points. In the induction phase in some of the studies included in the NMAs, for maintenance end points, patients in the placebo groups received varying amounts of active treatment prior to randomization. For example, patients in the placebo group of ACCENT I[67] received only a single infusion of active treatment (i.e., at week 0) compared with the two infusions of active treatment in the GEMINI II[28] trial (i.e., at weeks 0 and 2). This difference in exposure is a significant source of heterogeneity across trials included in the NMAs and could contribute to the differences in placebo-response rates.

Although the dosing in at least one treatment group of the maintenance phase of the adalimumab trials was consistent with recommendations in the Canadian product monograph, the doses provided in the induction phase of the maintenance trials were below the recommended doses: patients in CHARM,[86] CLASSIC II,[54] and Watanabe[85] could have also received suboptimal induction doses. Similar to the infliximab comparison, these differences in exposure to active treatment within the placebo groups is a significant source of heterogeneity between the vedolizumab and adalimumab trials and could contribute to the reduced placebo-response rates reported in the CHARM[86] and Watanabe[85] trials compared with those reported in GEMINI II.[28] For all safety comparisons, using less than the recommended doses of Crohn's disease treatment could underestimate the comparative harms associated with these treatments (with the exception of those associated with disease exacerbation).

Induction of clinical remission was evaluated at four weeks in the adalimumab and infliximab trials and six weeks in the vedolizumab trials. In addition, the efficacy end points in the maintenance phase studies were also evaluated at different time points (46 weeks with vedolizumab, 52 weeks with infliximab, and 52 to 56 weeks with adalimumab). Given that patients who failed to complete the trials were considered to be nonresponders in all of the included studies and that the proportion of patients who withdrew for any reason (including loss of efficacy and patients who were lost to follow-up) increases with time, having an earlier end point evaluation in the maintenance phase could favour vedolizumab treatment compared with the alternatives.

Study populations

The population of interest for the current CDR submission is patients with moderately to severely active Crohn's disease who have had an inadequate response to alternative therapies (as per the indication under review for vedolizumab). Mean baseline CDAI scores for the induction phase studies were all within the moderate to severe range and were generally similar across the different studies. However, there is substantial heterogeneity in the characteristics of the different study populations, including clinically relevant parameters such as prior exposure to TNF alpha antagonists and concomitant use of Crohn's disease treatments.

Patients were enrolled in the maintenance phase studies only if they had demonstrated a response to the active treatment in the induction phase. This introduces variation within the placebo groups across the studies, as the patients who were randomized to receive placebo in the maintenance phase had been previously treated with a different biologic therapy (e.g., vedolizumab, adalimumab, or infliximab). There were also differences in the placebo-response rates for maintaining clinical remission across the studies. The reason for these differences in the baseline risk for inducing and maintaining clinical remission is unclear; however, the manufacturer of vedolizumab has suggested that the differences in the maintenance phase could be attributed to the longer-lasting effect of vedolizumab compared with the TNF alpha antagonists (i.e., remission induced as a result of vedolizumab treatment is maintained longer than remission induced with the TNF alpha antagonists following removal of active treatment). Overall, these differences are an important source of between-study heterogeneity, and the implications for the results of the NMAs are unclear.

The placebo-response rate for inducing clinical remission was lower in the infliximab trials compared with the trials for vedolizumab and adalimumab. Similar to the maintenance phase analyses, the reasons for the differences in placebo-response rates are unclear for the induction phase.

As infliximab was the first biologic to be approved for use in the treatment of Crohn's disease, all patients enrolled in the infliximab trials were naive to biologic therapy for Crohn's disease. In contrast, the study populations for many of the other trials used in the NMAs were composed of a mix of treatment-naive and treatment-experienced patients who had previously failed at least one TNF alpha antagonist. In addition, a significant proportion of the patients in the vedolizumab trials had failed treatment with two TNF alpha antagonists, and a small proportion had failed treatment with three TNF alpha antagonists. Some of the adalimumab trials included patients with prior exposure to TNF antagonists, although few would have failed multiple TNF alpha antagonists as those enrolled in the vedolizumab trials. These differences in prior exposure to biologic therapy for Crohn's disease may be clinically relevant and may be an indication that the study populations included in the vedolizumab trials are composed of patients with Crohn's disease that is more refractory to treatment.

