CADTH

CADTH Common Drug Review

Clinical and Economic Review Report

Vedolizumab (ENTYVIO SC)

Takeda Canada Inc.

Indication: Crohn disease

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Table of Contents

Tables

Figures

Abbreviations

AE	adverse event
AESI	adverse event of serious interest
BIA	business impact analysis
CCC	Crohn's and Colitis Canada
CD	Crohn disease
CDAI	Crohn's Disease Activity Index
CDEC	CADTH Canadian Drug Expert Committee
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
FAS	full analysis set
GI	gastrointestinal
HCP	health care provider
HRQoL	health-related quality of life
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL	interleukin
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous
IWRS	interactive web response system
MAdCAM-1	mucosal addressin cell adhesion molecule 1
MCID	minimal clinically important difference
NMA	network meta-analysis
OLE	open-label extension
pCPA	pan-Canadian Pharmaceutical Alliance
PPS	per-protocol set
q.w.	every week
q.2.w.	every 2 weeks
RCT	randomized controlled trial
SAE	serious adverse event
SAF	safety analysis set
SC	subcutaneous
SEB	subsequent entry biologic
TEAE	treatment-emergent adverse event
TNF alpha	tumour necrosis factor alpha
UC	ulcerative colitis
ULN	upper limit of normal
VAS	Visual Analogue Scale
WPAI-CD	Work Productivity and Activity Impairment–Crohn's disease

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) solution for subcutaneous injection (108 mg/0.68 mL, single-use pre-filled syringe or pen)
Indication	Treatment of adult patients with moderately to severely active Crohn disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a tumour necrosis factor alpha (TNFα) antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids
Reimbursement request	As per indication
Health Canada approval status	Approved
Health Canada review pathway	Standard
NOC date	November 19, 2020
Sponsor	Takeda Canada Inc.

NOC = Notice of Compliance.

Introduction

Crohn disease (CD) is a chronic form of inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, but most commonly affects the ileum (small intestine), colon (beginning of the large intestine), and rectum. Common gastrointestinal symptoms experienced by patients with CD include abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, perianal disease, weight loss, and bloating.[1,2] CD-associated inflammation can also manifest outside the gastrointestinal tract, affecting the joints, eyes, and skin of the patient. Complications associated with CD can include fever, malnutrition, weight loss, anemia, bowel obstructions, fistulas, anal fissures, intra-abdominal and other abscesses, and ulcers.[2,3] In addition, patients with colonic CD have been shown to have an increased risk of developing colon cancer.[2] The predicted prevalence of CD in 2018 was 368 per 100,000 population, thus there are approximately 135,000 Canadians living with CD.[4,5]

Currently there is no cure for CD. Therapeutic goals include inducing and maintaining clinical and endoscopic remission. Pharmaceutical treatments for CD include aminosalicylates, immunosuppressants, corticosteroids, tumour necrosis factor alpha (TNF alpha) antagonists, interleukin (IL) inhibitors, and integrin inhibitors. Medical management is based on a stepwise approach, with treatments used sequentially and escalated to either newer therapies or higher doses as patients fail to respond to each step of treatment. Most drugs have important adverse effects that may have short-term or long-term consequences.[2,3]

Vedolizumab is a humanized immunoglobin G1 monoclonal antibody that binds exclusively to alpha 4 beta 7 integrin on pathogenic gut-homing lymphocytes and selectively inhibits adhesion of these cells to mucosal addressin cell adhesion molecule 1 (MAdCAM-1), which is primarily localized to blood vessels within intestinal muscosa and gut-associated lymphoid tissue. Vedolizumab is available as powder for solution for IV infusion, 300 mg per vial, or solution for subcutaneous (SC) injection, 108 mg/0.68 mL pre-filled syringe or pen.[6] Vedolizumab SC has been approved by Health Canada for the treatment of adult patients with CD and a Notice of Compliance was issued on November 19, 2020. Vedolizumab SC

has also been approved for the treatment of adult patients with moderately to severely active ulcerative colitis.

