CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

VEDOLIZUMAB (ENTYVIO SC)

Takeda Canada Inc.

Indication: For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a tumor necrosis factor-alpha antagonist.

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Abbreviations

6-MP	6-mercaptopurine
AE	adverse event
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
EQ-5D	EuroQol 5-Dimensions
FAS	full analysis set
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
ICC	intraclass coefficient
ISR	injection-site reaction
ITT	intention to treat
MID	minimal important difference
NMA	network meta-analysis
PP	per protocol
PPS	per-protocol set
RCT	randomized controlled trial
RD	risk difference
SAE	serious adverse event
SAF	safety analysis set
SAS-C	combined safety analysis set
SAFS-I	safety analysis set of the induction phase
SC	subcutaneous
SD	standard deviation
SF-36	Short Form (36) Health Survey
TNF	tumour necrosis factor
UC	ulcerative colitis
VAS	Visual Analogue Scale
WDAE	withdrawal due to adverse event
WPAI-UC	Work Productivity and Activity Questionnaire – Ulcerative Colitis

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Vedolizumab (Entyvio SC) solution for subcutaneous injection for maintenance treatment at 108 mg every 2 weeks (syringe with 108 mg/0.68 mL, single-use pre-filled syringe or pen).
Indication	For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.
Reimbursement request	As per indication.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	April 7, 2020
Sponsor	Takeda Canada Inc.

NOC = Notice of Compliance; SC = subcutaneous; TNF = tumour necrosis factor.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) with a complex etiology that involves inflammation of the intestinal mucosae affecting the rectum and variable levels of proximal extension into the colon. The age of onset of signs and/or symptoms is typically less than 30 years. It has a worldwide distribution with a global incidence of 1.2 to 20.3 cases per 100,000 people per year, and prevalence of 7.6 to 246.0 cases per 100,000 per year. Canada is among the countries with the highest incidence and prevalence of IBD, with approximately 270,000 Canadians living with UC or Crohn disease. The incidence of UC ranges in different Canadian provinces from 8.4 to 21.4 per 100,000 people.

Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds exclusively to the α4β7 human integrin on pathogenic gut-homing lymphocytes, acting as a gut-selective anti-inflammatory biologic. The IV formulation has been approved by Health Canada for adults with moderately to severely active Crohn disease who have had an inadequate response to, lost response to, or were intolerant to immunomodulators or a tumour necrosis factor (TNF) alpha antagonist, or who have had an inadequate response to or intolerance to or who have demonstrated dependence on corticosteroids. It is also approved for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or who were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist. The subcutaneous (SC) injection formulation of vedolizumab is the current focus of this review and its indication is "for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist." The IV formulation of vedolizumab has been previously reviewed by CADTH through the CADTH Common Drug Review (CDR) process for each of the Health Canada–approved indications.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of vedolizumab SC injection for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

The Gastrointestinal (GI) Society described the circumstances of living with IBD and what patients have to endure. In short, how UC represents a disabling, lifelong GI condition that primarily affects working-age individuals. Symptoms associated with UC such as bloody diarrhea, bloating, abdominal pain, cramping, and fatigue affect individuals' day-to-day lives, with patients sometimes experiencing isolation, anxiety, and debilitating, frequent, and urgent bowel movements. Their quality of life is deeply affected during periods of active disease, with patients spending a lot of time in the bathroom; even in periods of remission, patients have to stay near a bathroom. UC forces them to limit their activities, sometimes because of the stigma associated with IBD. The patient group described the concerns from patients' perspectives about future flares, which are sometimes worse and unpredictable.

Patients often seek treatment options that can reduce or eliminate their symptoms and are regularly longing for treatments that could protect their ability to work, attend school and social events, and perform basic day-to-day activities. The patient group reported that many current treatments can have undesirable effects due to the need for their long-term use (e.g., glucocorticoids) and that individuals with UC are continuously struggling for a normal life. They require new and effective options to achieve mucosal healing and decrease debilitating symptoms. Given that all individuals respond differently to therapies, it was considered imperative that patients have a variety of options for treatment, including easier ways to administrate medications that are used long term.

The GI Society reports Entyvio as being very effective for patients with Crohn disease and believes it has the potential to be another option for patients with UC in improving their health and quality of life. Ultimately, the patient group would like additional effective-therapy options to choose from.

Clinician Input

According to advice obtained from a clinical expert, vedolizumab is already approved in Canada for the treatment of UC in an IV formulation. It has demonstrated efficacy relative to placebo that is comparable to other targeted therapies approved to treat UC. All chronic immunosuppressive therapies used to treat UC are intended to modify the disease course, and several (particularly anti-TNF drugs) have been shown to reduce the risks of hospitalization and surgery. As such, the drug under review does not offer a novel mechanism of action or treatment response but, rather, a new mode of administration.

This drug could have an impact on the current treatment paradigm, as it offers an SC home-administration option for an effective class of therapy with a favourable safety profile. While there are other SC drugs available with a favourable safety profile, some individuals

may benefit from the gut selectivity of this class of therapy, such as patients with a history of serious opportunistic infections or non–GI tract malignancies, as well as those with contraindications to anti-TNF drugs or other therapies (such as patients with demyelinating neuropathy, advanced congestive heart failure, severe psoriasis, or chronic systemic infections, such as latent tuberculosis or hepatitis B).

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One double-blind, double-dummy, placebo-controlled, randomized controlled trial (RCT), the VISIBLE 1 trial, was included in this review with an accompanying open-label extension study (SC-3030). After screening, the first phase of the trial included patients with moderately to severely active UC who received an open-label administration of vedolizumab 300 mg IV infusion at weeks 0 and 2. At week 6, patients were assessed for clinical response, defined as a reduction in total Mayo score of three points or more and a reduction of 30% or more from baseline plus a decrease of one point or more in the rectal bleeding subscore or an absolute rectal bleeding subscore of 1 or lower.

Those who responded were randomized to maintenance treatment with vedolizumab SC (108 mg every two weeks), vedolizumab IV (300 mg every eight weeks), or placebo in a 2:1:1 ratio, with stratification by concomitant corticosteroid use, clinical remission status at week 6, and previous anti-TNF failure or concomitant immunomodulator use (Table 2).

Patients who did not achieve a clinical response at week 6 received a third open-label 300 mg vedolizumab IV dose and were reassessed for a clinical response (defined as a partial Mayo score of ≥ 2 points and a decrease of ≥ 25% from baseline with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point) at week 14. Those achieving a clinical response at week 14 had the option to enrol in the open-label extension study, while those who did not respond at week 14 were discontinued. All patients were then evaluated every eight weeks for a total follow-up of 52 weeks.

The primary efficacy end point was the proportion of patients in clinical remission at 52 weeks defined as a total Mayo score of 2 or less and no individual subscore higher than 1. Secondary efficacy outcomes, in ranked order, were the proportion of patients with endoscopic improvement at week 52 (e.g., mucosal healing) assessed as a Mayo endoscopic subscore of one or less at week 52 (normal/inactive disease or mild disease), durable clinical response (clinical response at weeks 6 and 52), durable clinical remission (clinical remission at weeks 6 and 52), and corticosteroid-free remission assessed in patients using oral corticosteroids at baseline (discontinuation of oral corticosteroids from baseline followed by clinical remission at week 52). Quality of life, using the EuroQol 5-Dimensions (EQ-5D) score index, Inflammatory Bowel Disease Questionnaire (IBDQ) scores, and the Work and Productivity and Activity Impairment – Ulcerative Colitis (WPAI-UC) instrument scores, was also assessed.

For the purpose of this review, these outcomes were assessed to compare vedolizumab SC with placebo; any assessment comparing vedolizumab SC with vedolizumab IV is descriptive in nature and not formally designed and tested as a noninferiority hypothesis.

The follow-up open-label Study SC-3030 is a long-term extension study to assess the long-term safety and tolerability of vedolizumab. Although it is still ongoing, Study SC-3030 includes patients with UC (n = 288) who participated in the VISIBLE 1 study and were randomized and completed the maintenance phase as of the week 52 assessment or who withdrew early (before week 52) because of sustained nonresponse, disease worsening, or the need for rescue medications. All of these patients were eligible to enrol in SC-3030 to receive open-label treatment with vedolizumab SC. Study SC-3030 also includes participants who did not achieve a clinical response at week 6 (and were not randomized but achieved a clinical response at week 14 after a third open-label dose of vedolizumab IV), patients who required (or were anticipated to require) surgical intervention for UC during or after participation in the VISIBLE 1 base study, and patients who withdrew from the base study due to a study drug–related adverse event (AE).

Efficacy Results

Of the 383 participants included in the induction open-label study of the VISIBLE 1 trial, 216 were enrolled in the maintenance phase and randomized to either vedolizumab SC (n = 106), vedolizumab IV (n = 54), or placebo (n = 56). Attrition was low during the induction phase (with 92.2% completing treatment); yet, during the maintenance phase, 64.4% of all patients completed treatment: 37.5% in the placebo group, 71.7% in the vedolizumab SC group, and 75.9% in the vedolizumab IV group. The main reason for discontinuation (of 28, 18, and 6 patients in the placebo, vedolizumab SC, and vedolizumab IV groups, respectively) in the maintenance phase was lack of efficacy, followed by voluntary withdrawal and AEs.

More patients in the vedolizumab SC group showed clinical remission at week 52 when compared with placebo (46.2% versus 14.3%, respectively; adjusted risk difference [RD] = 32.3%; 95% confidence interval [CI], 19.7% to 45%; P < 0.001), and these results occurred in both anti–TNF naive and experienced populations. Numerically similar rates of clinical remission were seen in the vedolizumab IV group when compared with placebo. Improvements were also noted in the outcomes of durable clinical response (64.2% versus 28.6%; RD = 36.1%; 95% CI, 21.2 to 50.9; P < 0.001) and endoscopic improvement/mucosal healing (56.6% versus 21.4%; RD = 35.7%; 95% CI, 22.1 to 49.3; P < 0.001), but not for corticosteroid-free remission (28.9% versus 8.3%; RD = 0.6%; 95% CI, −4.5 to 43.7). No colectomies were performed or required during the study. Vedolizumab SC had a statistically and clinically significant effect on the IBDQ total score and EQ-5D total index score. Also, the WPAI scores were improved statistically significantly in the vedolizumab SC group versus placebo. In all of these outcomes, vedolizumab SC performed similarly to vedolizumab IV when compared with placebo, although this comparison was not formally tested for noninferiority. Sensitivity analyses supported the robustness of the results. The trial was not powered for subgroup analyses.

Harms Results

Overall, there were no concerns from the VISIBLE 1 trial and the long-term extension SC-3030 study regarding harms, either for AEs or serious adverse events (SAEs), or harms of special interest. The most common AEs were worsening of UC disease activity, nasopharyngitis, anemia, and upper respiratory tract infections. Two infections in the vedolizumab SC group were considered serious (one anal abscess and one peritonitis), but were not deemed treatment-related and did not lead to discontinuation. Injection-site reactions (ISRs) (mainly rash, swelling, erythema, and pruritus) occurred in 11 patients (10.4%) receiving vedolizumab SC, in one patient (1.9%) receiving vedolizumab IV (plus

matching SC placebo), and in zero patients receiving placebo. No deaths or major adverse cardiovascular events were reported, and one malignancy in the reference vedolizumab IV group was reported.

Table 2: Summary of Key Results From Pivotal and Protocol Selected Studies

	VISIBLE 1		
	Vedolizumab SC N = 106	Vedolizumab IV N = 54	Placebo N = 56
Clinical remission at week 52			
Patients in clinical remission, n (%)	49 (46.2)	23 (42.6)	8 (14.3)
Adjusted difference versus placebo (95% CI)	32.3 (19.7, 45.0)	27.9 (12.3, 43.5)	–
P value, vedolizumab versus placebo	< 0.001	< 0.001	–
Durable clinical response at week 52			
Patients in durable clinical response, n (%)	68 (64.2)	39 (72.2)	16 (28.6)
Adjusted difference versus placebo (95% CI)	36.1 (21.2, 50.9)	44.5 (28.3, 60.6)	–
P value, vedolizumab versus placebo	< 0.001	< 0.001	–
HRQoL: IBDQ scores			
Baseline (week 0)	N = 105	N = 54	N = 55
Mean (SD)	117.15 (32.26)	108.51 (33.44)	113.82 (33.99)
Week 52	N = 106	N = 54	N = 56
Mean (SD)	180.65 (39.71)	170.65 (43.09)	135.16 (44.36)
Change from baseline to week 52	N = 105	N = 54	N = 55
LS mean (SE)	65.33 (3.93)	58.60 (5.50)	21.47 (5.43)
LS mean difference (SE), vedolizumab versus placebo	43.87 (6.71)	37.13 (7.72)	–
P value	< 0.001	< 0.001	–
HRQoL: EQ-5D index score			
Baseline (week 0)	N = 105	N = 54	N = 55
Mean (SD)	0.764 (0.159)	0.744 (0.181)	0.722 (0.175)
Week 52	N = 87	N = 43	N = 36
Mean (SD)	0.914 (0.131)	0.882 (0.122)	0.815 (0.141)
Change from baseline to week 52	N = 86	N = 43	N = 35
Mean (SD)	0.141 (0.201)	0.143 (0.195)	0.075 (0.206)
Mucosal healing			
Number (%) of patients achieving mucosal healing at week 52	60 (56.6)	29 (53.7)	12 (21.4)
Adjusted difference versus placebo (95% CI)	35.7 (22.1 to 49.3)	32.2 (15.7 to 48.7)	–
P value, vedolizumab versus placebo	< 0.001	< 0.001	–
Need for colectomy			
Patients with colectomies, n (%)	0	0	0
Work Productivity and Activity Impairment – Ulcerative Colitis score			
Baseline (week 0)	N = 105	N = 54	N = 54
Mean (SD)	56.6 (24.68)	57.0 (24.70)	55.0 (23.13)
Week 52	N = 87	N = 43	N = 36
Mean (SD)	16.6 (22.09)	17.7 (21.80)	36.9 (32.32)

	VISIBLE 1		
	Vedolizumab SC N = 106	Vedolizumab IV N = 54	Placebo N = 56
Change from baseline to week 52	N = 86	N = 43	N = 34
Mean (SD)	−39.5 (30.87)	−39.3 (29.79)	−13.5 (34.98)

CI = confidence interval; EQ-5D = EuroQol 5-Dimensions; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; SC = subcutaneous; SD = standard deviation; SE = standard error.

Source: Clinical Study Report for VISIBLE 1.[1]

Critical Appraisal

Overall, the VISIBLE 1 trial is a well conducted randomized clinical trial with a low risk of bias in the randomization process; proper blinding of participants, investigators, and clinicians; an adequate analysis based on the intention-to-treat (ITT) principle; adjustment for multiplicity to control for an overall type I error rate; and follow-up.

One concern and limitation of the study is the sample size obtained because, although it provides enough power for the main outcome and all secondary outcomes, it precludes any further conclusions in terms of safety and proper subgroup analyses (yet, the trial was not powered for subgroup analyses). The VISIBLE 1 study was not designed to provide a formal noninferiority test of vedolizumab IV versus vedolizumab SC. The attrition was high in the maintenance phase, mainly due to a lack of effect by the intervention (especially in the placebo group). This led to large and different rates of missingness across groups, which could bias conclusions toward the null due to a less symptomatic placebo group. Furthermore, missing patients were treated as nonresponders for the analyses, although the sensitivity analyses performed for the treatment of missing data generally resulted in consistent conclusions.

In terms of external validity, the strictly controlled settings of the RCT, in which patients were evaluated thoroughly and followed up closely, might not be applied in real-life settings, especially in relation to the SC application of the drug. SC-3030 could provide more information needed in terms of the real-life application of the new SC administration of vedolizumab.

Indirect Comparisons

[redacted]

[redacted]

Critical Appraisal

The applicability of the sponsor-submitted network meta-analysis (NMA) is affected by the lack of transparency in the systematic review, limited size of the evidence base, potential limitations in the submitted analysis, and heterogeneity in the design of the included studies and across populations. Additionally, there was insufficient analysis conducted to account for trial and clinical heterogeneity, thus limiting the utility and the robustness of the results. This lack of transparency in systematic review methods and analyses was considered an important limitation as were the similar effect sizes between biologic treatments and large credible intervals that result in an overall decrease in the confidence in the effect estimates of the NMA; any results must be interpreted with caution.

Other Relevant Evidence

A long-term extension of the VISIBLE 1 study to address the long-term safety and tolerability of vedolizumab SC in the treatment of UC is currently ongoing. The results of the second interim analysis in the SC-3030 report did not detect new safety signals and show that vedolizumab SC seems safe and tolerable. As in the base study, the most frequent

treatment-emergent adverse event (TEAE) was UC (i.e., disease worsening), followed by nasopharyngitis and upper respiratory tract infections. Furthermore, long-term exposure to vedolizumab SC did not result in an increase in the frequency of hypersensitivity reactions, including ISRs, serious infections, malignancy, or liver injury. The available efficacy results to date were limited by their descriptive nature and low numbers of evaluable patients. Results from this extension study to inform the long-term durability of the response of vedolizumab SC in responders on maintenance treatment should be interpreted with caution.

Conclusions

Based on one trial, vedolizumab SC is more effective than placebo for the maintenance of clinical remission, durable clinical response, and endoscopic healing, and for improving quality of life and work productivity scores in patients with moderate-to-severe UC, although not for maintaining a corticosteroid-free remission. The efficacy and safety of vedolizumab SC seems to be numerically similar to vedolizumab IV, although the data from this evidence are not suitable to declare the noninferiority of vedolizumab SC over the IV presentation. AEs were similar between vedolizumab SC and placebo. Results from an ongoing long-term study will provide more information to assess possible harms and the applicability of the intervention.

Based on one sponsor-submitted review of indirect treatment comparisons, [redacted] although there is high uncertainty due to limitations in how it was conducted, imprecision, and lack of transparency in the NMA , and these limitations decrease confidence in the results.

Introduction

Disease Background

UC is an IBD that commonly affects young people between 15 and 30 years of age, although it can affect any age group. This chronic GI condition comprises inflammation of the mucosae of the large intestine, starting distally in the rectum, and can potentially extend in variable levels proximally into the colon.[3,4]

UC has a worldwide distribution, with an incidence of 1.2 to 20.3 cases per 100,000 people per year and a prevalence of 7.6 to 246.0 cases per 100,000 per year.[5] However, it is preponderantly encountered in high-income, Western nations. In Canada, approximately 270,000 people live with UC or Crohn disease, with some authors reporting an incidence ranging from 8.4 to 21.4 per 100,000 people in different provinces.[6]

UC implies a burden for patients, families, and health care systems due to its impact in quality of life — including domains like school, work, and social interactions — and resource use. In Canada, approximately $1.2 billion is spent annually in patients with IBD, with an estimated indirect cost to society of nearly $1.5 billion in domains such as loss of work and productivity, disability coverage, and premature retirement or death.[7,8]

The etiology of UC is not completely understood, although evidence of the role of genetic and environmental factors, as well as correlations between UC and the microbiota, is accumulating.[5] UC starts gradually followed by periods of spontaneous remission and relapse. Bloody diarrhea with or without mucus is the most common initial manifestation. Depending on the extension and severity of disease, symptoms, beside frequent evacuations with blood and mucus, can include urgency or tenesmus, fever, abdominal pain, and weight loss.[5,9] Prognosis is usually good, with the majority of patients not needing a colectomy and remitting within the first decade.[10] Although the risk of death from UC is increased within the first year after diagnosis, beyond that point, patients remain at the same risk as the general population.[11]

Depending on the index or score used — for example, the Mayo Clinic score or the Montreal classification — the severity of disease may be defined differently. The extension of endoscopic disease is typically categorized as “proctitis” (distal to the rectosigmoid junction or within 18 cm of the anal verge), “left-sided colitis” (extending anywhere from the sigmoid to the splenic flexure), or “extensive colitis” (extending beyond the splenic flexure).[12] According to a recent systematic review of population cohorts, the majority of patients (76%) have a mild course and 24% present a moderate-to-severe course.[13]

Standards of Therapy

Treatment of patients with UC includes assessing first the level of clinical activity or severity (mild, moderate, severe) as well as the extension of the disease (proctitis, left-sided, or pancolitis).[12] Then, clinicians will aim to obtain a sustained remission free of steroids while managing other domains to increase quality of life, such as psychosocial support, while emphasizing the prevention of morbidity due to surgery or hospitalization.[11]

First-line treatments for inducing remission commonly include either orally or rectally administered sulfasalazine and 5-aminosalicylates (mesalamine, olsalazine, and balsalazide), after which it is expected that half of patients will enter remission within

two weeks. Rectal administration of 5-aminosalicylates or glucocorticoid is considered for patients who have distal disease (e.g., proctitis) only.[4] In cases where mild-to-moderate left-sided or extensive UC is present, a mixture of rectal and oral 5-aminosalicylate can be used, with escalating doses of oral 5-aminosalicylates. For patients whose condition exhibits a poor response to rectal therapies and 5-aminosalicylates, the next steps include oral glucocorticoids or immunosuppressive drugs such as azathioprine or 6-mercaptopurine (6-MP) as second-line therapy to induce complete remission. Glucocorticoids can also be considered first-line therapy if patients start with moderately to severely active UC.[4,11] Patients who continue to require glucocorticoids at this step are considered to have moderately to severely active UC and are candidates to receive vedolizumab or anti-TNF therapy to induce complete glucocorticoid-free remission. Vedolizumab (an α4β7 inhibitor), anti-TNF therapies (infliximab, adalimumab, golimumab), and tofacitinib — a selective Janus kinase (JAK) inhibitor — are part of the group of medications collectively known as biologics and are considered to be immune-modifying therapies for the induction and/or maintenance of remission of patients with UC.