In general, there were differences between the induction studies and maintenance studies in the proportion of patients using concomitant Crohn's disease treatments at baseline. Overall, there is insufficient evidence to evaluate whether or not these across-trial imbalances in concomitant Crohn's disease treatment usage could influence the results of the IDCs, particularly in the induction phase analyses, where the differences were most pronounced.

Systematic review methods

The methods for the literature search were incomplete in the NMA conducted by Hazelwood et al. and in the IDC conducted by Miligkos et al., which were missing information about the reporting strategy. Furthermore, the NMA submitted to NICE and the NMA by Hazelwood et al. as well as the IDC by Miligkos et al. lack any description about how definitions of moderate to severe Crohn's disease were considered in the study selection process. The NMA submitted to NICE did not provide a description of whether or how study durations were considered in the study selection process. In addition, the IDC conducted by Miligkos et al. appears to base the systematic review on published literature only, and makes no reference to the utilization of unpublished materials, which can lead to publication bias.

Analysis methods

The methodological descriptions of the Bayesian analyses were adequately reported in the all of the NMAs. Both direct (placebo comparisons) and indirect (active comparisons) estimates of effect are presented in the NMAs conducted by Singh et al. and Hazelwood et al.; however, the NMA submitted to NICE lacked the indirect (active comparisons) estimates of effect and reported only comparisons against placebo. The results of the NMAs for both efficacy and safety end points were adequately reported in summary tables, as RRs or ORs with 95% CrIs. In contrast, the methodological descriptions of the Bucher analyses were inadequately reported in the IDC conducted by Miligkos et al. The methods sections in the IDC conducted by Miligkos et al. lack any description about the Bucher analyses used to evaluate the results from the pooled trials included in the analysis. In addition, when considering trials with multiple active treatment arms, the IDC by Miligkos et al. combines the multiple treatment arms regardless of the dosing regimen in the evaluation of the pooled efficacy and safety, creating uncertainty in the overall dose-effect relationship. Furthermore, it appears that some of the included trials in the IDC by Miligkos et al. did not include consistent definitions for the measured outcomes (i.e., adverse events as defined in each of the included trials may have been different); consequently, any interpretation based on the pooling of safety outcomes must be made with caution, as this may not have been appropriate given the variation in definitions for safety outcomes. The results of the IDC for both efficacy and safety end points were adequately reported in summary tables, as ORs with 95% CIs.