Vedolizumab IV has been approved by Health Canada for the treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids.[6] The dosing of vedolizumab IV recommended by Health Canada for CD is 300 mg at 0, 2, and 6 weeks, and then every 8 weeks thereafter. When vedolizumab SC is used as a maintenance treatment following at least 2 IV infusions, the recommended dose regimen is 108 mg administered by SC injection once every 2 weeks.

Vedolizumab IV received CADTH Canadian Drug Expert Committee (CDEC) recommendations to reimburse with criteria and conditions for ulcerative colitis (UC) in October 2015 and for CD in October 2016. CDEC issued a recommendation to reimburse vedolizumab SC with criteria and conditions for UC in May 2020.

The objective of the current review was to perform a review of the beneficial and harmful effects of vedolizumab SC in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids.

The clinical and pharmacoeconomic evidence for the review were provided through the CADTH tailored review process. A tailored review consists of an appraisal of the clinical evidence and a pharmacoeconomic evaluation filed by the sponsor using a CADTH-provided review template that is specific to the type of drug product to be reviewed.

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 a clinical expert consulted by CADTH for the purpose of this review.

Patient Input

Two patient groups submitted input for this review: (1) the Gastrointestinal Society (GI Society) and (2) Crohn's and Colitis Canada (CCC). The GI Society is a national registered charity that is committed to improving the lives of patients with GI and liver conditions by supporting research, advocating for patient access to health care, and promoting overall GI and liver health. A national, volunteer-based charity, CCC is focused on finding cures for CD and UC and improving the lives of people affected by these diseases.

Patient input from these 2 groups was obtained through surveys, direct contact with patients affected with IBD, interviews, patient roundtables, telephone calls, emails, and social media, or via published reports. From the patients' point of view, CD is a chronic GI condition that primarily affects the small intestine and colon. The most frequent symptoms associated with CD are persistent diarrhea, rectal bleeding, abdominal pain, and weight loss. These symptoms vary from person to person and may change over time. Patients with CD may also experience symptoms outside of the GI tract. Fever, fatigue, and anemia are common. Serious complications such as fistula can occur. In addition to the physical symptoms, the patient groups stated that CD has a profound effect on patients' emotional

and social lives. Both patient groups indicated that patients are constantly concerned about future flare-ups, which can be unpredictable and severely disruptive.

The patient groups described treatment of CD as multifaceted as it involves managing symptoms and consequences of the disease, as well as trying to reduce the underlying inflammation. Many respondents have experienced multiple medications over many years. When one medication fails to treat their disease, patients switch to another type. Even though different treatment options are available, many patients still have difficulties obtaining remission and/or adequate symptom relief. Patients reporting experience with vedolizumab noted both benefits and side effects associated with this drug.

Both patient groups emphasized the importance of symptom relief, quality-of-life improvements, and achieving remission in patients with CD, as well as the importance of having access to a variety of treatment options, as patients respond differently to treatments. They also expressed concerns about the challenges in receiving medication for CD via infusion at clinics due to the significant time commitment and time away from work and school. A self-administered option, such as the SC formulation of vedolizumab, is desirable.

Clinician Input

Based on current standards of practice with existing therapies, the clinical expert consulted by CADTH identified several areas of unmet need where vedolizumab SC may play a role:

- As primary maintenance therapy for CD for patients who experience primary non-response to either conventional therapy with immunomodulators or TNF alpha antagonists
- In the setting of secondary non-response during maintenance therapy; an important proportion of CD patients will lose response to TNF alpha antagonist therapy during maintenance, either due to formation of anti-drug antibodies or to inflammatory mechanisms that are independent of TNF
- As salvage therapy for patients responding to immunomodulation therapy or TNF alpha antagonists who develop adverse effects to therapy; while immunomodulators such as azathioprine and methotrexate are generally safe medications, well-known side effects include the development of pancreatitis, neutropenia, hepatitis, and neoplasia (e.g., skin cancers); in addition, TNF alpha antagonists can be associated with severe allergic reactions, psoriatic skin diseases, neurological complications, congestive heart failure, lupus, and severe infections.