Drug

Vedolizumab is a humanized IgG1 monoclonal antibody that binds exclusively to the α4β7 human integrin on pathogenic gut-homing lymphocytes, acting as a gut-selective anti-inflammatory biologic. The IV formulation has been approved by Health Canada for the following:

- The treatment of adults with moderately to severely active Crohn disease 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, were intolerant to, or have demonstrated dependence on corticosteroids.
- The treatment of adult patients with moderately to severely active UC who have had an inadequate response to, a loss of response to, or who were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.

The SC injection formulation of vedolizumab is the current focus of this submission under review and its indication is “for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.” This new liquid formulation for SC injection has been developed to provide an alternative **maintenance** treatment option to patients who require community or at-home delivery of vedolizumab, thereby decreasing the burden on the patient and their caregiver(s).

Vedolizumab has been reviewed twice previously by CADTH through the CDR process. The first (July 15, 2015), for the treatment of patients with UC, was recommended by CADTH for the indication if conditions were met.[14] The second (September 21, 2016) was for the treatment of adult patients with Crohn disease, and CADTH recommended it be reimbursed if criteria were met.[15]

For this submission, the recommended dose regimen for SC vedolizumab as a maintenance treatment, following at least two IV infusions, is 108 mg administered by SC injection. The sponsor is suggesting that the first SC dose be administered in place of the next scheduled IV dose and every two weeks thereafter.[16] The product monograph for SC administration of vedolizumab notes that during maintenance treatment with vedolizumab, corticosteroids may be tapered in accordance with clinical practice guidelines.

The key characteristics of the drug and other main comparators are presented in Table 3.

Table 3: Key Characteristics of Vedolizumab and Comparators

	Vedolizumab	Ustekinumab	Infliximab	Golimumab	Tofacitinib	Adalimumab
Mechanism of action	IgG1 monoclonal antibody. Binds to the human α4β7 integrin, acting as a gut-selective anti-inflammatory biologic.	Human IgG1 monoclonal antibody. Neutralizes cellular responses mediated by IL-12 and IL-23.	Anti-TNF. IgG1κ monoclonal antibody that neutralizes the biological activity of TNF alpha by specifically binding to its receptors.	Anti-TNF. Human monoclonal antibody that binds to human TNF (p55 or p75 receptors).	Selective JAK inhibitor. Blocks several cytokine pathways and lymphocyte activation.	Anti-TNF. Human IgG1 monoclonal antibody. Binds and blocks TNF alpha and its interaction with p55 and p75 cell-surface TNF receptors.
Indication[a]	Treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.	Treatment of adult patients with moderately to severely acute UC who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a biologic, or have failed or were intolerant to treatment with a biologic (proposed).	Induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy.	Induction and maintenance of clinical response in adults with moderately to severely active UC who have had an inadequate response to, or have medical contraindications for conventional therapy, including corticosteroids, amino salicylates, azathioprine, or 6-MP.	For the treatment of adult patients with moderately to severely active UC with an inadequate response to, loss of response to, or intolerance to either conventional UC therapy or a TNF alpha inhibitor.	For the treatment of adult patients with moderately to severely active UC who have had an inadequate response to conventional therapy, including corticosteroids and/or azathioprine or 6-MP, or who are intolerant to such therapies.
Route of administration	Intravenous induction followed by SC injection for maintenance.	Intravenous induction followed by SC injection for maintenance.	Intravenous	SC	Oral	SC
Recommended dose	300 mg administered by intravenous infusion at 0, 2, and 6 weeks and then every 8 weeks thereafter. The SC maintenance dose	Induction: Intravenous infusion, single-use, weight-based dose (~6 mg/kg): 250 mg for those weighing ≤ 55 kg; 390 mg for those weighing > 55 kg to	Induction dose of 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 8 weeks thereafter.	200 mg initially administered by SC injection at week 0 followed by 100 mg at week 2 and then 50 mg every 4 weeks thereafter.	Tofacitinib tablets:10 mg (as tofacitinib citrate) orally twice a day.	160 mg at week 0 followed by 80 mg at week 2 administered by SC injection.

	Vedolizumab	Ustekinumab	Infliximab	Golimumab	Tofacitinib	Adalimumab
	is 108 mg every 8 weeks.	≤ 85 kg; or 520 mg for those weighing > 85 kg. Maintenance: 90 mg SC injection every 8 or 12 weeks.				
Serious adverse effects or safety issues	Infections and malignancies have been reported in patients taking vedolizumab but no clinically significant differences have been found.	Immunomodulating drugs have the potential to increase the risk of infections and malignancy. No clinically significant differences have been found in terms of malignancies.	Infections and malignancies have been observed in patients receiving infliximab.	Upper respiratory infections and reactions at the site of injection, but no clinically significant differences compared with placebo.	A Health Canada warning indicated an increased risk of thromboses (pulmonary and deep vein thrombosis) and death, and increased risk of serious infections, including herpes zoster infections.	Serious infections (pneumonia), malignancies, and neurologic events have been reported more frequently in patients taking adalimumab.
Other					Not recommended in combination with biological UC therapies or with potent immuno-suppressants such as azathioprine and cyclosporine.	

6-MP = 6-mercaptopurine; CI = confidence interval; Ig = immunoglobulin; IL = interleukin; JAK = Janus kinase; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] Health Canada–approved indication.

Source: Product monographs for ustekinumab (Stelara),[17] infliximab (Remicade),[18] vedolizumab (Entyvio),[16] golimumab (Simponi),[19] tofacitinib (Xeljanz),[20,21] and adalimumab (Humira).[22]

Stakeholder Engagement

Patient Group Input

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

About the Patient Groups and Information Gathered

One response to CADTH's call for patient input for vedolizumab (Entyvio SC) was received from the GI Society.

The GI Society is a national leader in providing trusted, evidence-based information on all areas related to the GI tract. The GI Society is committed to improving the lives of individuals with GI and liver conditions by supporting research, advocating for patient access to health care, and promoting overall GI and liver health. The GI Society delivers information through its useful resources, including the BadGut Basics pamphlets, which are distributed to Canadian health care professionals every year, and their quarterly newsletter, *Inside Tract/Du coeur au ventre*. Furthermore, the GI Society informs Canadians through its free BadGut Lectures, which are given coast to coast and cover various digestive conditions for patients, caregivers, and others, and through a website, available in both English and French, that includes additional information and resources. GI Society staff and advisors work closely with health care professionals, other patient groups, and government on behalf of patients with GI conditions; respond to information requests; and participate in community initiatives. The GI Society has also supported several significant GI research studies along with its sister charity, the Canadian Society of Intestinal Research.

The patient input used to inform this submission was obtained through two questionnaires: one questionnaire was completed by 133 individuals (105 in English and 28 in French) with an IBD such as UC, or by their caregivers or family members; a second was completed by 432 individuals with an IBD, including UC. Additionally, the GI Society has also had direct contact with patients with IBD at BadGut Lectures and patient roundtables, and through phone, email, and social media interactions.

Disease Experience

The patient group describes UC as a lifelong GI condition that affects primarily young people. With approximately 120,000 individuals diagnosed with UC, Canada is among the countries with the highest prevalence of UC reported in the world. The most frequent symptoms associated with UC are diarrhea, abdominal pain and cramping, and rectal bleeding. When diarrhea and blood loss are severe, anemia may also arise. UC can result in extra-intestinal manifestations, including fever, inflammation of the eyes or joints (arthritis), ulcers of the mouth or skin, tender and inflamed nodules on shins, and more. After having UC for more than 10 years, patients are at increased risk of colorectal cancer. In addition to the physical symptoms, the patient group describes experiences of anxiety and stress as major factors, with UC having a profound effect on their emotional and social lives. Particularly for children and young adults, UC can affect a person's sense of self.

Given that UC is a chronic disease, patients are constantly concerned about future flares, which can be unpredictable and severely disruptive. Many patients reported IBD as affecting all aspects of their day-to-day lives; one patient indicated: "I am constantly aware of where a bathroom is and always prepared for the urge to go. My activities are limited for the fear of not being able to find a washroom." Another patient reported: "My energy levels

have decreased, and I get fatigued much more easily; the fear of pain, bleeding, incontinence is horrible. The worst part is fearing the next big flare that will prevent me from being a mom to my 18-month-old." The patient group added that treatments should improve quality of life, not cause more symptoms, pain, frustration, or hardship.

Experience With Treatment

The patient group describes the treatment of UC as being multifaceted, as it involves managing the symptoms and consequences of the disease and trying to reduce the underlying inflammation. Most patients will try a medication and, if it fails to treat their disease, they switch to another type. First-line treatments for UC include anti-inflammatory drugs such as 5-aminosalicylates and corticosteroids to control disease flares. These drugs can settle acute inflammation and, for some, can keep inflammation inactive when taken long term (maintenance). Rectal formulations may also be used for topical relief; however, these can be ineffective for a patient with significant diarrhea. Patients whose condition does not respond to first-line treatment, or who have more severe cases of UC, are treated with second-line treatments such as immunomodulators or immunosuppressants, although it can take six months to see any results. When other medications fail to relieve symptoms, biologics are used. Some patients report remarkable, sometimes "miracle-like" results from biologics. The patient group added that biologics have demonstrated effectiveness in treating UC, with 63% of respondents reporting symptom reduction and 23% reporting clinical remission. Nonetheless, not everyone responds to the currently available treatments, including biologics, and, if they do, there is still a risk of treatment failure. Furthermore, these treatment options do not come without side effects.

While there are different treatment options available, many patients still have difficulties obtaining remission and/or adequate symptom relief; in one survey, 28% of respondents reported that the available medications are adequate, 54% reported them to be somewhat adequate, and 18% indicated they are not adequate.

No direct experience with Entyvio in patients with UC was included in the patient group submission. However, the GI Society reports Entyvio being very effective for patients with Crohn disease and believes it has the potential to be another option to improve the health and quality of life of patients with UC. Ultimately, the patient group would like additional effective-therapy options to choose from.

Improved Outcomes

The patient group indicated that achieving and maintaining remission or treatment response is more important than relieving any one symptom. Patients are still suffering, and they need new and effective options to achieve mucosal healing and decrease the debilitating symptoms of UC. Given that all individuals respond differently to treatment, it is important to patients to have access to a variety of treatment options. Inadequate access to medication can result in preventable patient suffering (both from UC and consequential secondary illnesses), excess usage of health care resources (such as hospital stays, surgeries, diagnostics, and treatments), and financial burden on the government due to patients' inability to work and long-term disability claims. The patient group believes that with access to a new drug, individuals with UC can live full, rewarding lives and contribute to the workforce and community.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of IBD, specifically, UC.

Description of the Current Treatment Paradigm for the Disease

In Canada, front-line therapy for most patients with UC is 5-aminosalicylates, which includes mesalamine and sulfasalazine. These drugs are topical anti-inflammatory therapies that possess a favourable side effect profile and can be used for both the induction and maintenance of remission in cases of mild-to-moderate and sometimes severe UC. Some individuals will require corticosteroid induction therapy and will then be transitioned to 5-aminosalicylates therapy for maintenance. Individuals with severe-to-fulminant UC are often treated up-front with systemic immunosuppressive therapy, including azathioprine/6-MP, biological therapies, such as anti-TNF drugs (infliximab, adalimumab, golimumab), anti-integrin drugs (vedolizumab) or anti–interleukin 12/23 [IL-12, IL-23] drugs (ustekinumab), and other targeted therapies, such as Janus kinase inhibitors (tofacitinib), often in conjunction with systemic corticosteroids for induction/co-induction. All of these drugs are approved by Health Canada for the treatment of UC, with the exception of corticosteroids and azathioprine/6-MP; however, these drugs are commonly used in Canadian clinical practice based on their historical evidence of efficacy and low cost. North American and European clinical guidelines support the use of all of these drugs in the appropriate clinical context, and with shared decision-making between patients and physicians regarding the risks and benefits of each treatment.

The goal of any therapy in UC is to achieve symptomatic, biochemical, and endoscopic normalization, sometimes termed “deep remission.” This requires close monitoring of the patient's symptoms, blood and stool inflammatory markers, and mucosal response, as evidenced by endoscopy. In general, biologic drugs and newer targeted therapies have better evidence for achieving deep remission than conventional therapies (i.e., 5-aminosalicylates, corticosteroids, azathioprine, 6-MP) and are often preferred in the setting of severe fulminant colitis or in the context of failure of conventional therapies. While any of these therapies generally do not modify the disease mechanism, they can modify the disease course and risk of severe complications (i.e., hospitalization for disease flare, fulminant colitis, bowel perforation, or surgery) through deep suppression of inflammation. In some instances, prolonged treatment with a therapy targeting a specific immune pathway (such as anti-TNF therapy) may promote a switch to a different cytokine-mediated inflammatory response, requiring a different treatment (mechanistic switch). This mechanism is not well established and is under investigation. Corticosteroid therapy has not been shown to be effective over the long term in modifying the disease course.

Ultimately, if medical therapies fail, individuals with active UC will require surgery, which typically involves complete excision of the colon and rectum and the creation of either an ileo-anal pouch or an end ileostomy.

Treatment Goals

The overarching treatment goals in UC are to eliminate an individual's disease-related symptoms, minimize the risks of disease-related complications (such as hospitalization, fulminant colitis, bowel perforation, or surgery) and allow the individual to re-establish a good quality of life. This is accomplished primarily through suppression of bowel inflammation using topical anti-inflammatories and/or systemic immunosuppressive therapies. From a clinical perspective, this requires the complete and lasting suppression of inflammation in the bowels and extra-intestinal tissues, as well as management of any superimposed GI symptoms and mental health conditions associated with UC.

Unmet Needs

The therapeutic landscape for UC has improved considerably over the past 15 years, with the introduction of multiple classes of targeted therapies with an improved capacity to achieve deep remission compared with conventional therapies. Moreover, newer targeted treatments have much better safety profiles than conventional drugs and targeted treatments are now available in IV, SC, and oral formulations. Currently, the goals not being met by available treatments for UC are long-term disease remission, predictable treatment responses, and cost-effective treatment options for the newer drugs. Long-term disease remission is generally less than 50% for all of the available drugs, and the costs of newer drugs are roughly 10 times higher than conventional therapies at baseline dosing, and increase linearly with dose escalation.

Place in Therapy

Vedolizumab is already approved in Canada for the treatment of UC in an IV formulation. It has demonstrated efficacy relative to placebo that is comparable to other targeted therapies that are approved to treat UC. All of the chronic immunosuppressive therapies that are used to treat UC are intended to modify the disease course, and several (particularly anti-TNF drugs) have been shown to reduce the risks of hospitalization and surgery. As such, the drug under review does not offer a novel mechanism of action, treatment response, or mode of administration. Vedolizumab is marketed as a gut-selective drug, based on its selective inhibition of gut-homing lymphocytes in the systemic circulation. In this way, vedolizumab may offer greater specificity and a better side effect profile for the treatment of UC compared with other classes of therapies. Long-term post-market surveillance data have confirmed the safety of this class of therapy.

Vedolizumab could be positioned as either first-line or second-line therapy for treatment-refractory disease. This drug could have an impact on the current treatment paradigm, as it offers an SC home-administration option for an effective class of therapy with a favourable safety profile. While there are other SC drugs available with a favourable safety profile, some individuals may benefit from the gut selectivity of this class of therapy, such as those with a history of serious opportunistic infections or non–GI tract malignancies, as well as those with contraindications to anti-TNF drugs or other therapies (such as demyelinating neuropathy, advanced congestive heart failure or severe psoriasis, or chronic systemic infections, such as latent tuberculosis or hepatitis B).

Patient Population

Patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, and patients who are at risk of incurring serious systemic complications with other therapies, are the best candidates for vedolizumab. Patients should also be capable of self-administering SC injection medication. Patients best suited for this treatment should be identified based on an experienced clinician's judgment using endoscopy and histology. Crohn disease and other causes of colitis (infectious or microscopic) would also need to be excluded, as vedolizumab SC is currently not indicated for those conditions. Treatment with vedolizumab should be reserved for those with active disease based on endoscopy or other parameters. Patients with mild-to-moderate UC who have not been tried on conventional therapy (i.e., 5-aminosalicylates therapy) and those who are unable to self-administer SC injections would be the least appropriate candidates for vedolizumab.

Currently, there are limited data guiding patient selection based on the probability of treatment response in patients with UC. One recent study[23] developed a prediction model for treatment response with IV vedolizumab in patients with Crohn disease that comprises common clinical factors that are often used to judge the likelihood of treatment response in clinical practice.

Assessing Response to Treatment

The primary outcome criteria used to judge treatment response is evidence of mucosal healing by endoscopy. Supportive criteria include normalization of blood and stool inflammatory markers and symptom response. Clinical trials have traditionally relied more heavily on symptom-based outcomes, largely because of ease of acquisition. However, newer regulatory criteria mandate the use of endoscopic response as a measure of treatment outcome. A clinically meaningful response to treatment would be a complete or near-complete resolution of GI and constitutional symptoms in the context of complete or near-complete mucosal healing of the bowel and normalization of serum inflammatory markers.

Symptom and biochemical response to treatment should be assessed four to six weeks after the start of treatment, while symptom, biochemical, and endoscopic response should be assessed three to six months after the start of treatment. If an individual has achieved deep remission by this time, then blood and stool inflammatory markers should be assessed every three to six months, and symptom response should be assessed every six to 12 months. Endoscopic treatment response should be reassessed at three- to five-year intervals in the absence of any symptomatic or biochemical suggestion of active disease. On the other hand, if the patient has persistent disease activity after the start of treatment but has shown a partial treatment response, symptom, biochemical, and endoscopic response should be assessed at three- to six-month intervals until deep remission is achieved.

Discontinuing Treatment

Treatment response and side effects/adverse reactions to medication should guide the decision to continue or discontinue therapy. In general, the absence of a near-complete endoscopic and biochemical response or the development of a serious adverse reaction to medication should warrant a change of treatment.

Prescribing Conditions

Vedolizumab should be prescribed in an outpatient specialty clinic, such as one specializing in gastroenterology or internal medicine. Following appropriate training, vedolizumab SC will likely be administered by the patient at home. A specialist, such as a gastroenterologist or internist, will be required to diagnose, treat, and monitor patients on vedolizumab.

Clinical Evidence

The clinical evidence included in the review of vedolizumab is presented in three sections. The first, the systematic review, includes the pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. The third section includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of vedolizumab SC injection for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab. Subgroups: • patients treated previously with conventional therapy versus those treated previously with anti-TNF drugs • disease severity (moderate versus severe) • disease extension (extensive versus no extensive colitis)
Intervention	Vedolizumab solution for subcutaneous injection for maintenance treatment at 108 mg every 2 weeks (syringe with 108 mg/0.68 mL).
Comparators	• Adalimumab • Golimumab • Infliximab • Tofacitinib • Ustekinumab • Conventional therapy: any combination of aminosalicylates, corticosteroids, and immunomodulators

Outcomes	**Efficacy outcomes:** • clinical remission, including corticosteroid-free clinical remission • clinical response • health-related quality of life • need for colectomy • mucosal healing determined by endoscopy and/or histology • work/life productivity • Harms outcomes: • AEs, SAEs, WDAEs, mortality • Notable harms and harms of special interest: thromboembolic events (any type), hypersensitivity (anaphylaxis and/or angioedema), serious infections (including herpes zoster), malignancy, major cardiovascular events
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; RCT = randomized controlled trial; SAE = serious adverse event; TNF = tumour necrosis factor; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist (www.cadth.ca/resources/finding-evidence/press).[24]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Entyvio (vedolizumab) and UC. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal.