TABLE 59: SUMMARY OF HETEROGENEITIES OF INDUCTION STUDIES INCLUDED IN THE INDIRECT COMPARISONS

Characteristics	Drug	Details	Potential Heterogeneity
Dosing of comparators	IFX	Administered at a dose consistent with recommendations in the Canadian PM (i.e., 5 mg/kg at weeks 0, 2, and 6); however, also administered as a single 5, 10, or 20 mg/kg dose, which is not reflective of the induction dosage regimen recommended in the Canadian PM in T16 (i.e., 5 mg/kg at weeks 0, 2, and 6).	Doses not recommended by the PM were utilized in the included IFX and ADA trials, which could bias efficacy and harms end points.
	ADA	Administered at a dose consistent with recommendations in the Canadian PM (i.e., 160 mg at week 0 and 80 mg at week 2); however, CLASSIC I and Watanabe could also administer at doses not recommended by the Canadian PM (i.e., 80 mg at week 0 and 40 mg at week 2), while EXTEND utilized 40 mg at week 0 and 20 mg at week 2.	
	VDZ	Administered multiple times prior to the evaluation of efficacy end points (i.e., 300 mg at weeks 0 and 2 in GEMINI II and 0, 2, and 6 in GEMINI III); however, Feagan could also administer at doses not recommended by the Canadian PM (i.e., 0.5 or 2.0 mg/kg at weeks 0 and 4).	
Disease severity	IFX	Mean CDAI was 312 in the IFX group and 288 in the PLA group.	Mean baseline CDAI scores for the induction phase studies were all within the moderate to severe range (220 to 450) and were generally similar across the different studies.
	ADA	Mean CDAI ranged from 295 to 318 in the ADA groups and 296 to 321 in the PLA groups.	
	VDZ	Mean CDAI ranged from 314 to 327 in the VDZ groups and 301 to 325 in the PLA groups.	
Concomitant CD treatment	IFX	CS usage ranged from 58% to 100% of patients in the IFX trials. IS usage ranged from 14% to 100% of patients in the IFX trials.	There were differences between the studies in the use concomitant CD treatments at baseline. The clinical expert consulted by CDR indicted that dependence on CS was more common in CD patients before the introduction of TNF inhibitors. Overall, there is insufficient evidence to evaluate whether or not these imbalances in concomitant CD treatment usage could influence the results of the IDCs.
	ADA	CS usage ranged from 21% to 39% of patients in the ADA trials. IS usage ranged from 29% to 49% of patients in the ADA trials.	
	VDZ	CS usage ranged from 0% to 54% in the VDZ trials. IS usage ranged from 0% to 34% in the VDZ trials.	
TNF exposure	IFX	All patients were naive to TNF antagonists.	All patients in the IFX trials were

Characteristics	Drug	Details	Potential Heterogeneity
	ADA	All patients in CLASSIC I were naive to TNF antagonists. All patients in GAIN had prior exposure to a TNF antagonist. The majority of patients in Watanabe had prior exposure to a TNF antagonist (58%), whereas approximately 47% and 67% of patients had prior exposure to a TNF antagonist in the EXTEND trial in the ADA and PLA groups, respectively.	naive to biologic therapy for CD. In contrast, some of the ADA trials included patients with prior exposure to TNF antagonists, though few would have failed multiple TNF antagonists (as many of those enrolled in the VDZ trials). These differences in prior exposure to TNF inhibitors may be an indication that the study populations of the VDZ trials were composed of patients with CD that is more refractory to treatment.
	VDZ	50% and 75% of patients in the VDZ trials had previously failed ≥ 1 TNF antagonist. A significant proportion of the patients had failed treatment with 2 or 3 TNF antagonists (20% to 40% and 5% to 8%, respectively). All patients in Feagan trial were TNF antagonists naive.	
Definition and timing of end point evaluation	IFX	• Clinical remission (CDAI ≤ 150) measured at week 4 or at week 12	Induction of clinical remission was evaluated at different time points across trials and across different treatments. Clinical remission was evaluated between weeks 4 and 12 in the IFX trials, at weeks 4 in the ADA trials and at 6 and 10 weeks in the VDZ trials. These differences could potentially bias efficacy results. The EXTEND trial did not define clinical remission as CDAI ≤ 150 and instead utilized mucosal healing at week 12. The timing for the evaluation of this end point along with the definition of remission can bias the efficacy results.
	ADA	• Clinical remission (CDAI ≤ 150) measured at week 4 • Mucosal healing measured at week 12	
	VDZ	• Clinical remission (CDAI ≤ 150) measured at week 6 or at week 10	
Placebo-response rates for inducing remission	IFX	Placebo-response rate was 4% in the IFX induction study.	The placebo-response rate for inducing clinical remission was lower in the IFX trial (4%) compared with the trials for VDZ (7% to 21%) and ADA (7% to 13%). The reasons for the differences are unclear and the analyses were not adjusted for differences in the placebo-response rates.
	ADA	Placebo-response rates ranged from 7% to 13% in the ADA induction studies.	
	VDZ	Placebo-response rates ranged from 7% to 21% in the VDZ induction studies.	