Patients with moderate to severe CD require treatment with biologic therapies (typically starting with the TNF alpha antagonists infliximab and adalimumab) after not meeting treatment goals with aminosalicylates, immunosuppressants, and corticosteroids. Biologic treatments are usually administered in combination with an immunosuppressant such as azathioprine or methotrexate. Patients who respond to this approach continue with biologic treatment for several years. However, some patients experience a reduction in response over time (e.g., due to the development of antibodies to a particular biologic treatment) or become intolerant of biologic treatment (e.g., due to side effects such as an allergic reaction or other drug-related complications), which necessitates a change in the treatment regimen to maintain clinical responsiveness. At present, patients who experience a loss of response to either infliximab or adalimumab can be switched to the other TNF alpha antagonist, although this is often associated with a weaker clinical response compared with the response in patients who have not been exposed previously to a TNF alpha antagonist. Therefore, patients with moderate to severe CD who are no longer responsive to or

intolerant of TNF alpha antagonists may benefit from a drug with a different mechanism of action.

Vedolizumab is an integrin inhibitor, and therefore represents a different class of biologic compared to the TNF alpha antagonists and the IL-12 and IL-23 inhibitor ustekinumab.

There are no barriers to identifying patients for whom vedolizumab treatment would be appropriate in a consistent manner, although a specialized diagnostic test, such as endoscopy, computed tomography scan, abdominal ultrasound, or magnetic resonance enterography, is usually required to assess disease activity and severity in all patients who require biologic therapy, in accordance with standard clinical practice. The following are also advisable to assess prior to initiating treatment:

- previous TB exposure
- hepatitis B serology
- pregnancy test in women of childbearing age
- immunization history and boosters for low antibody titers.

Clinical Evidence

Pivotal Studies

Description of Studies

One phase III, double-blind, placebo-controlled, randomized controlled trial (RCT), VISIBLE 2 (N = 410), was submitted by the sponsor.[7] VISIBLE 2 was designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC injection in adult patients with moderately to severely active CD who achieved a clinical response at week 6 to open-label therapy with 300 mg vedolizumab IV infusion at weeks 0 and 2. Patients with a clinical response at week 6 were randomized to maintenance treatment with vedolizumab SC (108 mg vedolizumab SC every 2 weeks), or placebo in a 2:1 ratio. The primary outcome was the proportion of patients with clinical remission, defined as a Crohn's Disease Activity Index (CDAI) score of 150 or less at week 52. To control for an overall type I error rate in the comparison between vedolizumab SC and the placebo for the primary and secondary end points, a hierarchical approach was applied to the statistical testing.

Efficacy Results

In VISIBLE 2, more patients in the vedolizumab SC group achieved clinical remission at week 52 (primary efficacy end point) when compared to placebo, with an adjusted risk difference of 13.7% (95% confidence interval [CI], 3.8 to 23.7; P = 0.008). In addition, numerically higher enhanced clinical response at week 52 was observed in the vedolizumab SC group compared with the placebo group; however, the between-group difference did not reach statistical significance (52% versus 44.8%; P = 0.167). Consequently, statistical significance cannot be formally claimed for any of the end points ranked after this end point in the hierarchy, such as corticosteroid-free remission at week 52. A numerically higher rate of corticosteroid-free remission at week 52 was reported for the vedolizumab group (45.3%) compared with placebo (18.2%).

For patient-reported outcomes, total scores in the Inflammatory Bowel Disease Questionnaire (IBDQ), a disease-specific tool to assess health-related quality of life (HRQoL), suggested improvements for both treatment groups; change from baseline was

63.3 points in the vedolizumab SC group and 55.1 points in the placebo group. It is unclear whether the between-groups difference can be considered clinically meaningful. Similar results were observed for the results of EuroQol 5-Dimensions questionnaire (EQ-5D) Visual Analogue Scale (VAS) score and index score.