Search filters were applied to limit retrieval to RCTs or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on December 17, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on April 15, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[25] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the drug sponsor was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Findings From the Literature

A total of 341 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

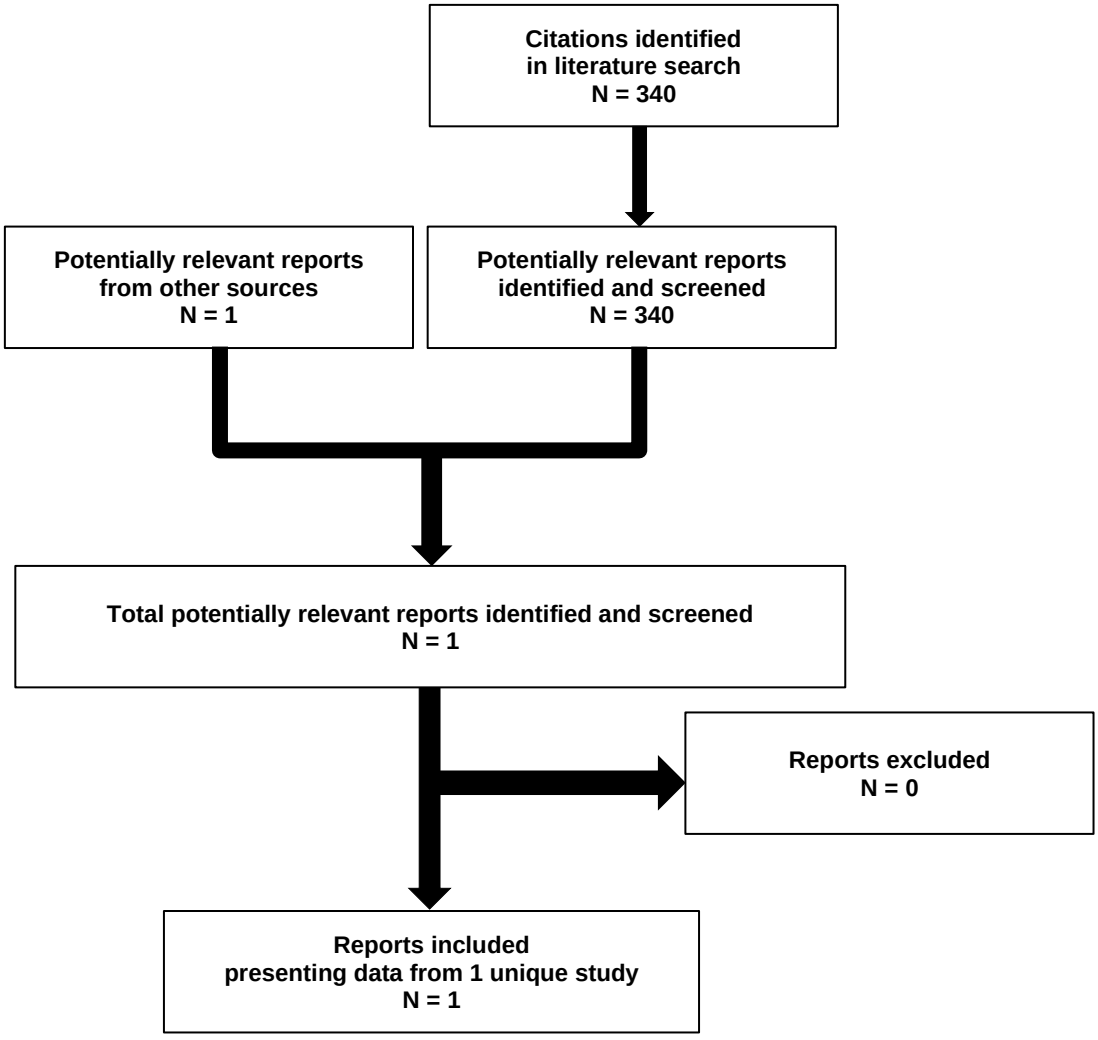


Table 5: Details of Included Studies

		VISIBLE 1
Designs and populations	**Study design**	Phase III, double-blind, double-dummy, placebo-controlled RCT with a vedolizumab IV reference arm
	Locations	US, Canada, Belgium, UK, Japan, India, Singapore, Australia
	Randomized (N)	216
	Inclusion criteria	• Male or female patients aged 18 to 80 years • A diagnosis of UC established at least 6 months before screening by clinical and endoscopic evidence and corroborated by a histopathology report • Moderately to severely active UC as determined by a complete Mayo score of 6 to 12 (with an endoscopic subscore of ≥ 2) within 10 days before the first dose of the study drug. The endoscopy could be performed during the screening period (day −10 to day −5) to allow for central reading prior to first dose at week 0 • Evidence of UC extending proximal to the rectum (≥ 15 cm of involved colon) • Patients with extensive colitis or pancolitis of > 8 years' duration or left-sided colitis of > 12 years' duration must have documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (if not performed in the previous 12 months it must have been performed during screening) • Inadequate response to, loss of response to, or intolerance to at least one other treatment that was either a corticosteroid (a dose equivalent to prednisone ≥ 30 mg), an immunomodulator (azathioprine or 6-mercaptopurine), or an anti-TNF (infliximab, adalimumab, golimumab) • Agreement to use appropriate contraception (both males and females)
	Exclusion criteria	• Patients with abdominal abscess or toxic megacolon at the initial screening visit • Colonic resection, subtotal or total colectomy • Unresected adenomatous colonic polyps • Colonic mucosal dysplasia • Prior exposure to any anti-integrin therapies (e.g., vedolizumab, natalizumab, efalizumab, etrolizumab, AMG181), anti-MAdCAM-1 antibodies, or rituximab • Evidence of an active infection, including chronic hepatitis B virus, latent tuberculosis, and *Clostridium difficile* infection, and/or previous treatment within 28 days before the first dose of the study drug • Congenital or acquired immunodeficiencies • Use of topical 5-aminosalicylic acid or corticosteroid (rectal)
Drugs	**Intervention**	Vedolizumab SC, for maintenance phase, 108 mg every two weeks subcutaneously
	Comparator(s)	• Vedolizumab IV for maintenance phase; 300 mg IV infusion every 8 weeks • Placebo SC, 0.9% sodium chloride; 1 mL subcutaneously every two weeks • Placebo IV, 0.9% sodium chloride; IV infusion every 8 weeks
Duration	**Phase**	
	Run-in	• 4-week screening period with a 6-week open-label vedolizumab IV induction phase
	Double-blind	• 48 weeks of a randomized, double-blind, double-dummy phase
	Follow-up	• 52 weeks
Outcomes	**Primary end point**	Clinical remission at week 52 in patients who achieved clinical response at week 6 following administration of vedolizumab IV at weeks 0 and 2
	Secondary and exploratory end points	**Secondary end points** (evaluated at week 52 in patients who achieved clinical response at week 6 following administration of vedolizumab IV at weeks 0 and 2): • mucosal healing • durable clinical response • durable clinical remission • corticosteroid-free remission

		VISIBLE 1
		Exploratory end points: • pharmacokinetics of multiple doses of vedolizumab SC • immunogenicity of multiple doses of vedolizumab SC • patient-reported outcomes • time to major UC-related events (hospitalizations, colectomies, and procedures) • WPAI-UC from baseline (week 0) to week 52 and from week 6 to week 52 • comparison of the efficacy, safety, and immunogenicity of the vedolizumab IV and vedolizumab SC presentations • correlation of UC-associated genetic polymorphisms and inflammation biomarkers with therapeutic response to vedolizumab SC • histological remission at week 52 • clinical remission as defined using alternate definitions
NOTES	**Publications**	Sanborn (2019).[26]

RCT = randomized controlled trial; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis; WPAI-UC = Work Productivity and Activity Impairment – Ulcerative Colitis.

Note: Two additional reports were included: MLN0002SC-3027[1] and the extension study MLN0002SC-3030.[27]

Source: VISIBLE 1 Clinical Study Report.[1]

Description of Studies

One study was included. The VISIBLE 1 study is a double-blind, double-dummy, placebo-controlled trial that was conducted at 141 sites in 29 countries from December 2015 to August 2018. It consisted of two phases: an induction six-week open-label phase where all patients received vedolizumab 300 mg IV, and a maintenance phase where patients responding at week 6 were randomly assigned to vedolizumab SC, vedolizumab IV, or placebo. A visual summary of the study is depicted in Figure 2 and the details are included in Table 5.

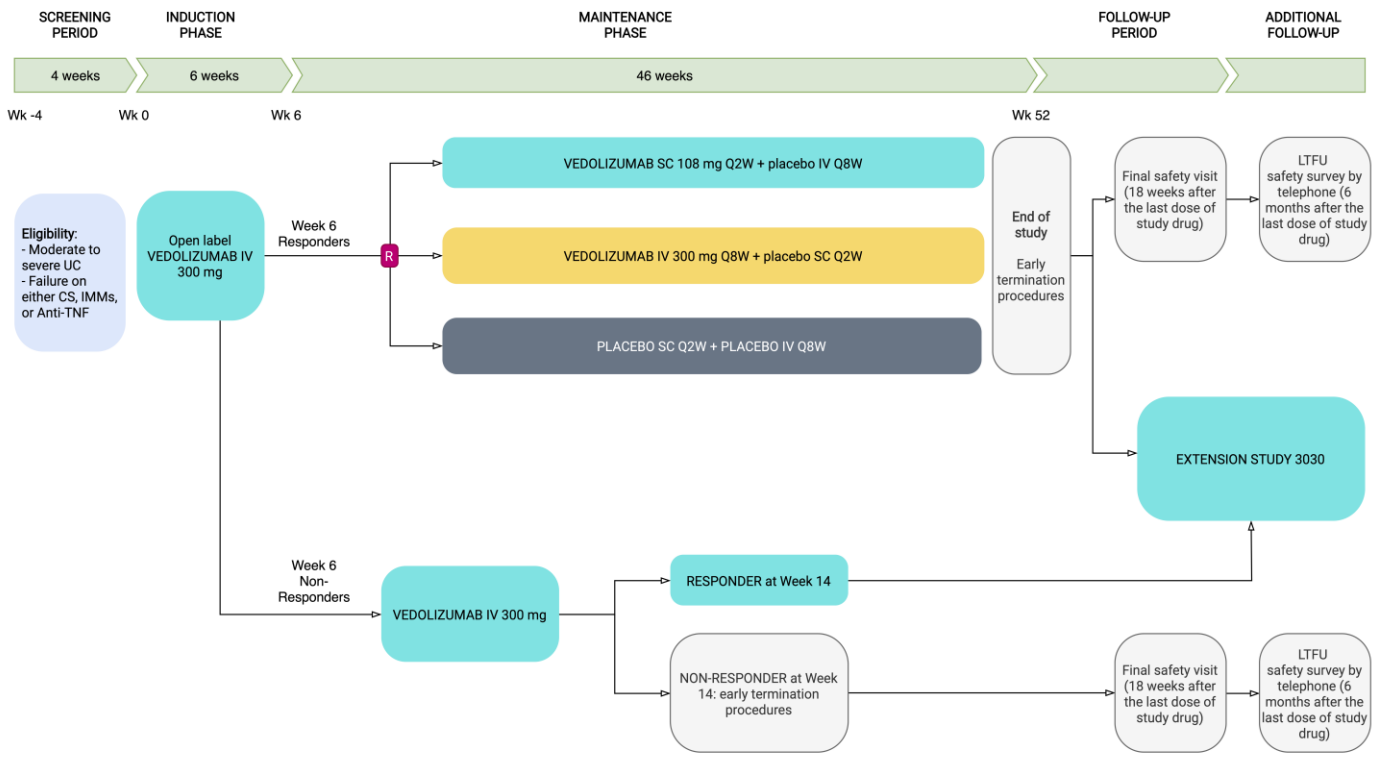
A screening period of 28 days was established where patients were considered eligible if they had moderately to severely active UC and experienced treatment failure on either corticosteroids, immunomodulators, or anti–TNF alpha drugs. During the screening period, 231 out of 614 (37.6%) patients did not enter the induction phase because they did not meet the enrolment criteria (n = 192), withdrew consent (n = 14), experienced pre-treatment events or AEs (n = 8), were lost to follow-up (n = 3), had significant protocol deviation (n = 1), or for other reasons (n = 13). Hence, a total of 383 patients were available to enter the open-label induction phase where each patient received 300 mg IV of vedolizumab: one dose at week 0 and a second dose at week 2. At week 6, all patients were assessed for clinical response, defined as a reduction in total Mayo score of 3 points or more and a 30% or greater reduction from baseline (week 0) with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 1 or lower. Those patients with a clinical response at week 6 (n = 215) were eligible to enter the randomized (maintenance) phase of the study. This was a double-blind, double-dummy, randomized study design where patients were assigned to three arms using a 2:1:1 ratio and stratified by concomitant use of corticosteroids, clinical remission at week 6, and prior anti–TNF alpha failure or concomitant immunomodulator use. Patients (n = 216) were randomized to vedolizumab SC 108 mg every two weeks plus placebo IV every eight weeks; vedolizumab IV 300 mg every eight weeks plus placebo SC every two weeks; or placebo SC every two weeks plus placebo IV every eight weeks (Figure 2 and Figure 3).

Primary and secondary outcomes were assessed at week 52. The vedolizumab IV reference group was included to allow for within-study descriptive comparisons of efficacy, safety, and immunogenicity between vedolizumab SC and vedolizumab IV and it is included in this review by CADTH to address important comparisons.

Patients who did not achieve a clinical response at week 6 were not randomized to the maintenance phase and instead received a third infusion of open-label vedolizumab IV 300 mg at week 6. Patients who did not respond in the induction phase at week 6 but achieved a clinical response at week 14 (measured by partial Mayo score) were eligible to enrol in the open-label extension study (MLN0002SC-3030),[27] while patients who did not achieve a clinical response were discontinued.

Patients who did not enter the open-label study completed a final study safety assessment at week 68 (or final safety visit 18 weeks after the last dose) during the maintenance phase. In addition, they were also to participate in a follow-up visit by telephone six months after the last dose of the study drug.

Figure 2: Design of the VISIBLE 1 Study



CS = corticosteroids; IMM = immunomodulator; LTFU = long-term follow-up; Q2W = every two weeks; Q8W = every eight weeks; SC = subcutaneous; TNF = tumour necrosis factor; UC = ulcerative colitis; wk = week.

Note: Open-label vedolizumab IV in the induction phase was administered at weeks 0 and 2. Patients who consented to participate in the extension study were permitted to begin the extension-study dosing after end-of-study visit procedures had been completed at the week 52 visit. Patients who did not enter the extension study (including early terminators and week 14 nonresponders) were to complete the final safety visit 18 weeks after their last dose of the study drug and participate in a follow-up safety survey by telephone six months after the last dose of the study drug. Patients who were not randomized to the maintenance phase (week 6 nonresponders) and who were responding to treatment with vedolizumab IV 300 mg at week 14 were also eligible for entry into the extension study.

Source: VISIBLE 1 Clinical Study Report.[1]

Populations

Inclusion and Exclusion Criteria

Investigators confirmed the entry criteria before the first dose of vedolizumab to ensure that only patients who were appropriate for treatment with vedolizumab IV under the drug's current labelled indication were enrolled into the study and received open-label vedolizumab IV induction treatment. These criteria also excluded patients who might not benefit from the drug or who might be at risk for toxicities. Patients had to be between 18 and 80 years old with a diagnosis of UC established at least six months before screening by clinical and endoscopic evidence and corroborated by a histopathology report. Investigators considered patients to have moderately to severely active UC if they had a complete Mayo score of 6 to 12 (with an endoscopic subscore ≥ 2) within 10 days before the first dose of the study drug. The endoscopy could be performed during the screening period (day −10 to day −5 to allow for central reading prior to the first dose at week 0). Also included were patients with evidence of UC extending proximal to the rectum (≥ 15 cm of involved colon), as well as patients with extensive colitis or pancolitis of more than 8 years' duration or with left-sided colitis of more than 12 years' duration. The participants had to demonstrate an inadequate response to, loss of response to, or intolerance to at least one other treatment that was either a corticosteroid (a dose equivalent to prednisone ≥ 30 mg), an immunomodulator (azathioprine or 6-MP), or an anti-TNF (infliximab, adalimumab, or golimumab). The exclusion criteria included GI, infectious, and general conditions as specified in Table 5.

Baseline Characteristics

The baseline demographic characteristics from both the induction and maintenance phases were obtained as a single timeline and are summarized in Table 6. All data were obtained from the efficacy populations.

Baseline characteristics were available for patients in each of the maintenance phase groups, that is, 106 patients in the vedolizumab SC group, 54 in the vedolizumab IV group, and 56 in the placebo group (216 patients in total). The data in Table 6 represent the combined safety analysis set (SAS-C), this is, the patients in the safety analysis set (SAS) (i.e., all patients who received at least one dose of vedolizumab and were randomized) plus the SAS of the induction phase (SAS-I) (i.e., all patients who received at least one dose of vedolizumab IV and were not randomized). Hence, data for the induction phase represent all patients who received at least one dose of vedolizumab IV but were not randomized.

In the maintenance phase, all of the variables measured, such as age, sex, weight, and race, were similar in their distribution between the vedolizumab SC, IV, and placebo groups. Baseline disease characteristics such as duration of UC, Mayo score, fecal calprotectin, disease extension and localization, and prior use of immunomodulators, corticosteroids, and anti-TNF drugs were all similar among the three groups. Although some differences were noted (for instance, prior use of an immunomodulator), the sample size and event rates were small and did not allow for a robust comparison among the groups of any of these variables.

Patients from the three groups had had a diagnosis of UC a median of 5.8 years previously and more than half of them (total average of 61.6%) presented with severe disease, as defined by a Mayo score of 9 to 12 (Table 6). Overall, 38.9% had previously had a poor response to an anti-TNF therapy, while 61.1% were patients who were anti–TNF naive. Still, there were no differences among the study groups in the distribution of these

variables. Also, 91.2% of all patients had taken at least one concomitant IBD medication during the study, with a similar distribution between groups (92.5%, 87%, and 92.9% in the vedolizumab SC, vedolizumab IV, and placebo groups, respectively).

Table 6: Summary of Baseline Demographics and Disease Characteristics

	Induction phase	Maintenance phase[a]			
	Vedolizumab IV 300 mg N = 167	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54		Total N = 216
Baseline demographics					
Age, years, mean (SD)	42.7 (15.01)	38.1 (13.12)	41.6 (14.11)	39.4 (11.70)	39.3 (13.05)
Sex female, n (%)	79 (47.3)	41 (38.7)	23 (42.6)	22 (39.3)	86 (39.8)
Weight (kg), mean (SD)	68.20 (17.13)	71.58 (17.17)	76.95 (16.93)	73.96 (20.91)	73.54 (18.20)
Race, n (%)					
American Indian or Alaskan Native	2 (1.2)	0	0	1 (1.8)	1 (0.5)
Asian	39 (23.4)	14 (13.2)	5 (9.3)	13 (23.2)	32 (14.8)
Black or African American	1 (0.6)	0	2 (3.7)	0	2 (0.9)
White	125 (74.9)	92 (86.8)	47 (87.0)	42 (75.0)	181 (83.8)
Ethnicity, n (%)					
Hispanic or Latino	0	0	0	1 (1.8)	1 (0.5)
Not Hispanic or Latino	24 (14.4)	7 (6.6)	8 (14.8)	6 (10.7)	21 (9.7)
Not reported	143 (85.6)	99 (93.4)	46 (85.2)	49 (87.5)	194 (89.8)
Baseline disease characteristics					
Duration of UC, years					
Mean (SD)	–	7.96 (6.22)	8.18 (5.93)	7.36 (7.15)	7.86 (6.38)
Median	–	5.93	6.79	5.32	5.85
Minimum, maximum	–	0.6, 29.8	0.5, 30.9	0.6, 30.3	0.5, 30.9
Duration of UC, categories, n (%)	–				
< 1 year	–	6 (5.7)	1 (1.9)	5 (8.9)	12 (5.6)
≥ 1 to < 3 years	–	16 (15.1)	10 (18.5)	14 (25.0)	40 (18.5)
≥ 3 to < 7 years	–	37 (34.9)	16 (29.6)	16 (28.6)	69 (31.9)
≥ 7 years	–	47 (44.3)	27 (50.0)	21 (37.5)	95 (44.0)
Baseline disease activity, n (%)					
Mild (Mayo score < 6)	–	0	0	0	0
Moderate (Mayo score = 6 to 8)	–	46 (43.4)	17 (31.5)	20 (35.7)	83 (38.4)
Severe (Mayo score = 9 to 12)	–	60 (56.6)	37 (68.5)	36 (64.3)	133 (61.6)
Baseline fecal calprotectin (mcg/g)					
N	–	102	52	56	210
Mean (SD)	–	2,607.2 (2,908.67)	3,173.5 (4,785.48)	2,393.4 (2,859.66)	2,690.4 (3,451.64)
Categorical baseline fecal calprotectin categories, n (%)					
≤ 250 mcg/g	–	9 (8.5)	2 (3.7)	5 (8.9)	16 (7.4)

	Induction phase	Maintenance phase[a]			
	Vedolizumab IV 300 mg N = 167	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54		Total N = 216
> 250 to ≤ 500 mcg/g	–	6 (5.7)	4 (7.4)	7 (12.5)	17 (7.9)
> 500 mcg/g	–	87 (82.1)	46 (85.2)	44 (78.6)	177 (81.9)
Missing	–	4 (3.8)	2 (3.7)	0	6 (2.8)
Disease localization, n (%)					
Proctosigmoiditis	–	15 (14.2)	7 (13.0)	7 (12.5)	29 (13.4)
Left-sided colitis	–	46 (43.4)	21 (38.9)	24 (42.9)	91 (42.1)
Extensive colitis	–	7 (6.6)	7 (13.0)	4 (7.1)	18 (8.3)
Pancolitis	–	37 (34.9)	19 (35.2)	21 (37.5)	77 (35.6)
Prior therapy, n (%)					
Prior TNF alpha antagonist use	–	40 (37.7)	24 (44.4)	20 (35.7)	84 (38.9)
No prior TNF alpha antagonist use	–	66 (62.3)	30 (55.6)	36 (64.3)	132 (61.1)
Any prior TNF alpha antagonist failure	–	40 (37.7)	24 (44.4)	20 (35.7)	84 (38.9)
Prior corticosteroids only	–	28 (26.4)	21 (38.9)	22 (39.3)	71 (32.9)
Prior corticosteroids and immunomodulators	–	71 (67.0)	32 (59.3)	32 (57.1)	135 (62.5)
Prior immunomodulators only	–	6 (5.7)	1 (1.9)	1 (1.8)	8 (3.7)
No prior immunomodulators or corticosteroids	–	1 (0.9)	0	1 (1.8)	2 (0.9)
Concomitant IBD therapy, n (%)					
Patients with ≥ 1 concomitant medication	–	98 (92.5)	47 (87.0)	52 (92.9)	197 (91.2)
Corticosteroids	–	54 (50.9)	27 (50.0)	28 (50.0)	109 (50.5)
5-aminosalicylic acids	–	85 (80.2)	44 (81.5)	44 (78.6)	173 (80.1)
Immunomodulators	–	36 (34.0)	17 (31.5)	18 (32.1)	71 (32.9)

CS = corticosteroids; IBD = inflammatory bowel disease; SAS = safety analysis set; SAS-C = combined SAS; SAS-I = SAS of the induction phase; SD = standard deviation; TNF = tumour necrosis factor; UC = ulcerative colitis.