ADA = adalimumab; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDR = CADTH Common Drug Review; CS = corticosteroid; IFX = infliximab; IS = immunosuppressant; IDC = indirect comparison; NICE = National Institute for Health and Care Excellence; PLA = placebo; PM = product monograph; TNF = tumour necrosis factor; VDZ = vedolizumab.
Source: Singh et al.,[51] Hazelwood et al.,[52] and NICE IDC.[88]

TABLE 60: SUMMARY OF HETEROGENEITIES OF MAINTENANCE STUDIES INCLUDED IN THE INDIRECT COMPARISONS

Characteristics	Drug	Details	Potential Heterogeneity
Dosing of comparators	IFX	Administered at dose of 5 mg/kg every 8 weeks in the maintenance phase which is consistent with recommendations in the PM; however, the induction phase dosing of the maintenance phase could have consisted of a single 5 mg/kg infusion at week 0 which is not consistent with the Canadian PM. In addition, it appears as if results based on both the 5 mg/kg and 10 mg/kg dose may have been pooled for the maintenance phase of the ACCENT I trial. In Rutgeerts, IFX was administered as 10 mg/kg every 8 weeks in the maintenance phase which is only recommended in the PM for patients who fail to respond or lose their response to the lower dosage.	When dosing in the maintenance phase was consistent with recommendations in the PM, the induction phase dosing for the maintenance trials was not consistent with recommendations; this creates inequalities in the exposure to active treatment within the placebo groups. Additionally, combining the results for multiple doses, of which some are not recommended in the PM can lead to heterogeneity in the exposure to treatment and may skew placebo-response rates. When dosing in the maintenance phase was not consistent with recommendations; this may limit the generalizability of the results to the Canadian population.
	ADA	Dosing in at least one treatment group of the maintenance phase was consistent with recommendations in the PM (i.e., 40 mg every 2 weeks); however, the doses provided in the induction phase of the maintenance trials were below the recommended doses (e.g., 80 mg at week 0 and 40 mg at week 2).	
	VDZ	Administered at dose of 300 mg every 8 weeks which is consistent with recommendations in the Canadian PM.	
Concomitant CD treatment	IFX[a]	CS usage ranged from 52% to 59% of patients in the IFX trials. IS usage ranged from 27% to 37% of patients in the IFX trials.	The use of corticosteroids in the maintenance phase was similar in the VDZ (GEMINI II; 53%), IFX (ACCENT I; 52%), and the smallest of the ADA trials (CLASSIC II; 49%). For the remaining ADA studies, corticosteroid usage was slightly lower in CHARM (42%) and substantially lower in Watanabe (16%). Overall, there is insufficient evidence to evaluate whether or not these across-trial imbalances in corticosteroid usage could influence the results of the IDCs.
	ADA	CS usage ranged from 16% to 49% of patients in the ADA trials. IS usage ranged from 22% to 47% of patients in the ADA trials.	
	VDZ	CS were used by approximately 53% in the VDZ trial. IS were used by approximately 33% in the VDZ trial.	
TNF exposure	IFX	All patients were naive to TNF antagonists.	All patients in the IFX trial were naive to biologic therapy for CD. In contrast, some of the ADA trials included patients with prior exposure to TNF antagonists, though few would have failed multiple TNF
	ADA	All patients in CLASSIC II were naive to TNF antagonists. Approximately half of patients in EXTEND, CHARM and Watanabe had previously failed ≥ 1 TNF antagonist.	