Harms Results

Overall, data from the VISIBLE 2 trial do not provide important concerns in terms of adverse events (AEs) or serious adverse events (SAEs), or harms of special interest established a priori in this review. The incidence of treatment-emergent adverse events (TEAEs) was 73.5% in the vedolizumab SC group and 76.1% in the placebo group. The most common AEs were worsening of CD disease activity, abdominal pain, nasopharyngitis, arthralgia, and upper respiratory tract infections. The incidence of SAEs was comparative between the 2 groups, at 8.4% in the vedolizumab SC group and 10.4% in the placebo group. The incidence of withdrawals due to AEs was higher in the placebo group (8.2%) compared to vedolizumab SC (4%).

Table 2: Summary of Key Results from Pivotal Studies

Results	VISIBLE 2	
	Placebo N = 134	Vedolizumab SC N = 275
Efficacy (FAS)		
Clinical remission at week 52		
Patients in clinical remission, n (%)	46 (34.3)	132 (48.0)
Adjusted difference vs. placebo (95% CI)	13.7 (3.8 to 23.7)	
Vedolizumab vs. placebo, P value	0.008	
Enhanced clinical response at week 52		
Patients in enhanced clinical response, n (%)	60 (44.8)	143 (52.0)
Adjusted difference vs. placebo (95% CI)	7.3 (−3.0 to 17.5)	
Vedolizumab vs. placebo, P value	0.167[a]	
Corticosteroid-free remission at week 52		
Patients in enhanced clinical response, n (%)	8 (18.2)	43 (45.3)
Adjusted difference vs. placebo (95% CI)	27.1 (11.9 to 42.3)	
Vedolizumab vs. placebo, P value	0.002[b]	
Harm (SAF)		
At least 1 AE, n (%)	102 (76.1)	202 (73.5)
At least 1 SAE, n (%)	14 (10.4)	23 (8.4)
WDAE, n (%)	11 (8.2)	11 (4.0)
Deaths	0	0

AE = adverse event; CI = confidence interval; FAS = full analysis set; SAE = serious adverse event; SAF = safety analysis set; SC = subcutaneous; vs. = versus; WDAE = withdrawal due to adverse event.

[a] The hierarchy failed at this level.

[b] This cannot be interpreted as statistically significant because the hierarchy failed at a higher level.

Source: Clinical Study Report for the VISIBLE 2 study.[7]

CADTH Critical Appraisal

The only pivotal study included in this review was VISIBLE 2. A hierarchical statistical testing was used to control for the overall type I error rate. As statistical significance was not achieved for one of the secondary efficacy end points, "enhanced clinical response at week 52," statistical significance cannot be formally claimed for any of the end points ranked after this end point, including "corticosteroid-free remission," although numerically greater differences in these end points were reported in the vedolizumab SC group compared with the placebo group.

During the maintenance phase, 41% of the participants discontinued treatment, 45.2% in the placebo group and 38.9% in the vedolizumab SC group. The main reason for discontinuation in the maintenance phase was lack of efficacy (with 32% and 28% on placebo and vedolizumab SC, respectively) followed by voluntary withdrawal and AEs. This difference in missing data could bias the results. Sensitivity analyses were conducted to examine the robustness of study findings to missing data assumptions, and the results supported the primary analysis.

Subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary and all secondary outcomes based on age, gender, race, duration of CD, 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. However, conclusions in regard to these subgroups are uncertain due to the [redacted] in the subgroups. In addition, subgroup analyses were exploratory in VISIBLE 2, and there was also a lack of adjustment for multiplicity. All of these increase uncertainty in interpretation of results in the subgroups. The VISIBLE 2 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 all secondary end points, such as enhanced clinical response and corticosteroid-free clinical remission.

Indirect Comparisons

Description of Studies

The sponsor submitted a single network meta-analysis (NMA) aimed at evaluating the comparative efficacy and safety of vedolizumab SC relative to other comparators with similar indications.[8]

[redacted]

Efficacy Results

[redacted]

Little should be inferred regarding the comparative efficacy or safety based solely on this submitted NMA. The applicability of the sponsor's NMA is affected by the 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.