[a] The data represent the SAS-C (combined) population set, this is, the SAS-I and SAS populations. The SAS-I represents all patients who received at least one dose of vedolizumab IV and were not randomized. The SAS population presents those who were randomized and received at least one dose of vedolizumab.

Source: VISIBLE 1 Clinical Study Report.[1]

Interventions

During the induction study, all patients received two (open-label) doses of vedolizumab IV 300 mg. The first dose was administered at week 0 in a 300 mg/vial infusion, with the next dose at week 2 using the same dose and procedures. A health care professional administered the 300 mg dose of vedolizumab IV over approximately 30 minutes, with longer infusion times up to 60 minutes, if needed. All patients were observed for two hours after the infusion to assess for any possible reactions.

Patients with a clinical response at week 6 after the induction phase (i.e., endoscopic subscore determined by a central reader) were randomized to receive, in a 2:1:1 ratio, one of the following:

- vedolizumab SC 108 mg every two weeks plus placebo IV infusions every eight weeks
- infusions of vedolizumab IV 300 mg every eight weeks plus placebo SC every two weeks
- placebo SC every two weeks plus placebo IV every eight weeks.

The IV infusions were administered and managed similar to the induction phase. The SC injections were administered by the health care provider in the outer area of the upper arms, abdomen, or the front of the thighs.

The placebo solutions consisted of 0.9% sodium chloride. The SC placebo was pre-filled in 1 mL syringes with a formulation composition similar to the vedolizumab SC solution. The IV placebo was 250 mL (100 mL in Japan) of 0.9% sodium chloride IV supplied in polyvinyl chloride or alternative IV bags or alternative IV bottles listed in the pharmacy manual.

The randomization schedule was generated by the sponsor before the start of the study. All randomization information was stored in a secured area, accessible only by authorized personnel. An interactive web response system (IWRS) was used to randomly assign patients to each arm of the study. All study-site personnel were blinded to treatment assignments for the duration of the study. Only the pharmacist or pharmacy designee was unblinded; they obtained treatment assignments through the IWRS and prepared the investigational drug according to the procedures outlined in the study manual. In case of the need for emergency unblinding, it was to be conducted via the IWRS.

Concomitant medications for the treatment of UC were allowed and recorded during the entire study. Medications for medical conditions other than UC were also allowed. Among the medications permitted were oral 5-aminosalicylates, oral corticosteroids, probiotics, antidiarrheals, azathioprine, or 6-MP. For immunosuppressive therapies, oral 5-aminosalicylates, probiotics, and antibiotics for UC, dose reduction or discontinuation per label was allowed only due to adverse reactions. For oral corticosteroids, dose reductions were made per the tapering schedule. All live vaccines, other biological drugs for the treatment of non-IBD conditions, chronic anti-inflammatory drugs, and blood apheresis were not allowed. Any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC symptoms (other than antidiarrheals for control of chronic diarrhea) was considered a rescue medication, except for corticosteroids that were increased to baseline in patients undergoing tapering.

Outcomes

The main objective of the VISIBLE 1 trial was to evaluate the efficacy of vedolizumab SC maintenance treatment at week 52 in patients with moderately to severely active UC who had achieved a clinical response at week 6 following administration of vedolizumab IV at weeks 0 and 2. For a complete description of the validity and measurement of these outcomes, see Appendix 4. The following outcomes were assessed:

Clinical remission: This was the study's primary outcome (and among CADTH's main efficacy outcomes). It was defined as a complete Mayo score of 2 points or less and no individual subscore greater than 1 point at week 52. The investigators defined clinical remission to be "durable" as long the remission was present at week 6 and week 52 of the study.

Corticosteroid-free remission: This was a secondary outcome in the VISIBLE 1 study. Patients were considered to have achieved corticosteroid-free remission if they had been using oral corticosteroids at baseline (week 0) but had discontinued oral corticosteroids and were in clinical remission at week 52. This outcome was considered in this review as a main efficacy outcome.

Clinical response: This was a secondary end point of the VISIBLE 1 study but a main efficacy outcome in this review. It was defined as a reduction of three or more points in complete Mayo score and a 30% or greater reduction from baseline (week 0) with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 1 or lower. Also, a clinical response was considered "durable" if it was present at weeks 6 and 52.

Health-related quality of life: This also was a main efficacy outcome for CADTH and was included as a patient-reported outcome in the VISIBLE 1 study, where it was measured using the IBDQ total score by visit, the EQ-5D index score, and the EQ-5D Visual Analogue Scale (VAS), assessed as the change from baseline to week 52.

Need for colectomy: This was a patient-reported (exploratory) outcome in the VISIBLE 1 study and defined as any occurrence of this type of surgery at any point during the study follow-up. For CADTH, this was included among the main efficacy outcomes.

Mucosal healing: This was another secondary outcome in the VISIBLE 1 trial but a main efficacy outcome for this review. It was defined as a Mayo endoscopic subscore of 1 or lower at week 52.

Work productivity: Work productivity or activity impairment was measured using the change in WPAI-UC score from baseline (week 0) to week 52 and from week 6 to week 52. This was among CADTH's main efficacy outcomes, while the VISIBLE 1 study evaluated it as a patient-reported outcome.

Adverse (harms) outcomes: For this review, we aimed to address harm outcomes, including AEs, SAEs, withdrawal due to adverse events (WDAEs), and mortality. We also looked for notable harms such as thrombosis (any type), hypersensitivity (anaphylaxis or angioedema), serious infections, malignancies, and major cardiovascular events. In the VISIBLE 1 study, safety was evaluated based on the frequency of AEs in the safety population. No statistical inference was made for the safety analyses. AEs were coded in accordance with version 21.0 of the Medical Dictionary for Regulatory Activities (MedDRA) and were monitored by treatment group. The SAS population, which included all patients who received at least one dose of the study drug (placebo or vedolizumab) subcutaneously, was used for all safety analyses. The SAS-I population included all patients who received at least one induction dose but were not randomized to the maintenance phase. The SAS-C population included all patients who received at least one dose of vedolizumab IV. The harm outcomes evaluated in the VISIBLE 1 study were:

- any AE, as any event with a relationship to the study drug
- SAEs
- AEs leading to discontinuation of the study drug
- infections, including infections requiring oral or parenteral antibiotic treatment
- serious infections; however, no specific definition of "serious" was given
- ISRs.

Exploratory outcomes from the VISIBLE 1 study included: pharmacokinetics outcomes, with summary statistics results of serum concentrations measured on multiple doses of vedolizumab SC; immunogenicity outcomes of multiple doses of vedolizumab SC; correlation of UC-associated genetic polymorphisms and inflammation biomarkers with therapeutic response to vedolizumab SC; histological remission at week 52; and clinical remission with alternate definitions.

Statistical Analysis

Sample size and power were calculated assuming a clinical remission rate of 42% for vedolizumab and 16% for placebo at week 52, obtaining a needed sample size of 94 patients in the vedolizumab SC group and 47 patients in the placebo group to provide 90% power at a two-sided 0.05 level of significance. To ensure a randomized sample size of 188 patients, assuming 47% of the patients entering induction would achieve clinical response at week 6, the investigators projected that approximately 400 patients would need to be enrolled into the study. Using the outcome of mucosal healing — assuming a healing rate of 52% for vedolizumab and 20% for placebo at week 52 — with a sample size of 94 patients in the vedolizumab group and 47 patients in the placebo group, the first secondary end point of mucosal healing at week 52 would have a power of at least 97% at a two-sided 0.05 level of significance.

For the primary and key secondary outcomes, multiplicity was addressed using a hierarchical approach to control the overall type I error rate. In this sense, the statistical inference for the first secondary end point of mucosal healing was performed only if the primary outcome (clinical remission at week 52) was statistically significant. The second secondary outcome (durable clinical response) was tested only if the first secondary outcome was significant, the third secondary end point (durable clinical remission) only if the second secondary outcome was significant, and the fourth secondary outcome (corticosteroid-free clinical remission) was tested only if the third secondary end point was statistically significant. The main statistical comparison for all efficacy outcomes was between vedolizumab SC and placebo. Any statistical analysis of vedolizumab IV versus placebo for the efficacy outcomes was considered exploratory and not controlled for multiplicity, nor were any other exploratory outcomes. Also, no formal testing (either as superiority or noninferiority hypothesis testing) was performed for either vedolizumab SC or vedolizumab IV.

For the primary efficacy outcome of clinical remission at week 52, the proportion of patients with remission was first summarized descriptively by treatment group. Count, percentage, and associated 95% CI using the Clopper-Pearson method was provided. The primary outcome was analyzed using the Cochran-Mantel-Haenszel (CMH) test, stratified by randomization stratification factors (i.e., concomitant use of oral corticosteroids [yes/no], clinical remission status at week 6 [yes/no], and previous TNF alpha antagonist failure or concomitant immunomodulator [azathioprine or 6-MP] use [yes/no]). Investigators presented the P value and point estimate of the treatment difference based on the CMH method adjusted for stratification factors with their respective 95% CIs. If the number of patients with clinical remissions was too small (≤ 5), the Fisher's exact method with exact unconditional confidence limits was used. For secondary outcomes of efficacy, the analysis was similar to that done for the primary outcome set, that is, by using a CMH test for treatment differences, stratified by randomization stratification factors. The exact method would be performed if the number of observations was too small (≤ 5). Descriptive statistics

and 95% CIs for vedolizumab IV versus placebo were also presented for each secondary outcome.

All efficacy analyses were based on the ITT principle using the full analysis set (FAS) of patients. Missing data for dichotomous outcomes were handled using the nonresponder imputation method in which any patient with missing information was considered in the analysis to be a nonresponder or to have experienced treatment failure. Authors used a sensitivity analysis to assess the impact of drop-outs for different missing mechanisms using a hybrid approach in which discontinuation due to an AE or lack of efficacy was imputed as nonresponder (under missing not at random [MNAR]) and other discontinuations and missing data were imputed using multiple imputation (under missing at random [MAR]) for primary and all secondary efficacy outcomes. Missing data for continuous outcomes were imputed using the last available (post-baseline) observation carried forward (LOCF) method. For patients with a missing post-baseline measurement, the missing data were imputed using the baseline observation carried forward method.

Subgroup analyses were performed on the primary and all secondary end points to summarize the treatment effects across sub-populations. For these, the investigators presented the proportional treatment effects for vedolizumab SC and placebo, together with the 95% CI for each subgroup. For the subgroup analysis of the prior use of anti–TNF alpha antagonists only, nominal P values were obtained by the CMH test stratifying by baseline concomitant use of oral corticosteroids (yes/no) and remission status at week 6 (yes/no), or the Fisher's exact test in the event of a small number responders (i.e., ≤ 5). The subgroups included are:

- age (< 35, ≥ 35 to < 65, ≥ 65 years)
- sex
- race (Asian, black or African American, white, other)
- duration of UC (< 1 year, ≥ 1 to < 3 years, ≥ 3 to < 7 years, ≥ 7 years)
- geographic region (North America, South America, Western/Northern Europe, Central Europe, Eastern Europe, and Asia/Africa/Australia)
- baseline disease activity (baseline Mayo score: mild < 6, moderate = 6 to 8, severe = 9 to 12)
- baseline fecal calprotectin (≤ 250 mcg/g, > 250 to ≤ 500 mcg/g, > 500 mcg/g)
- disease localization (proctosigmoiditis, left-sided colitis, extensive colitis, or pancolitis)
- clinical remission status at week 6
- prior TNF alpha antagonist therapy (failure or naive; type of failure: inadequate response, loss of response, intolerance)
- prior immunomodulator and TNF alpha antagonist failure (yes/no)
- prior corticosteroids failure (yes/no)
- prior immunomodulator failure (yes/no)
- prior therapies: corticosteroids and immunomodulators (prior corticosteroids only, prior immunomodulators only, prior corticosteroids and immunomodulators, no concomitant corticosteroids or immunomodulators)
- worst prior treatment failure (patients with prior TNF alpha antagonist failure, patients with prior immunomodulator failure but not TNF alpha antagonist failure, patients with prior corticosteroid failure).

If the grouping variable could not be determined for a specific patient, the patient would not be included; if the number of patients in any subgroup across the three treatment arms was fewer than 10, the subgroup would not be presented.

Sensitivity analyses were conducted to test the robustness of the primary outcome. The following pre-specified sensitivity analyses were performed for primary and/or secondary efficacy end points:

- The complete Mayo score and partial Mayo score for each patient were recalculated for the post-screening visit in accordance with the FDA Ulcerative Colitis Clinical Trial Endpoints guidance. The primary efficacy end point and all secondary end points were rederived accordingly. The primary analysis was repeated for the primary efficacy end point, all secondary end points, and the subgroup analysis of the prior use of TNF alpha antagonists in the FAS using the Mayo score convention defined in the FDA UC guidance.[28]
- The primary analysis was repeated for the primary efficacy outcome using a subset of the FAS, excluding sites that reported significant non-compliance with regulatory requirements during the study.
- The primary analysis was repeated for the primary and secondary efficacy end points using the per-protocol set (PPS).
- To assess the impact of drop-outs for different missing mechanisms for binary outcomes, a hybrid approach was performed as a sensitivity analysis, where discontinuations due to an AE or lack of efficacy were imputed using the nonresponder imputation (under MNAR), and other discontinuations and missing data were imputed using multiple imputation (under MAR). For this multiple imputation, missing patient subscores for each component of the complete Mayo score were imputed by treatment group by means of a multivariate stepwise approach using fully conditional specification (FCS) (FCS ordinal logistic) methods, respectively. This sensitivity analysis was performed for the primary efficacy and all secondary outcomes.

Analysis Populations

There were four main analysis population sets: First, the FAS, which comprised all randomized patients who received at least one dose of the study drug. Patients who received only induction IV therapy and who were not randomized to the maintenance phase were not included in the FAS. Patients in this set were analyzed according to the treatment they were randomized to receive, e.g., in an ITT analysis. Second, the PPS, which was a subset of the FAS population and consisted of all patients who did not violate the terms of the protocol in a way that would impact the study output. (These decisions to exclude patients from the PPS were made before the unblinding of the study.) Third, the safety analysis set (SAF), which included all patients who were randomized to the maintenance phase and received at least one dose of the study drug (SC placebo or SC vedolizumab). Patients in this set were analyzed according to the treatment they actually received (i.e., in a per-protocol fashion). The SAS-I included all patients who received at least one induction dose but were not randomized to the maintenance phase (i.e., week 6 nonresponders). The SAS-C included all patients who received at least one dose of vedolizumab IV, that is, including the SAS and SAS-I. Lastly, there was a pharmacokinetics evaluable population comprising all randomized patients who received at least one dose of the study drug with at least one documented concentration.

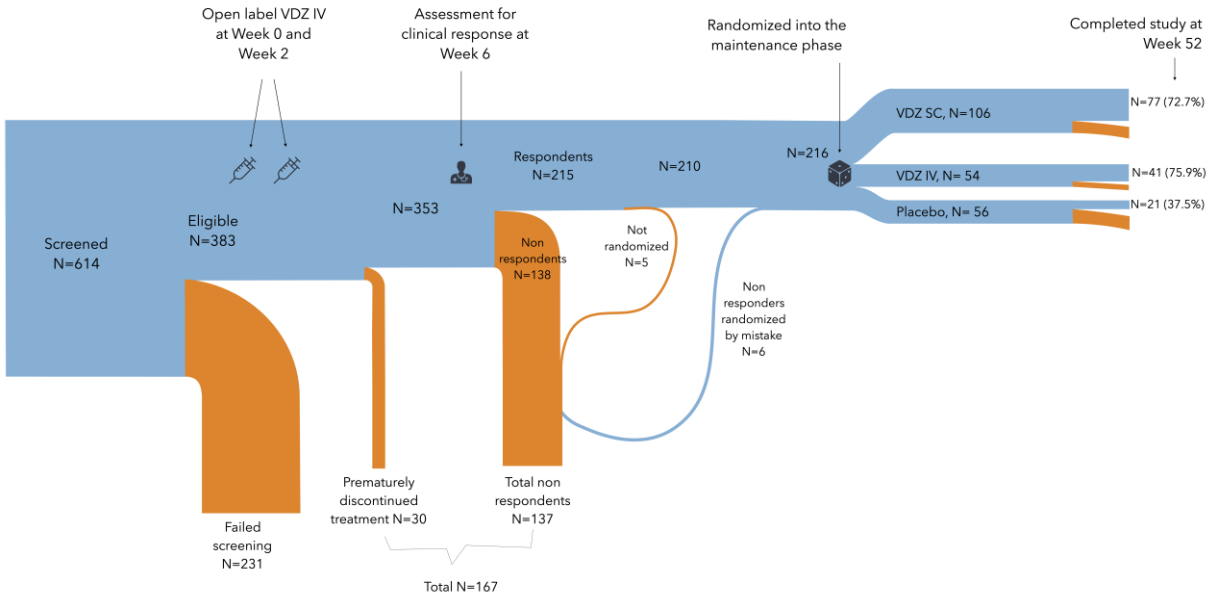
During the study, there were five protocol amendments that took place in November 2015 and in February, May, July, and September 2016, mainly to add, update, or clarify definitions and exploratory outcomes.

Results

Patient Disposition

In the VISIBLE 1 study, a total of 614 patients were screened for eligibility. Of these, 231 failed screening with the following reasons reported: did not meet enrolment criteria (n = 192); withdrew consent (n = 14); pre-treatment event (PTE)/AE (n = 8); lost to follow-up (n = 3); significant protocol deviation (n = 1); and other reason (n = 13) (Table 7). Thus, a total of 383 patients were enrolled in the open-label induction phase (Figure 3).

Figure 3: Patient Disposition in the Induction and Maintenance Phase of the VISIBLE 1 Study



Note: Blue areas represent inclusion of patients through the study up to week 52. Orange areas represent withdrawals or non-completeness of the study interventions. The height of the areas represents the number of patients through the flowchart. The horizontal timeline has been formatted and scaled down for adequate space distribution.

Source: Data obtained from the VISIBLE 1 Clinical Study Report.[1]

Of the 383 patients who received at least one vedolizumab IV induction treatment, 30 (7.8%) discontinued the induction phase due to PTE/AE or lack of efficacy; hence, 353 completed the vedolizumab IV 300 mg induction treatment. Of these 353 patients, 215 achieved a clinical response to the induction treatment, but five were not randomized (no specific reasons given). Six patients among the nonresponders, however, were randomized by mistake (3 in the vedolizumab SC group, 3 in the IV group, and 0 in the placebo group); thus, a total of 216 patients were randomly allocated to either vedolizumab SC (n = 106), vedolizumab IV (n = 54), or placebo (n = 56).