Characteristics	Drug	Details	Potential Heterogeneity
	VDZ	Approximately 54% of patients in the VDZ trial had previously failed ≥ 1 TNF antagonist.	antagonists as those enrolled in the VDZ trials. These differences in prior exposure to biologic therapy for CD may be clinically relevant and may be an indication that the study populations of the VDZ trials were composed of patients with CD that is more refractory to treatment.
Definition and timing of end point evaluation	IFX	Clinical remission (CDAI ≤ 150) measured at week 54 or 44.	All of the maintenance trials used clinical response as the threshold for inclusion; however, this was assessed at week 6 in the VDZ trial, week 4 in the ADA trials, and week 2 in the IFX trial. In addition, the efficacy end points in the maintenance phase were evaluated at different time points (52 weeks with VDZ, 54 or 44 weeks with IFX, and 52, 56, or 60 weeks with ADA). Given that patients who failed to complete the trials were considered to be nonresponders and that the proportion of patients who withdraw for any reason increases with time, having an earlier end point evaluation in the maintenance phase could bias results. The EXTEND trial did not define clinical remission as CDAI ≤ 150 and instead utilized mucosal healing at week 52. The timing for the evaluation of this end point along with the definition of remission could bias the efficacy results.
	ADA	Clinical remission (CDAI ≤ 150) measured at week 52, 56 or 60. Mucosal healing at week 52.	
	VDZ	Clinical remission (CDAI ≤ 150) measured at week 52.	
Placebo-response rates for maintaining clinical remission	IFX	Placebo-response rate ranged from 19% to 21% in the IFX trials.	There were differences in the placebo-response rates for maintaining clinical remission across the studies (44% and 9% in the ADA trials, 19% and 21% in the IFX trial, and 22% in the VDZ trial). The reasons for these differences are unclear; however, the manufacturer of VDZ has suggested that the differences could be attributed to the longer-lasting effect of VDZ compared with the TNF inhibitors. As noted previously, there was variation in exposure to active treatment across the placebo groups.
	ADA	Placebo-response rate ranged from 9% to 44% in the ADA trials.	
	VDZ	Placebo-response rate was 22% in the VDZ trials.	

Characteristics	Drug	Details	Potential Heterogeneity
Exposure to active treatment in the placebo group	IFX	Patients in the placebo group of ACCENT I received only a single infusion of active treatment (i.e., at week 0).	The patients in the placebo groups of ACCENT I, CHARM, and Watanabe received induction doses of active treatment that were below those recommended in the Canadian PMs for IFX and ADA. This could contribute to the reduced placebo-response rates reported in the IFX and ADA trials compared with those reported in GEMINI II.
	ADA	Patients in the placebo group received two infusions of active treatment (i.e., at weeks 0 and 2); however, the doses were below those recommended in the PM. All patients in CHARM received 80 mg at week 0 and 40 mg week 2. Patients in Watanabe could have received 160 mg/80 mg or 80 mg/40 mg at weeks 0 and 2 (respectively).	
	VDZ	Patients in the placebo group received two infusions of active treatment (i.e., 300 mg at week 0 and 2).	

ADA = adalimumab; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CDR = CADTH Common Drug Review; CS = corticosteroid; IFX = infliximab; IS = immunosuppressant; IDC = indirect comparison; NICE = National Institute for Health and Care Excellence; PM = product monograph; TNF = tumour necrosis factor; VDZ = vedolizumab.
[a] Concomitant CD treatment not reported for the maintenance Rutgeerts et al. 1999 trial.
Source: Singh et al.,[51] Hazelwood et al.,[52] and NICE IDC.[88]

Summary

Four published NMAs in which vedolizumab was compared with infliximab and adalimumab were identified. Overall, there was substantial heterogeneity with respect to study design and patient characteristics (e.g., follow-up duration, treatment doses, TNF alpha antagonist experience, and placebo-response rates) across the studies included in the NMAs, making any comparisons of relative efficacy in inducing and maintaining clinical remission of vedolizumab versus infliximab and adalimumab difficult. Given the limitations, the comparative efficacy of these agents is uncertain in both the induction and maintenance phases of treatment.

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