A total of 167 patients were excluded; these included the 30 patients who prematurely ceased the IV induction, plus the 143 who failed to achieve clinical response at week 6, minus the six patients who were allocated to the randomization groups by mistake. Of the 143 patients who failed to achieve a clinical response, 114 (79.7%) exhibited a clinical response at week 14 and could opt to enrol in Study SC-3030.

In the maintenance phase, 139 of 216 randomized patients (64.4%) completed the study at week 52, with 77 patients (72.7%) and 41 patients (75.9%) in the vedolizumab SC and vedolizumab IV treatment groups completing the study at week 52, respectively, while only 21 patients (37.5%) in the placebo group achieved this milestone. Of those who discontinued, the most frequent reason for discontinuation across all treatment groups was lack of efficacy, which was highest in the placebo group (80%) compared with 62.1% and 46.2% of the vedolizumab SC and vedolizumab IV groups, respectively, followed by voluntary withdrawal and AEs. AEs leading to discontinuation occurred in 14.3% of patients in the placebo group, 17.2% in the vedolizumab SC group, and 15.4% in the vedolizumab IV group (Table 8 and Figure 3).

Table 7: Patient Disposition – Induction Phase

	Vedolizumab IV 300 mg N = 167
Screened, N	614
Enrolled and treated in open-label induction phase, N	383
Completed vedolizumab IV in open-label induction phase, N	353
Prematurely discontinued vedolizumab IV in open-label induction phase	30
Reason for discontinuation of open-label vedolizumab IV in induction phase, N (%)	
Pre-treatment event/adverse event	9 (30.0)
Significant protocol deviation	4 (13.3)
Lost to follow-up	0
Voluntary withdrawal	5 (16.7)
Pregnancy	0
Lack of efficacy	9 (30.0)
Other	3 (10.0)

[a] For the induction phase, the safety analysis set consisted of all 383 patients who received at least one dose of vedolizumab IV regardless whether they entered into the maintenance phase.

Source: VISIBLE 1 Clinical Study Report.[1]

Table 8: Patient Disposition – Maintenance Phase

	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Placebo N = 56
Randomized, N (%)	106	54	56
Completed maintenance study, N (%)	77 (72.6)	41 (75.9)	21 (37.5)
Prematurely discontinued the study drug in maintenance phase, N (%)	29 (27.4)	13 (24.1)	35 (62.5)
Reason for discontinuation of the study drug in maintenance phase, N (%)			

	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Placebo N = 56
Adverse events	5 (17.2)	2 (15.4)	5 (14.3)
Lost to follow-up	0	0	0
Protocol deviation	1 (3.4)	1 (7.7)	0
Voluntary withdrawal	1 (3.4)	4 (30.8)	1 (2.9)
Pregnancy	1 (3.4)	0	0
Lack of efficacy	18 (62.1)	6 (46.2)	28 (80.0)
Other	3 (10.3)	0	1 (2.9)
ITT, N	106	54	56
PP, N	79	41	46
SAF, N [a]	106	54	56

ITT = intention to treat; PP = per protocol; SAF = safety analysis set; SC = subcutaneous.

Source: VISIBLE 1 Clinical Study Report.[1]

Exposure to Study Treatments

Study-drug exposure was defined as the total number of days on the study drug calculated as the date of the last dose of the study drug minus the date of the first dose of the study drug plus 127 days. Overall study drug compliance was defined as the total number of complete injections or infusions administered out of the total number of injections or infusions expected during study treatment. A patient must have received at least 75% of the infusion or injection for it to be considered complete.

Of the 167 week 6 nonresponders, 143 non-randomized patients (85.6%) completed all three open-label vedolizumab infusions. The week 6 nonresponders who exhibited a clinical response at week 14 were eligible to enrol in the open-label extension of Study SC-3030. Patients who were nonresponders at week 14 discontinued participation in Study SC-3027 and were not eligible for Study SC-3030.

Exposure was higher for the vedolizumab treatment groups than for the placebo treatment group when measured by either the total number of completed injections or exposure in days during the study. The lower exposure observed in the placebo group likely reflects those patients who discontinued the study early. Study-drug compliance for SC injections and IV infusions was comparable in all treatment groups. Of the 216 patients in the SAF population, treatment compliance was comparable across the treatment groups (90.22%, 92.90%, and 90.08% for placebo, vedolizumab SC, and vedolizumab IV, respectively).

Overall, there were no significant differences between groups in terms of concomitant medications. During the maintenance phase, 92.5%, 87%, and 92.6% of patients in the vedolizumab SC, vedolizumab IV, and placebo groups, respectively, had concomitant IBD medications, and all of them had at least one medication of any class during the study, with no significant differences in the type of medications between groups.

Efficacy

Only those efficacy outcomes and analyses of the subgroups identified in the review protocol are reported subsequently. See Appendix 3 for detailed efficacy data. Clinical

response from the induction phase occurred in 215 out of 383 patients (56.1%) receiving the open-label IV dose of vedolizumab.

Clinical Remission

At week 52, patients receiving vedolizumab SC maintenance treatment were more likely to show clinical remission (49 out of 106 patients [46.2%]) when compared with placebo (8 of 56 [14.3%]), with an adjusted RD of 32.3% (95% CI, 19.7% to 45.0%; P < 0.001) (Table 9). Clinical remission rates were greater in the vedolizumab SC group compared with placebo in both the anti–TNF naive (RD = 32.1%; 95% CI, 15.2% to 49.0%) and anti–TNF failure subgroups (RD = 28.1%; 95% CI, 1.3% to 52.9%). No formal hypothesis testing was performed on rates of clinical remission between the vedolizumab SC (46.2%) and vedolizumab IV (42.6%) groups. Sensitivity analyses conducted in accordance with the 2016 FDA draft UC guidance and those set a priori showed results consistent with the primary efficacy outcome. Similarly, subgroup analyses demonstrated that, in all subgroups, the proportion of patients in clinical remission at week 52 favoured vedolizumab SC versus placebo.

Clinical Response

This outcome was defined as durable clinical response (i.e., a reduction in complete Mayo score of ≥ 3 points and ≥ 30% reduction from baseline with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point) at weeks 6 and 52. Patients receiving vedolizumab SC maintenance treatment were more likely to achieve a durable clinical response (64.2%) than patients on placebo (28.6%), with an adjusted RD of 36.1% (95% CI, 21.2 to 50.9; P < 0.001), while patients in the vedolizumab IV group achieved a 72% response rate. No statistical comparison between vedolizumab SC and IV was conducted. On sensitivity analyses, vedolizumab SC showed similar superiority over placebo in achieving a durable clinical response when the Mayo score calculation was performed in accordance with the FDA UC guidance; also, the proportion of patients with a durable clinical response at week 52 in the PPS population was similar to that of the FAS population, and were similar when assessing the impact of drop-outs for different missing mechanisms. Subgroup analyses also showed no difference in effect estimates based on age, race, duration of UC, and the rest of the variables assessed.

Health-Related Quality of Life

During the induction phase, the IBDQ and EQ-5D VAS instrument scores increased by week 6 in all patients after the open-label vedolizumab IV induction at weeks 0 and 2, where higher scores mean improvement in quality of life.

During maintenance treatment, IBDQ scores in patients in the placebo group increased to a lesser degree compared with the vedolizumab SC group. In the placebo group, the score increased from a mean of 113.8 points (standard deviation [SD] = 33.9) at week 0 to 135.1 points (SD = 44.35) at week 52, a change from baseline of 21.47 points (SD = 5.43). In the vedolizumab SC group, the IBDQ score increased from a mean of 117.1 points (SD = 32.2) at week 0 to 180.6 points (SD = 39.7) at week 52, a change from baseline of 65.3 points (SD = 3.94) with a mean difference of 43.87 points (SD = 6.71; P < 0.001) in change from baseline, thus favouring the vedolizumab SC group over the placebo group.

Similarly, when measuring the EQ-5D total index score, all patients improved after the open-label induction phase and were similar at week 6 in all three treatment groups. During

the maintenance phase, the scores gradually decreased (worsened) in the placebo group, while in both vedolizumab treatment groups, the EQ-5D was maintained up to week 52. A similar trend was observed in the EQ-5D VAS score analysis and in the EQ-5D subscore analyses (Table 9).

Need for Colectomy

There were no reports of patients undergoing a colectomy during the study and follow-up.

Mucosal Healing

The proportion of patients with mucosal healing — defined as a Mayo endoscopic subscore of 1 or less — at week 52 was greater in the vedolizumab SC group (56.6%) as compared with the group on placebo (21.4%), with an adjusted difference favouring vedolizumab treatment over placebo (adjusted RD = 35.7%; 95% CI, 22.1 to 49.3; P < 0.001), while 53.7% of patients in the vedolizumab IV arm had mucosal healing. Also, in the analysis of the PPS population, the results were similar to those of the FAS population. Other results of sensitivity analyses were consistent with the primary analysis of the FAS. No differences were noted in any of the subgroup variables analyzed by the investigators.

Work Productivity

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. Patients treated with vedolizumab SC had a greater improvement (a decrease of −39.5 [SD = 30.8] points from baseline) in their WPAI-UC total score compared with placebo (a decrease of −13.5 [SD = 34.9] points from baseline). The effect estimate in the vedolizumab SC group was similar to that of the vedolizumab IV group.

Other Exploratory Outcomes and Subgroup Analyses

There were other key exploratory outcomes in the VISIBLE 1 study, as well as in the subgroup analyses assessed by the investigators. Among these:

- The proportion of patients who were in clinical remission in at least 60% and 80% of clinic visits during the maintenance phase of the study, analyzed based on the partial Mayo score, where a higher proportion of vedolizumab SC–treated patients had clinical remission compared with placebo-treated patients.
- An alternative clinical remission definition using a modified Mayo score based on the FDA guidance on UC clinical trial end points. The proportion of patients in clinical remission was greater with vedolizumab SC over placebo (P < 0.001) in all sensitivity analyses using the alternative definitions, in accordance with the FDA draft UC guidance.
- Durable clinical remission in patients who achieved remission at week 6. This subgroup analysis included only patients who were in clinical remission at week 6. Of these patients, 12.0% in the placebo group maintained clinical remission at week 52 versus 29.8% in the vedolizumab SC group.
- Time from randomization to disease worsening (defined as an increase in partial Mayo score of ≥ 3 points from the week 6 value on two consecutive visits or an increase to a score of 9 points on two consecutive visits if the week 6 value was > 6) and a minimum partial Mayo score of 5 or higher. The hazard ratio for vedolizumab SC versus placebo was 0.21 (95% CI, 0.0 to 1.2). However, the number of events was too small for an adequate interpretation.

- Time from randomization to treatment failure (defined as disease worsening, need for rescue medications, or surgical intervention for treatment of UC). Also, there was a limited number of events to interpret the data.
- Clinical remission at week 52 and corticosteroid-free for 90 and 180 days. These were the proportions of patients who achieved corticosteroid-free remission and were corticosteroid-free for 90 days and 180 days before week 52. The proportion of patients who achieved clinical remission and were corticosteroid-free for 90 days was numerically higher in the vedolizumab SC group (26.7%) than in the placebo group (8.3%).
- Reduction in oral corticosteroid use. As stated in the protocol, patients started on corticosteroids tapered at week 6 if they achieved clinical response. Patients in the vedolizumab SC treatment group appeared to have greater reductions in mean corticosteroid dose (expressed as mg/day of prednisone or equivalent) compared with placebo in an LOCF analysis.
- Reduction in fecal calprotectin. The investigators calculated the proportion of patients in the least-severe category (< 250 mcg/g) from week 6 to week 30 and week 52. The percentage of patients in this category continued to increase with vedolizumab SC maintenance treatment (40.2%, 55.6%, and 69.4%, respectively). In the placebo group, a lower increase in the same category occurred (30.0%, 39.1%, and 44.4% at weeks 6, 30, and 52, respectively).
- Histological remission, defined by a Geboes criteria grade below 2 or by a Robarts histopathology index, was assessed. However, the number of patients achieving histological remission (one in the placebo group and one in the vedolizumab IV group) was too small for a proper interpretation of the results.
- The number of hospitalizations related to UC was lower in the vedolizumab SC group (3 of 106 [2.8%]) than in the placebo group (6 of 56 [10.7%]). However, the number of events was also considered small.
- Pharmacokinetic outcomes. Median vedolizumab trough serum concentrations at week 46 in patients receiving vedolizumab SC 108 mg every two weeks were 3.5-fold higher than trough serum concentrations for patients receiving vedolizumab IV 300 mg every eight weeks.

As exploratory subgroup analyses, the primary and pre-specified secondary outcomes (clinical remission at week 52, mucosal healing at week 52, durable clinical response, durable clinical remission, and corticosteroid-free clinical remission at week 52), were analyzed by treatment group for patients who were anti–TNF naive and those classified as anti–TNF experienced population. For the analyses of the primary and secondary outcomes in patients who were anti–TNF naive, the treatment differences between vedolizumab SC and placebo were generally consistent with those observed in the FAS population. Vedolizumab SC was superior to placebo for all of these outcomes. However, for both subgroups, the number of patients with durable clinical remission and those included in the analyses of corticosteroid-free remission were small, giving imprecise results.

Table 9: Efficacy Outcomes – Maintenance Phase (ITT)

	VISIBLE 1		
	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Placebo N = 56
Clinical remission at week 52			
Patients achieving clinical remission, n (%)	49 (46.2)	23 (42.6)	8 (14.3)
Adjusted difference versus placebo (95% CI)[a]	32.3 (19.7 to 45.0)	27.9 (12.3 to 43.5)	–
P value, vedolizumab versus placebo[b]	< 0.001	< 0.001	–
Durable clinical response at week 52[c]			
Patients achieving a durable clinical response, n (%)	68 (64.2)	39 (72.2)	16 (28.6)
Adjusted difference versus placebo (95% CI)[a]	36.1 (21.2 to 50.9)	44.5 (28.3 to 60.6)	–
P value, vedolizumab versus placebo[b]	< 0.001	< 0.001	–
Corticosteroid-free remission at week 52			
Patients achieving corticosteroid-free remission, n (%)	13 (28.9)	6 (28.6)	2 (8.3)
Difference versus placebo (95% CI)[a]	20.6 (–4.5 to 43.7)	20.2 (–9.8 to 47.8)	–
P value, vedolizumab versus placebo[b]	0.067	0.121	–
Mucosal healing			
Patients achieving mucosal healing at week 52, n (%)	60 (56.6)	29 (53.7)	12 (21.4)
Adjusted difference versus placebo (95% CI)[a]	35.7 (22.1 to 49.3)	32.2 (15.7 to 48.7)	–
P value, vedolizumab versus placebo[b]	< 0.001	< 0.001	–
Need for colectomy			
Patients requiring a colectomy, n (%)	0	0	0
IBDQ total score			
Baseline (week 0)			
N	105	54	55
Mean (SD)	117.15 (32.26)	108.51 (33.45)	113.82 (33.99)
Week 52			
N	106	54	56
Mean (SD)	180.65 (39.72)	170.65 (43.09)	135.16 (44.35)
Change from baseline to week 52[d]			
N	105	54	55
LS mean (SE)	65.33 (3.94)	58.60 (5.50)	21.47 (5.43)
LS mean difference (SE); vedolizumab versus placebo	43.87 (6.71)	37.13 (7.72)	–
P value	< 0.001	< 0.001	–
EQ-5D total index score			
Baseline (week 0)			
N	105	54	55
Mean (SD)	0.764 (0.159)	0.744 (0.181)	0.722 (0.175)
Week 52			
N	87	43	36

	VISIBLE 1		
	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Placebo N = 56
Mean (SD)	0.914 (0.131)	0.882 (0.122)	0.815 (0.141)
Change from baseline to week 52			
N	86	43	35
Mean (SD)	0.141 (0.201)	0.143 (0.195)	0.075 (0.206)
WPAI-UC total score			
Baseline (week 0)			
N	105	54	54
Mean (SD)	56.6 (24.68)	57.0 (24.70)	55.0 (23.13)
Week 52			
N	87	43	36
Mean (SD)	16.6 (22.09)	17.7 (21.80)	36.9 (32.32)
Change from baseline to week 52			
N	86	43	34
Mean (SD)	–39.5 (30.87)	–39.3 (29.79)	–13.5 (34.98)

CI = confidence interval; EQ-5D = EuroQoL-5 Dimensions; IBDQ = Inflammatory Bowel Disease Questionnaire; ITT = intention to treat; LS = least squares; SC = subcutaneous; SD = standard deviation; SE = standard error; TNF = tumour necrosis factor; WPAI-UC = Work Productivity and Activity Impairment – Ulcerative Colitis.

[a] The 95% CIs of the clinical remission rate at week 52 were based on the Clopper-Pearson method. The 95% CI of the adjusted difference was based on the normal approximation method, or the exact method if the number of remissions in either treatment group was ≤ 5.

[b] P values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization strata (concomitant use of corticosteroids, clinical remission status at week 6, and previous TNF alpha antagonist failure or concomitant immunomodulator use) or Fisher's exact test if the number of remissions in either treatment group was ≤ 5.

[c] Defined as durable clinical response, i.e., clinical response at week 6 and 52.

[d] Based on last observation carried forward (LOCF). LS means and P values were obtained using an analysis of covariance model with treatment as a factor and baseline/week 6 score as a covariate. Higher scores indicate a higher quality of life.

Source: VISIBLE 1 Clinical Study Report.[1]

Harms

Only those harms identified in the review protocol are reported subsequently. See Table 10 for detailed harms data.

Adverse Events

A TEAE was defined as any AE whose date of onset occurred after the first dose of the study drug in the induction phase through 126 days after the last dose study drug, or before the first dose in the open-label Study SC-3030, whichever was earlier. A related TEAE was a TEAE that was considered by an investigator to be related to the study drug.

During the induction phase, out of 167 patients, 87 (52.1%) reported at least one AE, with most patients (72 out of 87) experiencing AEs that were mild to moderate in intensity, and 17 (10.2%) experiencing one or more SAEs; 5 of these 17 patients (2.9%) discontinued the study drug due to the SAE (Table 10).

Based on the SAS population, the percentages of randomized patients who experienced at least one AE was similar between the placebo (76.8%) and vedolizumab IV (75.9%) groups, but lower in the vedolizumab SC group (65.1%). The number of placebo patients

who had AEs leading to the stopping of the study medication (8.9%) was nearly twice that of the vedolizumab SC (4.7%) and vedolizumab IV (3.7%) treatment groups. The most common event was anemia, followed by UC and infections (Table 10).

Approximately 10% of patients experienced an SAE and the frequency of this was comparable across all treatment groups.

No deaths occurred during the study. A sizable proportion of patients (56%) experienced AEs that were mild (28.2%) to moderate (27.9%) in intensity.

Among the notable harms, specified a priori by CADTH, very few to no events of serious infections, malignancies, major adverse cardiovascular events, or thrombosis were noted. Hypersensitivity reactions were less common in the placebo group (3.6%) compared with the vedolizumab SC (15.1%) and vedolizumab IV groups (13.0%).

Table 10: Summary of Harms (SAF Population Set)

	Induction	Maintenance			
	Vedolizumab IV 300 mg N = 167	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Placebo N = 56	Total N = 216
Patients with ≥ 1 adverse event					
n (%)	87 (52.1)	69 (65.1)	41 (75.9)	43 (76.8)	153 (70.8)
Patients with any of the most frequent TEAEs	–	43 (40.6)	31 (57.4)	32 (57.1)	106 (49.1)
Most common events[a]					
Anemia	–	6 (5.7)	5 (9.3)	2 (3.6)	13 (6.0)
Colitis, ulcerative	–	15 (14.2)	6 (11.1)	18 (32.1)	39 (18.1)
Infections and infestations	–	21 (19.8)	15 (27.8)	14 (25.0)	50 (23.1)
Nasopharyngitis	–	11 (10.4)	10 (18.5)	11 (19.6)	32 (14.8)
Upper respiratory tract infection	–	10 (9.4)	2 (3.7)	1 (1.8)	13 (6.0)
Sinusitis	–	1 (0.9)	0	3 (5.4)	4 (1.9)
Urinary tract infection	–	0	4 (7.4)	2 (3.6)	6 (2.8)
Alanine aminotransferase increased	–	1 (0.9)	3 (5.6)	0	4 (1.9)
Blood creatine phosphokinase increased	–	1 (0.9)	3 (5.6)	1 (1.8)	5 (2.3)
Arthralgia	–	6 (5.7)	4 (7.4)	1 (1.8)	11 (5.1)
Headache	–	9 (8.5)	0	6 (10.7)	15 (6.9)
Insomnia	–	1 (0.9)	3 (5.6)	0	4 (1.9)
Rash	–	1 (0.9)	3 (5.6)	1 (1.8)	5 (2.3)
Patients with ≥ 1 SAE					
n (%)	17 (10.2)	10 (9.4)	7 (13.0)	6 (10.7)	23 (10.6)
Discontinuation of drug due to SAE	5 (3.0)	1 (0.9)	2 (3.7)	1 (1.8)	9 (2.3)
Most common events[a]					
Colitis, ulcerative		3 (2.8)	1 (1.9)	5 (8.9)	9 (4.2)
Patients who stopped treatment due to adverse events					
n (%)	9 (5.4)	5 (4.7)	2 (3.7)	5 (8.9)	12 (5.6)
Most common events[a]					

	Induction	Maintenance			
	Vedolizumab IV 300 mg N = 167	Vedolizumab SC 108 mg N = 106	Vedolizumab IV 300 mg N = 54	Placebo N = 56	Total N = 216
Colitis, ulcerative	5 (2.9)	4 (3.8)	1 (1.9)	5 (8.9)	10 (4.6)
Deaths					
n (%)	0	0	0	0	0
Notable harms					
Serious infections, n (%)	–	3 (2.8)	0	0	3 (1.4)
Malignancies, n (%)	–	0	1 (1.9)	0	1 (0.5)
Hypersensitivity/anaphylactic reactions, n (%)	–	16 (15.1)	7 (13.0)	2 (3.6)	25 (11.6)
MACE, n (%)	–	0	0	0	0
Thrombosis (any kind), n (%)	–	1 (0.9)	1 (1.9)	0	2 (0.9)

MACE = major adverse cardiovascular event; SAE = serious adverse event; SAF = safety analysis set; TEAE = treatment-emergent adverse event.

[a] Frequency > 5%.

Source: VISIBLE 1 Clinical Study Report.[1]

Critical Appraisal

Internal Validity

The VISIBLE 1 trial was the only study included in this review. This was a properly conducted study with a low risk of bias from the randomization process. The investigators adequately produced a randomization sequence, with proper concealment of the random sequence using a central randomization scheme, under the supervision of the sponsor, by means of an IWRS until participants were enrolled and assigned to the interventions. The differences noted in the characteristics of patients after the induction phase and measured at the baseline of the maintenance phase were small and unlikely to have a meaningful impact on the validity of the results. The blinding of participants, clinicians, and researchers was achieved through identical placebo and vedolizumab presentations, which avoided important and unbalanced deviations from the intended interventions. There is no evidence that participants were aware of their assigned intervention due to the double-dummy design of the trial. Patients who stopped or deviated from the interventions were properly accounted for and analyzed based on an ITT principle.

Multiplicity was properly considered, and adequate tests were conducted (i.e., the hierarchical approach used) to control for an overall type I error rate.

For the maintenance phase, 64.4% completed treatment: 37.5% in the placebo group, 71.7% in the vedolizumab SC group, and 75.9% in the vedolizumab IV group. The main reason for discontinuation in the maintenance phase was lack of efficacy (by 28, 18, and 6 patients on placebo, vedolizumab SC, and vedolizumab IV, respectively), followed by voluntary withdrawal and AEs. This difference in missing data could bias the results (toward the null), although the authors performed appropriate sensitivity analyses (considering all missing data as treatment failures).

Outcomes were objectively obtained with validated tools (see Appendix 4) and the processes to carry out outcome measurements were well described and assessed in a blinded fashion. There is a low risk of bias due to the selection of the reported results. A

protocol was well described, and the results presented followed the pre-specified analysis plan. As mentioned before, there were some amendments during the study, but these were well addressed and unlikely to affect the end results or imply bias due to selection of participants.

The use of separate induction and maintenance studies is consistent with European Medicines Agency guidance and is similar to other studies assessing drugs for the treatment of UC. This design is reasonable because these are also the group of patients who would be continuing treatment in clinical practice.

Subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary and all secondary outcomes based on age, sex, race, duration of UC, geographic region, baseline disease activity, baseline fecal calprotectin, disease localization, clinical remission status at week 6, prior TNF alpha antagonist therapy, prior immunomodulator and TNF alpha antagonist failure, prior corticosteroid failure, prior immunomodulator failure, concomitant therapies, and worst prior treatment failure. Because the sample size of the subgroups precludes a proper interpretation of the data, even though the clinical rationale for the analysis of subgroups is sound, the analyses can be considered underpowered to detect a significant effect from modifiers (Appendix 3).

The VISIBLE 1 study was powered to assess the primary outcome of clinical remission after 52 weeks but was not sufficient to assess other secondary end points. This limitation contributed to the findings of numerically greater but not statistically significant differences between treatment arms for some secondary end points, such as durable clinical remission and corticosteroid-free clinical remission. The lack of formal testing between the vedolizumab SC and vedolizumab IV groups (i.e., no formal hypothesis testing for noninferiority was planned) precludes any statistical and clinically meaningful comparison between the IV and SC formulations, although numerically similar outcomes were observed.

External Validity

The populations included in the VISIBLE 1 trial are to an extent, and within the limitations of a controlled setting of a clinical trial, similar to what is encountered in clinical practice and relevant to the population of interest for this review, which focuses in the SC administration and specific doses that are in accordance with what has been approved by Health Canada and planned to be used in real-life practice. However, adherence could be overstated, as it is in well-controlled randomized trials; hence, generalizability might be an issue when the medication is applied in real clinical settings. In the same vein, a possible limitation of the VISIBLE 1 study is that all patients enrolled in the maintenance phase can be considered a select population due to the inclusion of patients whose condition responded to the induction IV therapy and who were able to tolerate treatment with vedolizumab.

The amount and type of co-interventions allowed during the study can be considered close to what happens in clinical practice, although more frequent clinical visits and assessments can be overestimated. Patients needed little training to apply the SC vedolizumab doses and, apparently, the study participants performed well in this sense. It is likely this training would be similar in real clinical practice.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

Vedolizumab has been approved by Health Canada for the treatment of adult patients with moderate-to-severe active UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist. Vedolizumab is a monoclonal antibody that is an integrin antagonist. There are presently six other approved biologic UC treatments is Canada. Given that other treatments are already on market and there is an absence of head-to-head studies with the exception of a single vedolizumab IV head-to-head study, the objective of this section is to critically appraise the sponsor-submitted NMA that assesses the efficacy of vedolizumab compared with other biologic treatments and tofacitinib.

Description of Indirect Comparison

The sponsor-submitted NMA involves a systematic review and analysis aimed at evaluating the efficacy of vedolizumab compared with other biologics and tofacitinib for the treatment of moderate-to-severe UC.[2]

Table 11: [redacted]

[redacted]	[redacted]
[redacted]	• [redacted] • [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

Table 12: [redacted]

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

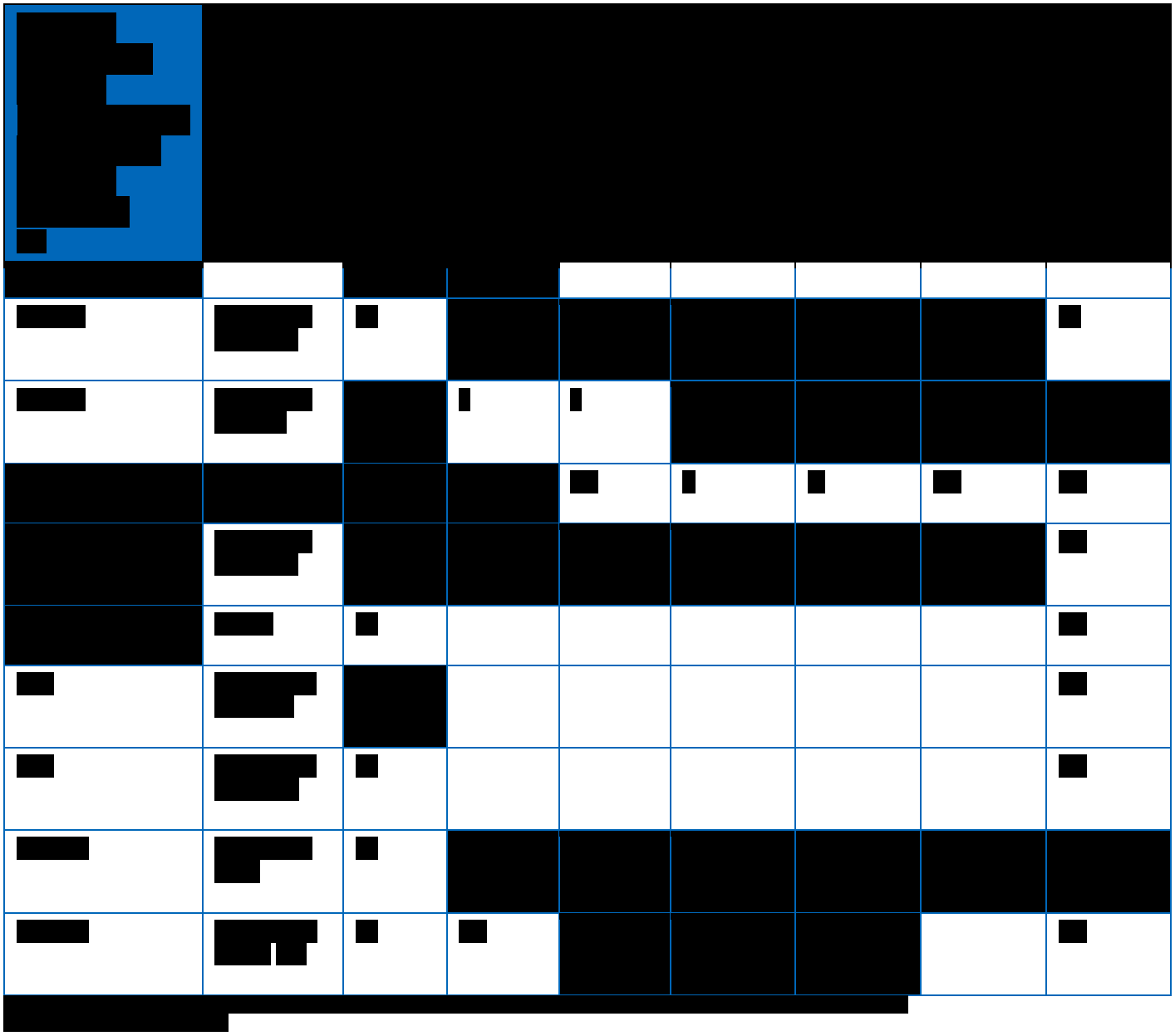

Figure 4: [redacted]

[redacted]

Figure 5: [redacted]

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Figure 6: [redacted]

[redacted]

[redacted]

Table 13: [redacted]

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Figure 7: [redacted]

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Figure 8: [redacted]

[redacted]

Source: Sponsor submitted NMA[2]

[redacted]

[redacted]

Figure 9: [redacted]

[redacted]

[redacted]

[redacted]

Figure 10: [redacted]

[redacted]

[redacted]

Critical Appraisal of the NMA

[redacted] However, due to limitations of the submitted NMA, the results should be interpreted with caution. These limitations hinder the potential applicability of the comparative results. The major concerns with the submitted NMA are related to the transparency and quality of the literature review, the limited size of the evidence base, and heterogeneity across trials in both design and populations.

Among the limitations, there is no information given on how the studies were located. Also, no specific inclusion and exclusion criteria were presented. This lack of transparency in the literature review introduces the potential for bias and provides little ability to appraise the selection of trials. It does raise the potential of including or excluding trials that may vary the results, and this risk is even more pronounced given the limited evidence base of only [redacted]. Importantly, when compared with other recently conducted analyses, we noted that other systematic reviews also found limited studies. Importantly, when compared with other reviews, this review was not an exact match. Given the small number of trials included in the evidence base, there is the potential that one or two trials would vary the results. For example, a recent systematic review with a similar research question found 17 different clinical trials and, of those, three were not included in the submitted NMA. [redacted]. In addition to the lack of transparency in the literature reviews, there was also no screening for or assessment of bias in the included studies. This should be a standard practice to minimize bias when selecting studies for inclusion, and greater clarity is required. Lastly, there is a concern with the statistical analysis completed due to the lack of transparency and evidence of potential poor quality in the analysis conducted.

A significant concern with the NMA presented is that the studies included in the analyses were highly heterogeneous in terms of both study design and patient characteristics. The major concern with design heterogeneity is how trials transition from the induction to the maintenance phase. For example, in five of the trials, the patients are re-randomized between phases that include only responders, while the other trials allowed the nonresponders to continue through. This difference in design may vary the response between groups and may not allow groups to be comparable. Additionally, there are differences in outcome definitions, which may also make it more challenging to compare across trials indirectly in meaningful ways. For example, the VARSITY trial (vedolizumab versus adalimumab), the only head-to-head trial in the network, used only a partial Mayo score, which may limit the ability to compare between trials. Additionally, significant differences were noted in baseline characteristics, including factors that may be associated with disease severity such as age, C-reactive protein, prior treatment failure, and years of active disease. Hence, caution is warranted in drawing firm conclusions.

The analysis of [redacted] presented was limited by the size of the evidence base. Importantly, due to the small evidence base and low incidence of serious events across all studies, the results of this analysis are largely non-informative. This is especially true when looking at comparative safety issues, especially for inclusion in economic models and comparative efficacy studies, resulting also in imprecision due to small effect sizes and large credible intervals. This analysis also did not report or conduct any analyses related to safety, particularly on tolerability, which is an important consideration when comparing drugs within a drug class and indication. Additionally, analyses of discontinuation due to AEs would have been an important outcome measure that was also not included in the submitted analysis.

Summary

Based on the results of the submitted NMA [redacted] Little can be said about the study drug's efficacy or safety compared with other products based solely on this submitted NMA. The applicability of the sponsor's NMA is impacted by the lack of transparency in the systematic

review, limited size of the evidence base (i.e., small effect sizes and large credible intervals), potential limitations in the submitted analysis, and heterogeneity in trial design and patient populations across trials. Overall, the results of this analysis must be interpreted with caution.

Other Relevant Evidence

This section includes the submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

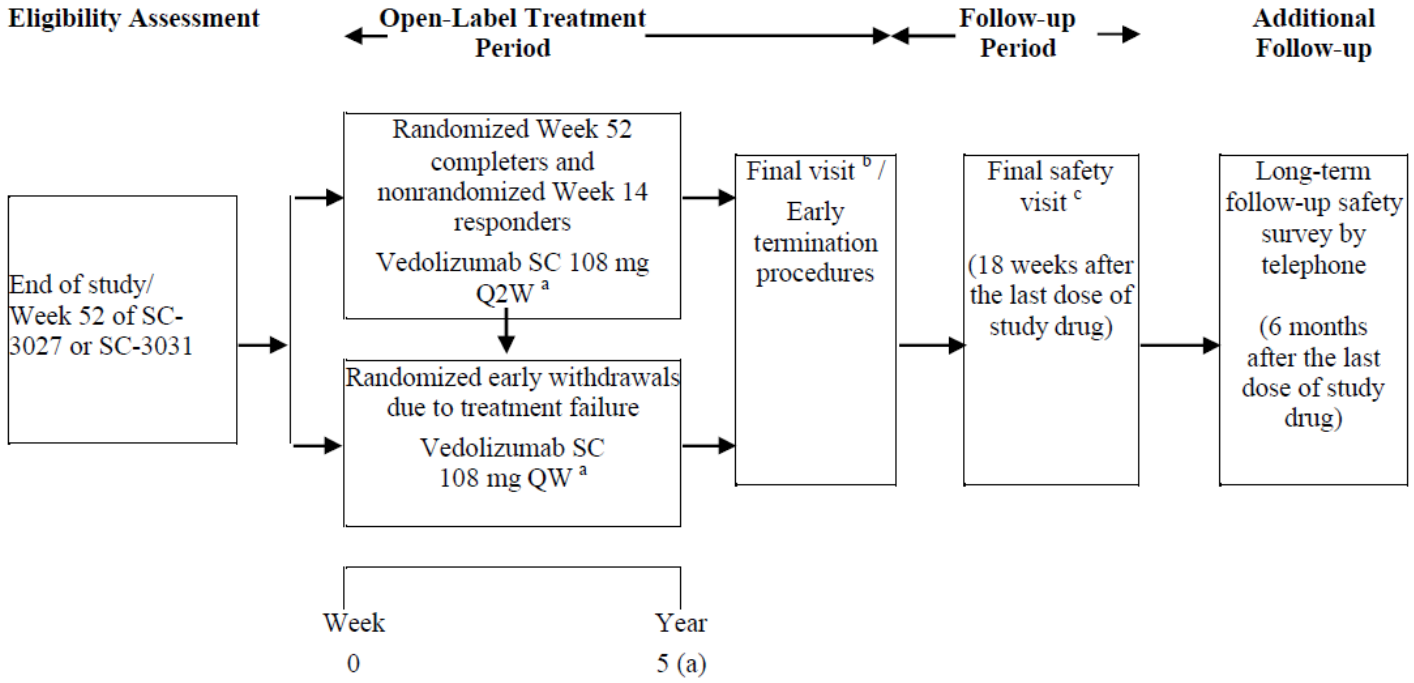
VISIBLE 1 Long-Term Extension Study

Study SC-3030 is an open-label long-term extension study of VISIBLE 1 (Study SC-3027) to determine the long-term safety and efficacy of vedolizumab SC in patients with UC and was ongoing at the time of this review (Study SC-3030; NCT02620046; estimated completion date of February 2022). The sponsor provided data from two interim analyses: the first had a cut-off date of May 31, 2018 and the second had a cut-off date of May 17, 2019. Of note, the efficacy outcomes, including patient-reported outcomes, were not included in the second interim analysis. As a result, the cut-off date for the safety analysis reviewed subsequently is May 17, 2019 (the second interim analysis), and the cut-off date for the efficacy analysis is May 31, 2018 (the first interim analysis).[27]

Methods

The VISIBLE 1 long-term extension study, Study SC-3030, is a phase IIIb, open-label extension study to gather long-term safety and efficacy data for vedolizumab SC in patients with UC who participated in the VISIBLE 1 base study (Study SC-3027).[27] Patients were eligible to enter the extension study if they participated in the maintenance phase of the VISIBLE 1 base study (i.e., were part of the randomized population) or if they did not achieve a clinical response at week 6 of the base study but achieved a clinical response at week 14 after a third vedolizumab IV induction dose (i.e., the nonrandomized population). Patients in the extension study received open-label vedolizumab SC 108 mg either every week or every two weeks. Participants continue the study drug for up to five years. Participants complete a final safety visit 18 weeks after the last dose of vedolizumab SC while on the study, followed by a six-month safety survey. The last dose of the study drug was defined as the last dose before study completion, or the last dose before an early withdrawal time point. An overview of the study design is depicted in Figure 11, and details of the study can be found in Table 14.[27]

Figure 11: Study Design of VISIBLE 1 Long-Term Extension Study



QW = every week; Q2W = every two weeks; SC = subcutaneous.

Source: Interim case study report for VISIBLE 1 long-term extension study.[27]

Table 14: Details of the VISIBLE 1 Long-Term Extension Study

		VISIBLE 1 Long-term Extension Study
Designs and Populations	**Study design**	Open-label long-term extension study
	Locations	164 sites in US, Canada, Australia, Europe, Japan, Korea, South Africa, UK, Brazil, Mexico
	Sample size	N = [redacted]
	Inclusion criteria	Patients with UC who participated in the VISIBLE 1 base study, including: • participants who withdrew early from the base study due to treatment failure during the maintenance phase (as determined by disease worsening or need for rescue medications from week 14) • participants who did not achieve a clinical response at week 6 and were not randomized to the maintenance phase but achieved a clinical response at week 14 after receiving a third open-label vedolizumab IV infusion
	Exclusion criteria	• Patients who required surgical intervention for UC during or after participation in the VISIBLE 1 base study or were anticipated to require surgical intervention for UC during this study • Patients who withdrew from the base study due to a study drug–related AE
Drugs	**Intervention**	• **Randomized study completers:** Vedolizumab SC 108 mg q.2.w. • Participants who experience treatment failure (i.e., disease worsening or need for rescue medications) may undergo a dose escalation to receive vedolizumab SC 108 mg q.w. • Randomized early terminators: Vedolizumab SC 108 mg q.w. • Nonrandomized late responders: Vedolizumab SC 108 mg q.2.w.

		VISIBLE 1 Long-term Extension Study
Duration	**Treatment phase**	Up to 5 years
	Safety follow-up	18 weeks and 6 months after the last dose of vedolizumab SC
Outcomes	**Primary End point**	Patient year–adjusted TEAEs and SAEs
	Other End points	**Secondary end points:** • patient year–adjusted AESIs • proportion of patients achieving clinical response (defined as a reduction in partial Mayo score of ≥ 2 points and ≥ a 25% reduction from baseline with an accompanying decrease in rectal bleeding score of ≥ 1 or an absolute rectal bleeding subscore of ≤ 1) • proportion of patients achieving clinical remission (defined as a partial Mayo score of ≤ 2 and no individual subscore > 1 point) • change from baseline in IBDQ total and subscale scores • change from baseline in EQ-5D utility and VAS scores • change from baseline in WPAI-UC scores • time to major UC-related events (hospitalizations, bowel surgeries, and procedures) **Exploratory end points:** • reduction in corticosteroid use during long-term vedolizumab SC treatment • immunogenicity of long-term vedolizumab SC treatment in patients with UC • vedolizumab SC serum concentrations • biomarkers of inflammation associated with loss of clinical efficacy during long-term vedolizumab SC treatment

AE = adverse event; AESI = adverse event of special interest; EQ-5D = EuroQol 5-Dimensions; IBDQ = Inflammatory Bowel Disease Questionnaire; q.2.w. = every two weeks; q.w. = every week; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event; UC = ulcerative colitis; VAS = visual analogue scale; WPAI-UC = Work Productivity and Activity Impairment – Ulcerative Colitis.

Source: Interim case study report for the VISIBLE 1 long-term extension study.[27]

Populations

Inclusion and Exclusion Criteria

The following three groups of patients were eligible for the VISIBLE 1 long-term extension study:[27]

- **Randomized study completers:** Patients with UC who completed the maintenance phase of the VISIBLE 1 base study up to week 52.
- **Randomized early terminators:** Patients with UC who withdrew from the maintenance phase of the VISIBLE 1 base study due to disease worsening or need for rescue medications.
- **Nonrandomized late responders:** Patients with UC who did not achieve a clinical response at week 6 in the induction phase of the VISIBLE 1 base study but achieved a clinical response at week 14 after receiving a third vedolizumab IV induction dose at week 6.

Patients who withdrew from the base study due to a drug-related AE were not eligible to enter the extension study. Additionally, patients who required surgical intervention for UC during or after participation in the VISIBLE 1 base study or were anticipated to require surgical intervention for UC during this study were not eligible to enter the extension study.[27]

Baseline and Demographic Characteristics

[redacted] Data are reported by previous treatment group in the base study, i.e., placebo, vedolizumab SC 108 mg every two weeks, and vedolizumab IV 300 mg every eight weeks, including the group that received only three vedolizumab IV induction doses, i.e., the nonrandomized late responders.[27] Unless otherwise specified, baseline was defined as the last assessment before the first dose of the study drug in the VISIBLE 1 base study. [redacted]

Table 15: [redacted]

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[redacted]

Table 16:

Table 17:

Interventions

All patients enrolled in the extension study were administered open-label vedolizumab SC 108 mg every two weeks, with the exception of the early terminators, who were administered vedolizumab SC 108 mg weekly. Patients who experience treatment failure (i.e., disease worsening or need for rescue medication) while receiving vedolizumab SC 108 mg every two weeks during the open-label extension study are permitted a dose escalation to vedolizumab SC 108 mg weekly. Disease worsening was defined as in the base study: an increase of three or more points from the week 0 value in partial Mayo score on two consecutive visits (or an increase to nine points on two consecutive visits if the week 0 value was greater than 6), and a minimum partial Mayo score of 5 or higher. Patients who completed the base study (i.e., the randomized population) or terminated the base study early (i.e., early terminators) received their first dose of open-label vedolizumab SC four weeks after the last dose of the study drug or placebo in the base study. For the late responders, patients received their first open-label vedolizumab SC dose within seven days of week 14 of the base study; these patients received training on how to inject the SC dose, while the injection-experienced patients received a training refresher.[27]

Background therapy, including oral or topical 5-aminosalicylates compounds, topical corticosteroids, probiotics, antidiarrheals, antibiotics, azathioprine or 6-MP, or methotrexate were permitted, provided the patients were receiving this medication at a stable dose during the base study.[27] Oral corticosteroids were permitted but could not be increased above the dose at week 0 through six months after enrolment. [redacted] A concomitant medication was defined as a medication that was ongoing as of day 1, ended on or after day 1, or started on or after day 1 of the open-label extension study and started no more than 127 days after the last dose of the study drug. [redacted]

Table 18: [redacted]

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Outcomes

The primary objective of the VISIBLE 1 open-label extension study was to obtain data on the long-term safety and tolerability of vedolizumab SC.[27] The primary end point is patient year–adjusted TEAEs. Secondary efficacy outcomes include patient year–adjusted AEs of special interest, clinical response and clinical remission. Additional secondary end points include changes from baseline in IBDQ total and subscale scores, EQ-5D utility and VAS scores, and WPAI-UC scores, as well as time to major UC-related events such as hospitalizations, bowel surgeries, and procedures. Finally, exploratory end points include reduction in corticosteroid use, immunogenicity of long-term vedolizumab SC treatment (i.e., positive anti-drug antibodies), vedolizumab SC serum concentrations, and biomarkers of inflammation associated with loss of clinical efficacy during long-term vedolizumab SC treatment.[27]

The efficacy results include secondary end point analyses of the proportions of patients who achieved clinical remission and clinical response at each time point (week 0, 2, 4, 8, 16, and 24). Clinical remission was defined as a partial Mayo score of 2 or less and no individual subscore greater than 1. Clinical response was defined as a reduction of two or more points in partial Mayo score and a reduction from baseline of 25% or more with an accompanying decrease of at least one point in the rectal bleeding score or an absolute rectal bleeding subscore of 1 or less at a selected time point. To evaluate the effectiveness of vedolizumab SC beyond 52 weeks, exploratory efficacy analyses of mean partial Mayo scores were also reported. For these long-term assessments, the sponsor indicates that the partial Mayo score was selected over the complete Mayo score because it does not include an endoscopy assessment and, therefore, was more feasible during long-term follow-up. Given that Study SC-3030 was ongoing at the time of this review, not all participants have reached up to the week 24 cut-off (May 31, 2018), and, therefore, the results reported are based on the number of evaluable participants per visit.[27]

Statistical Analysis

The SAF includes all participants who received at least one dose of the study drug during the open-label extension.[27] The safety data are summarized by previous treatment group in the base study. Safety results are reported up to the cut-off for the second interim analysis (May 17, 2019), while efficacy results are reported up to the cut-off of the first interim analysis (May 31, 2018). The efficacy population is defined as the FAS, which includes all patients enrolled in the open-label extension study. As described earlier, the efficacy results were reported for three groups, stratified by their previous treatment group in the base study, i.e., placebo every two weeks and every eight weeks, vedolizumab SC 108 mg every two weeks, or vedolizumab IV 300 mg every eight weeks:[27]

- **Randomized study completers:** Patients with UC who completed the maintenance phase of the VISIBLE 1 base study up to week 52.
- **Randomized early terminators:** Patients with UC who withdrew from the maintenance phase of the VISIBLE 1 base study due to disease worsening or need for rescue medications.
- **Nonrandomized late responders:** Patients with UC who did not achieve a clinical response at week 6 in the induction phase of the VISIBLE 1 base study but achieved a clinical response at week 14 after receiving a third vedolizumab IV induction dose at week 6.

Efficacy values for the randomized study completers and the nonrandomized late responders were compared with baseline in the base study. Efficacy values for randomized early terminators were compared with week 0 of the extension study. Efficacy data were descriptively summarized with no formal statistical testing performed.[27]

Missing data for dichotomous end points were imputed using the nonresponders imputation method, where all participants with missing data are categorized as nonresponders. Missing data for continuous end points were imputed using the LOCF method. Data for future visits that had not taken place by the time of the interim data analysis were not imputed. All patients whose dose was escalated from every two weeks to every week were regarded as nonresponders (i.e., failed to achieve a response to a treatment administered every two weeks) for the purposes of the efficacy end points.[27]

Subgroup analyses were performed in the SAFS population by the sponsor: age (< 65, ≥ 65 years), race (white, black, Asian, and other), sex (male, female), baseline disease activity (moderate [baseline partial Mayo score < 6] or severe [baseline partial Mayo score ≥ 6]) and body weight (< 70 kg, 70 to 90 kg, > 90 kg).[27]

Patient Disposition

At the second interim analysis cut-off date of May 17, 2018, a total of 746 participants were enrolled in the VISIBLE 1 long-term extension study, Study SC-3030, of which 288 participants were patients with UC and 458 were patients with Crohn disease. [redacted]

Table 19: [redacted]

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Table 20: [redacted]

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Efficacy

The long-term efficacy of vedolizumab SC administered every two weeks beyond the initial 52-week treatment period (six-week IV induction phase and 46-week maintenance phase) was assessed through secondary end point analyses of the proportions of patients who achieved clinical remission and clinical response at each follow-up time point. In these analyses, dose escalation was considered a treatment failure. Mean partial Mayo scores over time were also reported to evaluate the persistency of the efficacy of vedolizumab with long-term treatment beyond 52 weeks by longitudinally integrating data collected during the base and extension studies. [redacted]

[redacted]

Table 21: [redacted]

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Figure 12: [redacted]

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Table 22: [redacted]

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Figure 13: [redacted]

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Table 23: [redacted]

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Figure 14: [redacted]

Figure 15: [redacted]

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Figure 16: [redacted]

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Table 25:

Critical Appraisal

As with most long-term extension studies, the VISIBLE 1 long-term extension study is limited by the open-label administration of the study drug, the absence of an active or placebo comparator group, the reporting of descriptive summary statistics, and the absence of health-related quality-of-life (HRQoL) outcome results. Additionally, given that the study is ongoing, results were limited to the interim analyses, which consisted of the data as of two different cut-off dates for the efficacy (May 2018) and safety (May 2019) analyses. Open-label administration can bias the reporting of end points, specifically, subjective end points in the Mayo score, and reporting of AEs. The lack of a comparator such as a placebo may overestimate the magnitude of clinical benefit reported to date. All efficacy end points were secondary end points and, as a result, are descriptive. Furthermore, the number of evaluable patients at the most recent end point for the randomized population, week 24, was low. Results for HRQoL outcomes, such as the EQ-5D, IBDQ, and WPAI-UC, were not available in the interim analyses to date and, therefore, the long-term benefit of vedolizumab on HRQoL outcomes remains unknown. One strength of the study is that the sponsor reported the baseline characteristics of the patients enrolled into the long-term extension study; this allows for comparison to the randomized study population or to patients in clinical practice. It is important to note, however, that patients enrolled in the open-label extension study had highly different clinical response histories. For example, these patients included randomized study completers, early terminators due to disease worsening, and initial nonresponders whose condition did not respond to the two vedolizumab IV induction doses. Furthermore, the early terminators were dosed more frequently than the other two groups, and dose escalation to every week was allowed in the randomized study completers group for patients who experienced treatment failure; dose adjustments throughout the study may confound the efficacy and safety results.

, which is representative of the Canadian population with UC. Additionally, administration of vedolizumab SC in the extension study is representative of how the drug would be used in clinical practice, i.e., self-administered by the patient. However, a limitation in the generalizability of the results is that the study population is not reflective of patients who would be treated with vedolizumab SC over the long term. The clinical expert consulted in this review indicated that what would be relevant would be patients who received either formulation of vedolizumab in the base study and were responders, as investigating the permanence or sustainability of a response would inform clinical practice. In contrast, demonstrating whether late responders or early terminators might be able to achieve a response much later is not clinically relevant, as those patients would be taken off therapy much earlier.

The second interim analysis provided comprehensive data on the primary end point, which was exposure-adjusted AEs and SAEs. [redacted] These factors may limit the applicability of the preliminary results.

Conclusion

A long-term extension study of the VISIBLE 1 study to assess the long-term safety and tolerability of vedolizumab SC in the treatment of UC is currently ongoing. [redacted] The available efficacy results to date were limited by their descriptive nature and low number of evaluable patients. Results from this extension study to inform the long-term durability of the response of vedolizumab SC in responders on maintenance therapy should be interpreted with caution.

Discussion

Summary of Available Evidence

The body of evidence comprising this review includes an individual study, the VISIBLE 1 trial, with an accompanying open-label extension study (the SC-3030 study, currently ongoing), and an indirect treatment comparison (NMA) submitted by the sponsor. The VISIBLE 1 study represents the only randomized trial available that has assessed the use of vedolizumab SC as maintenance therapy in patients with moderate-to-severe UC. The results from this study are included in the submitted NMA.

The VISIBLE 1 study is a double-blind, double-dummy, randomized placebo-controlled trial consisting of an IV induction phase using open-label vedolizumab 300 mg at weeks 0 and 2, with a clinical assessment at week 6 for clinical response (using the total Mayo score). Patients with a clinical response at week 6 were randomized to maintenance treatment with vedolizumab SC (108 mg vedolizumab SC every two weeks along with IV placebo every eight weeks), vedolizumab IV (300 mg every eight weeks along with SC placebo every two weeks), or placebo (SC placebo every two weeks and IV placebo every eight weeks) in a 2:1:1 ratio, with stratification by concomitant corticosteroid use, clinical remission status at week 6, and previous anti-TNF failure or concomitant immunomodulator use. Patients who did not achieve a clinical response at week 6 received a third open-label 300 mg vedolizumab IV dose at week 6 and were reassessed for clinical response (defined with partial Mayo score) at week 14. Those achieving a clinical response at week 14 had the option to enroll in the open-label extension study, while those who did not respond at week 14 were discontinued. All patients were then evaluated every eight weeks for a total follow-up of 52 weeks. The primary efficacy end point was the proportion of patients in clinical remission, defined as a total Mayo score of 2 or less and no individual subscore greater than 1 at week 52. Secondary efficacy outcomes at week 52, in ranked order, were the proportion of patients with endoscopic improvement (mucosal healing) assessed as a Mayo endoscopic subscore of 1 or lower (normal/inactive disease or mild disease), durable clinical response (clinical response at weeks 6 and 52), durable clinical remission (clinical remission at weeks 6 and 52), and corticosteroid-free remission (discontinuation of oral corticosteroids, followed by clinical remission at week 52). Authors also assessed quality of life with the EQ-5D score index and IBDQ scores, as well as the WPAI-UC instrument scores. All of these outcomes were compared between vedolizumab SC and placebo, but not formally tested between vedolizumab SC and vedolizumab IV.

Safety/harms were evaluated in the VISIBLE 1 study together with the follow-up open-label study, namely, SC-3030. This is a long-term extension, open-label study to assess the long-term safety and tolerability of vedolizumab SC in the treatment of UC. The study is currently ongoing and includes 288 patients with UC who participated in the VISIBLE 1 base study, including the following:

- participants who withdrew early from the base study due to treatment failure during the maintenance phase (as determined by disease worsening or need for rescue medications from week 14)
- participants who did not achieve a clinical response at week 6 and were not randomized to the maintenance phase but achieved a clinical response at week 14 after receiving a third open-label vedolizumab IV infusion

- patients who required surgical intervention for UC during or after participation in the VISIBLE 1 base study or were anticipated to require surgical intervention for UC during this study
- patients who withdrew from the base study due to a study drug–related AE.

Interpretation of Results

Efficacy

From only one study, VISIBLE 1, there were 383 patients evaluated in the induction phase that demonstrated improvement during this open-label phase, with 92.2% completing the vedolizumab induction treatment. At week 6, 216 patients were enrolled and randomized to vedolizumab SC (n = 106), vedolizumab IV (n = 54), or placebo (n = 56), with no important differences in their baseline characteristics. During the maintenance phase, 139 of 216 randomized patients (64.4%) completed treatment: 21 patients (37.5%) in the placebo group, 77 (71.7%) in the vedolizumab SC group, and 41 (75.9%) in the vedolizumab IV group. The main reason for discontinuation in the maintenance phase was lack of efficacy (for 28, 18, and 6 patients on placebo, vedolizumab SC, and vedolizumab IV, respectively) followed by voluntary withdrawal and AEs. More patients in the vedolizumab SC group were likely to show clinical remission at week 52 when compared with placebo, with an adjusted RD of 32.3% (95% CI, 19.7 to 45), and these results occurred in both the anti–TNF naive and experienced populations (this would imply an improvement in one out of every three patients treated with vedolizumab SC). Numerically similar rates of clinical remission were seen in the vedolizumab IV group when compared with placebo. Improvements were also noted in the outcomes of durable clinical response and endoscopic improvement (i.e.,

mucosal healing), but not for corticosteroid-free remission. No colectomies were performed or required during the study. Vedolizumab SC had a statistically and clinically significant effect in IBDQ total score (using a minimal important difference [MID] of > 15 points over placebo) and in the EQ-5D total index score (using an MID > 0.05; see Appendix 4 for more about MIDs). In the same vein, the improvement in WPAI scores was statistically significant in the vedolizumab SC group versus placebo. In all these outcomes, vedolizumab SC had numerically similar effects when compared with vedolizumab IV, and vedolizumab IV performed better when compared with placebo, although there was no formal testing in these two comparisons. Sensitivity analyses supported the robustness of the results. The trial was not powered for subgroup analyses; hence, any conclusions drawn from evaluating different subgroups will be uncertain due to this imprecision. Furthermore, a higher proportion of missing participants was noted in the placebo group, mostly due to lack of efficacy.

Based on indirect treatment comparisons, [redacted], with important limitations due to how the review was conducted, imprecision (i.e., large credible intervals), and risk of bias that decrease our confidence in this result. When comparing vedolizumab with other similar comparators with the same indication, it is difficult to address the relative effects of vedolizumab and its superiority over treatments other than placebo.

Harms

Overall, data from the VISIBLE 1 trial, the NMA, [redacted], do not provide important concerns in terms of AEs or SAEs, or harms of special interest established a priori in this review. The most common AEs were worsening of UC disease activity, nasopharyngitis, anemia, and upper respiratory tract infections. Two infections in the vedolizumab SC group were considered serious (one anal abscess and one peritonitis) but were not deemed treatment-related and did not lead to discontinuation. There were no *Clostridium difficile* infections. The mode of administration for this indication of vedolizumab is of importance for this submission, particularly the ISRs (mainly rash, swelling, erythema, and pruritus) that occurred in 11 patients (10.4%) receiving vedolizumab SC, in one patient (1.9%) receiving vedolizumab IV (plus matching SC placebo), and in zero patients receiving placebo.

The VISIBLE 1 long-term extension study to assess the long-term safety and tolerability of vedolizumab SC in the treatment of UC is currently ongoing, and the results from its second interim analysis demonstrate that long-term treatment with vedolizumab SC did not identify new safety signals.

[redacted]

Conclusions

Based on one trial, vedolizumab SC is more effective than placebo for the maintenance of clinical remission, durable clinical response, and endoscopic healing, as well as for improving quality of life and work productivity scores in patients with moderate-to-severe UC, although not for maintaining a corticosteroid-free remission. The efficacy and safety of vedolizumab SC seems to be numerically similar to vedolizumab IV, although the data from this evidence are not suitable to declare noninferiority of vedolizumab SC over the IV presentation. AEs are unlikely to be different between vedolizumab SC and placebo, although the number of events is still low. Results from an ongoing long-term study will provide more information to assess possible harms and applicability of the intervention.

Based on one sponsor-submitted review of indirect treatment comparisons, [redacted], although there is high uncertainty due to limitations in how it was conducted, imprecision, and lack of transparency in the NMA that decrease confidence in the results.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 17, 2019
Alerts:	Weekly search updates until project completion
Study Types:	Randomized controlled trials; controlled clinical trials
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.nm	Name of substance word
.rn	Registry number
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Entyvio* or vedolizumab* or MLN0002 or "MLN 0002" or MLN02 or "MLN 02" or LDP02 or "LDP 02" or 9RV78Q2002).ti,ab,kf,ot,hw,nm,rn.
2	exp Colitis/
3	(colitis* or colorectitis* or proctocolitis* or ulcerative proctitis* or proctosigmoiditis* or pancolitis* or rectocolitis* or rectosigmoiditis*).ti,ab,kf.
4	(ulcer* adj5 colon*).ti,ab,kf.
5	or/2-4
6	1 and 5
7	6 use medall
8	*vedolizumab/ or (Entyvio* or vedolizumab* or MLN0002 or "MLN 0002" or MLN02 or "MLN 02" or LDP02 or "LDP 02").ti,ab,kw,dq.
9	exp Colitis/
10	(colitis* or colorectitis* or proctocolitis* or ulcerative proctitis* or proctosigmoiditis* or pancolitis* or rectocolitis* or rectosigmoiditis*).ti,ab,kw,dq.
11	(ulcer* adj5 colon*).ti,ab,kw,dq.
12	or/9-11
13	8 and 12
14	13 use oemezd
15	14 not (conference review or conference abstract).pt.
16	7 or 15
17	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
18	Randomized Controlled Trial/
19	exp Randomized Controlled Trials as Topic/
20	"Randomized Controlled Trial (topic)"/
21	Controlled Clinical Trial/
22	exp Controlled Clinical Trials as Topic/
23	"Controlled Clinical Trial (topic)"/
24	Randomization/
25	Random Allocation/
26	Double-Blind Method/
27	Double Blind Procedure/
28	Double-Blind Studies/
29	Single-Blind Method/
30	Single Blind Procedure/

MULTI-DATABASE STRATEGY	
#	**Searches**
31	Single-Blind Studies/
32	Placebos/
33	Placebo/
34	Control Groups/
35	Control Group/
36	(random* or sham or placebo*).ti,ab,hw,kf,kw.
37	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
38	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
39	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
40	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
41	allocated.ti,ab,hw.
42	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
43	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
44	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
45	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
46	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
47	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
48	or/17-47
49	16 and 48
50	remove duplicates from 49

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search terms -- Entyvio, vedolizumab, mln0002, mln 0002, mln 02, ldp02, ldp 02, and ulcerative colitis	
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. Search terms -- Entyvio, vedolizumab, mln0002, mln 0002, mln 02, ldp02, ldp 02, and ulcerative colitis	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	December 2019
Keywords:	Entyvio (vedolizumab); ulcerative colitis
Limits:	Publication years: none

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
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals.

Appendix 2: Excluded Studies

Table 26: Excluded Studies

Reference	Reason for Exclusion
Not applicable	All studies were excluded during the title and abstract screening.

Appendix 3: Detailed Outcome Data

Figure 17: [redacted]

Table 27: [redacted]

	[redacted]		
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Figure 18: [redacted]

[redacted]

Table 28:

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Mayo scoring system
- IBDQ
- EQ-5D
- WPAI-UC.

Table 29: Outcome Measures Included in Each Study

Outcome Measure	VISIBLE 1
Mayo score	Primary
IBDQ	Secondary
EQ-5D	Secondary
WPAI-UC	Secondary

EQ-5D = EuroQol 5-Dimensions; IBDQ = Inflammatory Bowel Disease Questionnaire; WPAI-UC = Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis.

Findings

The validity, reliability, responsiveness and MID of each outcome measure were summarized and evaluated. Interpretation of the reliability and validity metrics were based on the following criteria:

- Inter-rater reliability, kappa statistics (level of agreement):[30]
  - < 0 = poor agreement
  - to 0.21 = slight agreement
  - 0.21 to 0.40 = fair agreement
  - 0.41 to 0.60 = moderate agreement
  - 0.61 to 0.8 = substantial agreement
  - 0.81 to 1.00 = almost perfect agreement
- Internal consistency (Cronbach's alpha) and test–retest reliability: ≥ 0.7 is considered acceptable.[31]
- Validity; i.e., between-scale comparison (correlation coefficient, r):[32]
  - ≤ 0.3 = weak
  - 0.3 to ≤ 0.5 = moderate
  - > 0.5 = strong

Table 30: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Mayo score	Disease-specific physician-measured score with the following parts: rectal bleeding, stool frequency, PGA, and endoscopy findings.	**Validity:** There was limited evidence on the validity for the total Mayo score. Construct validity of the Mayo endoscopic subscore was found to be strongly correlated with the total Mayo score (rho ≥ 0.97), as well as two histologic indices (r ≥ 0.55).[33] **Reliability and responsiveness:** The endoscopic subscore was found to have moderate-to-substantial agreement in the inter-rater reliability estimates, as well as responsiveness of the subscore to change over time with treatment.[33-36]	**Clinical response:** ≥ 3 points reduction in total Mayo score **Clinical remission:** ≤ 2 points in total Mayo score with or without an individual subscore > 1.[36]
IBDQ	Disease-specific, Likert-based questionnaire consisting of 32 items classified into four dimensions: bowel symptoms, systemic symptoms, emotional function, and social function. The IBDQ can be interviewer- or self-administered.	**Validity:** There was limited evidence on the validity of the IBDQ in the UC population. **Reliability and responsiveness:** The IBDQ was shown to be highly reliable through evaluation of internal consistency (Cronbach's alpha 0.7) and test–retest assessments (ICC 0.9 to 0.99 or Pearson's r ≥ 0.8). The IBDQ was also shown to be responsive to change in IBD patients.[37,38]	Absolute score change of ≥ 30 points, or ≥ 15 points above the placebo score among IBD patients.[39]
EQ-5D	Generic preference-based HRQoL instrument consisting of a VAS, and a composite index score of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	**Validity:** Stark et al. assessed the validity, reliability, and responsiveness of EQ-5D in a German population of IBD patients (including UC). Construct validity was supported by strong correlation of the scores with the Clinical Activity Index (CAI) (Spearman rank correlation [r] of between 0.65 and 0.67). The CAI score and VAS as well as all but one domain of the scale (self-care domain) showed discriminative validity. Konig et al. also demonstrated strong correlation between the EQ-5D VAS and CAI scores with the IBDQ total score (0.70 and 0.62, respectively) and moderate-to-strong correlation with the SF-36 subscores (0.37 to 0.72).[40]	Not found in UC patients; among IBD patients: VAS 10.9 and index score 0.05 for improved health, VAS −14.4 and index score −0.067 for deteriorated health.[41]

Outcome measure	Type	Conclusions about measurement properties	MID
		Reliability and responsiveness: Test–retest reliability was generally high for the index score (0.67 ≤ ICC ≤ 0.73), VAS (ICC, 0.93), and all five items of the scale (0.67 ≤ κ ≤ 1.00). Konig et al. reported similar results (ICC 0.89 for the index score, and 0.77 for the VAS score).[40] Both the index score and VAS were shown to be responsive to detecting change in health status.[41]	
WPAI-UC	Self-rated disease-specific questionnaire consisting of six items divided into four domains: absenteeism, presenteeism, percent overall work impairment, and regular activities impairment.	**Validity:** Convergent validity was demonstrated between all WPAI domains with the SIBDQ Bowel symptoms (Spearman rank-order coefficient, –0.47 to –0.68) and SF-12v2 Bodily Pain (–0.52 to –0.55) subscores, as well as between the WPAI and measures of disease activity (median 0.45)[42]. Known-group validity data demonstrated that patients with worse health outcomes scored worse on the WPAI than patients with better health outcomes, based on partial Mayo, SCCAI, UC-DAI, and FACIT fatigue disease severity measures.[42] **Reliability and responsiveness:** Test–retest assessment demonstrated that differences in each domain were < 5% over a 12-month period. However, no ICC was reported for this data.[42] One study demonstrated that patients with active UC disease who achieved remission at week 8 reported a 25% to 30% decrease in presenteeism, overall work impairment, and activity impairment, and a 9% decrease in absenteeism. Responsiveness of the WPAI domains to effective treatment was demonstrated with an approximate 20% decrease in presenteeism, overall work impairment, and activity impairment, and an 8% decrease in absenteeism.[42]	Not found in UC patients, however a 7-point change has been estimated in Crohn disease.[43]

EQ-5D = EuroQol 5-Dimensions; FACIT = Functional Assessment of Chronic Illness Therapy; IBD = inflammatory bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; ICC = intraclass correlation; MID = minimal important difference; PGA = Physician's Global Assessment; SCCAI = Simple Clinical Colitis Activity Index; SF-12v2 = Short Form (12) Health Survey, version 2; SF-36 = Short Form (36) Health Survey; SIBDQ = Short Inflammatory Bowel Disease Questionnaire; UC = ulcerative colitis; UC-DAI = UC Disease Activity Index; VAS = visual analogue scale; WPAI-GH = Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis.

Mayo Score

The Mayo scoring system is a combined endoscopic and clinical scale used to assess the severity of UC. It was first developed by Dr. Schroeder in 1987 and is now one of the most commonly used disease activity indices in UC.[36,44] In its complete form, the Mayo score is composed of four components: rectal bleeding, stool frequency, Physician's Global Assessment (PGA), and endoscopy findings. Each part is rated from 0 to 3, yielding a total score of 0 to 12. A score of 3 to 5 points indicates mildly active disease, while a score of 6 to 10 points indicates moderately active disease and a score of 11 to 12 points indicates severe disease. Two abridged versions have been developed and validated: the partial Mayo score that excludes the endoscopy subscore, and the non-invasive six-point score comprising only the bleeding and stool frequency subscores.[33] Mucosal healing has been defined in major trials of biological therapies in UC as a Mayo endoscopic subscore of 0 or 1. The grading of each component is defined in Table 31.

Table 31: Components and Grading of the Mayo Score in UC

Component	Grading
Stool frequency	0 = Normal 1 = 1 to 2 stools/day more than normal 2 = 3 to 4 stools/day more than normal 3 = > 4 stools/day more than normal
Rectal bleeding	0 = None 1 = Visible blood with stool less than half the time 2 = Visible blood with stool half of the time or more 3 = Passing blood alone
Mucosal appearance at endoscopy[a]	0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician rating of disease activity	0 = Normal 1 = Mild 2 = Moderate 3 = Severe

UC = ulcerative colitis.

[a] The mucosal appearance at endoscopy score is not included in the partial Mayo score.

Validity

A recent Cochrane systematic review by Mohammed et al. assessed the validity, reliability, and responsiveness of endoscopic scoring incidences for evaluation of disease activity in UC, which included 6 of 20 studies evaluating the Mayo score.[33] None of the included studies assessed content validity.[33] Construct validity of the Mayo endoscopic subscore was reported in two studies with UC patients, and a strong correlation was found between the endoscopic subscore and two histologic indices (the Riley score and Rubin histologic score; r ≥ 0.55 for both). However, the endoscopic subscore was shown to fail in discriminating between patients who achieved remission and response compared with those who did not.[33] Dhanda et al. also demonstrated a strong correlation between the partial and total Mayo scores (rho ≥ 0.97 at weeks 4 and 8).[45]

Reliability and Responsiveness

The endoscopic subscore was evaluated for reliability and responsiveness in a placebo-controlled trial designed to assess change in UC disease activity with mesalamine treatment.[34] The authors reported excellent inter- and intra-observer reliability (intraclass correlation [ICC] of 0.79 and 0.89, respectively) as well as responsiveness of the subscore to change over time with treatment.[34] Mohammed et al. reported a moderate-to-substantial agreement in the inter-rater reliability estimates (range 0.45 to 0.75) and a substantial agreement in the intra-rater reliability estimates (0.75) for the endoscopic subscore.[33] Another study by Walsh et al. evaluated the comparative inter-rater variation for three UC disease activity indices, including the Mayo score.[35] The inter-rater agreement for the total Mayo score was high (kappa = 0.72); however, the agreement was lower for the relatively subjective PGA and endoscopic subscores (kappa = 0.56 and 0.38, respectively). The Mayo score has been demonstrated to correlate with patient assessment of change in UC activity,[36] as well as to correlate with improvement in quality-of-life measures.[46]

Minimal Important Difference

Lewis et al. reported that a reduction of at least 3.5 points in the total Mayo score reflected an optimum cut point for clinical improvement or response (based on sensitivity, specificity, and area under the curve [AUC]) in UC, using patient's rating of the improvement as an anchor.[36] The optimum cut point for clinical remission varies; Lewis et al. reported a cut point of 4.5 (based on sensitivity, specificity, and AUC), although other cut points ranging from a Mayo score of 2 or lower to a score of 0.6 were reported in clinical trials.[36] The FDA defines clinical remission in relation to the Mayo score as a total score of 2 or less with no individual subscore greater than 1, a rectal bleeding subscore of 0, a stool frequency subscore of 0 (≤ 1 point decrease in the stool frequency subscore from baseline to achieve a stool frequency subscore = 0 or 1 is considered), and an endoscopy subscore of 0 or 1 modified on Mayo score. Clinical response is defined as a reduction in total Mayo score of three or more points and a reduction from baseline of 30% or more in the rectal bleeding subscore with a rectal bleeding subscore below 1.25.

Limitations

Although the Mayo score is a widely recognized UC activity index and is accepted by Canadian and American regulatory bodies, it may not be optimal. Cooney et al. argued that two components of the Mayo score — the PGA and the endoscopy subscore — are subjective and introduce variability and lack of precision into the index. The PGA also includes a sigmoidoscopy score, which introduces double counting of some elements.[47] Additionally, a single general item in the PGA is not sensitive enough to adequately capture benefits in all or some of the important signs and symptoms. As a result, the FDA does not recommend the PGA subscore or the full Mayo score as end point measures to support a marketing decision; however, it does recommend the endoscopy, stool frequency, and rectal bleeding subscores as end point measures for clinical trials until the availability of well-defined and reliable end points.[28]

Inflammatory Bowel Disease Questionnaire

The IBDQ, developed by Guyatt et al., is an interviewer- or self-administered questionnaire to assess HRQoL in patients with IBD.[48,49] 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 seven-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 represent better quality of life). A total IBDQ score of at least 170 points or higher is considered clinical remission. This questionnaire has been validated in a variety of settings, countries, and languages, and is available in a 9-, 10-, and 36-item form.[50]

Validity

Two systematic reviews published in the last three years reported the measurement properties and methodological quality of a number of IBD-specific HRQoL instruments, including the IBDQ.[37,38] Overall, the IBDQ was proven to be a valid, reliable, and responsive scale; however, the methodological quality was poor to fair for some of these measurement properties. The IBDQ demonstrated content validity, as it was developed through patient interviews and covered the most frequent and important items. Results from factor analysis showed the items/domains of the scale explained at least 50% of the variance. The scale showed strong correlation with the Crohn's Disease Activity Index ($r = -0.67$), proving convergent validity. In addition, criterion validity was proven with similar correlation of changes in IBDQ and other measures. The scale showed lower discriminant validity, particularly in patients who required surgery.[37,38]

Reliability and Responsiveness

The reliability parameters showed high internal consistency (Cronbach's alpha 0.7), test–retest reliability (ICC 0.9 to 0.99 or Pearson's $r \geq 0.8$), and low measurement error (i.e., standard deviations of the score changes were of similar magnitude and the smallest detectable change was less than the MID). Responsiveness was satisfactory, as the scale was sensitive to change corresponding to clinical improvement or deterioration. Floor and ceiling effects were not found, as less than 15% of the respondents achieved the highest or lowest possible score.[37,38]

Minimal Important Difference

Irvine et al. reported that a change of 30 points or more in actual score, or an improvement of 15 points or more above the placebo score, is associated with clinical benefits in IBD patients, including UC.[39] Several other studies have reported an increase of more than 15 to 32 points from baseline as clinically meaningful improvement.[51]

EuroQol 5-Dimensions Questionnaire

The EQ-5D questionnaire is a generic, preference-based, HRQoL measure consisting of descriptive questions and a VAS.[52] The EQ-5D-3L has been applied to a wide range of health conditions and treatments, including IBD.[52,53] The descriptive questions comprise five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is divided into three levels (1, 2, 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents (aged ≥ 12 years) are asked to choose one level that reflects their own health state for each of the five dimensions. The five questions are scored and together contribute to an EQ-5D index (utility) score of between 0 and 1, where 0 represents death, and 1 represents perfect health. Different utility functions are available that reflect the preferences of specific populations (e.g., US, UK). The second part of the tool records the patient's self-rated health on a 20 cm scale with end points of 0 and 100, with respective anchors of "the worst health you can imagine" and "the best health you can imagine," respectively.

Validity

Stark et al. assessed the validity, reliability, and responsiveness of the EQ-5D in a German population of IBD patients (including UC).[41] Respondents completed the EQ-5D twice, four weeks apart. At the four-week follow-up, patients were asked to report, in response to a transition question, whether their health status was better, worse, or the same. Construct validity was evaluated using two methods: assessing the correlation between the EQ-5D index and VAS scores with disease activity, and comparing responses between patients with active disease versus those in remission.[41] The construct validity of the EQ-5D index score and VAS was supported by the strong correlation of these scores with the Clinical Activity Index (CAI) (Spearman rank correlation [r] of between 0.65 and 0.67). The CAI score and VAS as well as all but one domain of the scale (self-care domain) showed discriminative validity by correctly differentiating patients in remission and active disease. A smaller study by Konig et al. (29 patients with UC, two-week recall period) also demonstrated strong correlation between the EQ-5D VAS and index scores and the IBDQ total score (0.70 and 0.62, respectively) and moderate-to-strong correlation with the SF-36 subscores (0.37 to 0.72).[40]

Reliability and Responsiveness

Stark et al. assessed test–retest reliability by comparing the baseline and follow-up measurements of the EQ-5D in the subset of patients who indicated no change in HRQoL in their response to the transition question. Test–retest reliability was generally high for the index score ($0.67 \leq ICC \leq 0.73$), VAS (ICC 0.93), and all five items of the scale ($0.67 \leq \kappa \leq 1.00$). Konig et al. reported similar results (ICC of 0.89 for the index score and 0.77 for the VAS score).[40] Responsiveness (sensitivity to change) of the EQ-5D VAS scores and the index scores was tested in patients who indicated a change in their health status in their response to the transition question by using paired t-tests, effect size, and standardized response mean.[41] Both the index score and VAS were shown to be responsive to detecting change in health status; however, VAS was found to be more responsive for deterioration in health than for improvement in health and was more responsive than the index score.[41]

Minimal Important Difference

Stark et al. estimated a disease-specific MID using a regression model; the MIDs for improved health were reported to be 10.9 for the VAS, and 0.050 (EU) and 0.076 (UK) for the index score.[41] This is within the range of other reported MIDs for the index score of 0.033 to 0.074.[54]

Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

The WPAI is one of the most frequently used patient-reported, work-related outcome measures.[42,55] The WPAI questionnaire is an instrument used to measure the impact of an individual's health status on their work and daily activities.[56] The WPAI measures the impact of general health problems (WPAI – General Health) or the impact of a specific disease, such as UC (WPAI-UC) on four domains: absenteeism (missing work), presenteeism (impaired productivity at work), overall work performance (combined absenteeism and presenteeism), and non-work activities (activity impairment).[42] It is a self-administered six-item questionnaire with a recall period of seven days.[55] The items include employment status (employed or not employed); hours at work missed because of UC; hours at work missed because of other reasons; hours actually worked; overall impairment in productivity while working (VAS from 0 to 10) and overall impairment in regular activities

(VAS from 0 to 10) due to UC. Scores from all four domains are expressed as percentages (0% to 100%) of impairment, with lower values indicating less impairment due to the health problem.[42] The WPAI has been shown to be reliable, valid, and responsive when used with patients across several disease areas, including other GI conditions such as irritable bowel syndrome, gastroesophageal reflux disease, and Crohn disease.[42]

Validity

A recent systematic review by Yarlas et al. assessed eight articles and five posters evaluating the psychometric validation of the WPAI in UC.[42] One study was found assessing convergent validity between the WPAI domains and other HRQoL measures, including the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and version 2 of the Short Form (12) Health Survey (SF-12v2).[42] The strongest evidence for convergent validity was reported between all WPAI domains and the SIBDQ "bowel" symptoms (Spearman rank-order coefficient, –0.47 to –0.68) and SF-12v2 "bodily pain" (–0.52 to –0.55) subscores. With the exception of absenteeism, the WPAI domains also converged with the SIBDQ "social" function, and SF-12v2 "role physical" and "role emotional" subscores.[42] Convergent validity was also assessed between the WPAI and measures of disease activity, specifically, the Simple Clinical Colitis Activity Index (SCCAI), the UC Disease Activity Index (UC-DAI), and the partial Mayo score in three individual studies.[42] Inter-scale correlations between the WPAI domains and disease activity measures ranged from 0.32 to 0.85 (median, 0.45). Across the three studies, convergence with disease activity was supported for presenteeism, overall work impairment, and activity impairment (0.43 to 0.60), although the median correlation for absenteeism was not far behind (0.39).[42] Furthermore, a known-group validity assessment demonstrated that patients with worse health outcomes scored worse on the WPAI than patients with better health outcomes, based on partial Mayo, SCCAI, UC-DAI, and Functional Assessment of Chronic Illness Therapy (FACIT) – Fatigue disease severity measures.[42]

Reliability and Responsiveness

Test–retest reliability of the WPAI domains was assessed in one study by Yarlas et al. in 2015 (N = 98), which compared scores at the start and end of an open-label maintenance treatment period in patients whose remission status was unchanged (as determined by the UC-DAI).[42] Results demonstrated that differences in each domain were less than 5% over a 12-month period, and none exceeding the proposed MID in Crohn disease of 7%. However, no ICC was reported for this data.[42] The ability of WPAI domains to detect changes was evaluated in one study by Yarlas et al.[42] by assessing the magnitude of change in the WPAI domains for patients demonstrating changes in disease states (i.e., change from active disease to remission, or vice versa). The study demonstrated that patients with active UC disease who achieved remission at week 8 reported a 25% to 30% decrease in presenteeism, overall work impairment, and activity impairment, and a 9% decrease in absenteeism. The inverse was also found in patients with disease relapse.[42] The responsiveness of the WPAI domains to effective treatment was also demonstrated with data from three RCTs investigating either multi-matrix mesalamine treatment or adalimumab in UC patients; results indicated that patients reported an approximate 20% decrease in presenteeism, overall work impairment, and activity impairment, and an 8% decrease in absenteeism.[42]

Minimal Important Difference

There is currently no MID defined for the WPAI in UC patients. However, the MID estimated in Crohn disease is a decrease of seven points.[43]

Further References of Interest

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