Harms Results

Results of the NMA suggest that [redacted]

CADTH Critical Appraisal

The major concerns with the submitted NMA are related to the limited size of the evidence [redacted] and heterogeneity across trials in both design and patient baseline characteristics.

A significant concern with the NMA presented is that studies included in the analyses were highly heterogeneous in terms of both study design and patient characteristics. Some of the important patient characteristics, such as disease duration and CDAI score at baseline, were reported graphically. Significant differences were noted in these baseline characteristics, including factors that may be associated with disease severity such as C-reactive protein (CRP) levels, disease duration, and CDAI score at baseline. Another major concern with design heterogeneity is how trials transition from induction to the maintenance phase. The evidence base in the maintenance phase is a mix of treat-through trials and re-randomization trials. Re-randomization within some trials, such as VISIBLE 2, occurs at the end of the induction phase. This difference in design may vary the response between groups and may limit the comparability of treatment groups across trials for the maintenance phase. [redacted], there remain major concerns regarding the validity of conclusions from this NMA due to the differing designs across studies.

Other Relevant Evidence

Description of Studies

An open-label extension (OLE) study (SC-3030) to evaluate the long-term safety and efficacy of vedolizumab SC in patients with CD and UC is ongoing at the time of this review. This study is intended to collect long-term safety data for vedolizumab SC dosing to complement the safety data gathered in VISIBLE 2 of patients with CD and Study SC-3027 of patients with UC.

[redacted]

Patients are eligible to enter this OLE study if they participated in the SC-3027 (UC) or SC-3031 (CD) study. They receive open-label vedolizumab SC 108 mg either weekly or every 2 weeks. Patients with UC or CD who completed the maintenance phase (week 52) will receive vedolizumab SC 108 mg every 2 weeks. Patients with UC or CD who withdrew early from the maintenance phase due to disease worsening or need for rescue medications will receive vedolizumab SC 108 mg weekly Patients with UC or CD who did not achieve a clinical response at week 6, but after receiving a third vedolizumab IV infusion at week 6 achieved a clinical response at week 14, will receive vedolizumab SC 108 mg every 2 weeks. Participants continue the study drug for up to 5 years.

Results

[redacted]. The available efficacy results to date were limited by their descriptive nature and [redacted] of evaluable patients.

CADTH Critical Appraisal

The VISIBLE 2 long-term extension study is limited by the open-label administration of the study drug, the absence of an active or placebo comparator group, and the reporting of descriptive summary statistics. Furthermore, the number of evaluable patients at the most recent data cut was low. [redacted] In addition, patients enrolled in the OLE study [redacted], making interpretation of results difficult.

Cost Information

The sponsor included the following comparators in its cost comparison, in which differences in annual cost were considered: vedolizumab IV, adalimumab, infliximab, and ustekinumab. The sponsor estimated the reimbursement of vedolizumab SC to be cost-neutral when compared to vedolizumab IV, as the annual costs based on the recommended maintenance dosing regimen were the same between vedolizumab SC and vedolizumab IV.

CADTH identified 2 main limitations in the sponsor's cost information: The comparative efficacy of vedolizumab SC is uncertain, based on the submitted indirect treatment comparison (ITC). [redacted]. The sponsor also did not consider induction costs, which are expected to be higher in the first year compared with costs associated with maintenance treatment. Total treatment costs for the introduction of vedolizumab SC are therefore likely underestimated versus other comparators.

CADTH also noted a few issues for consideration, including the availability of ustekinumab; historical claims data and pan-Canadian Pharmaceutical Alliance (pCPA) negotiations indicate there may be limited uptake of this treatment for CD by participating public drug plans. In addition, there may be an impact on health care resource utilization from vedolizumab SC, mainly in the form of potential reduction of IV administration costs and increased pharmacy dispensing fees. Last, CADTH considered the outcome of the 2016 submission for vedolizumab IV, which recommended a price reduction such that it not exceed the least-costly alternative biologic treatment. Where participating drug plans were able to negotiate a price reduction for vedolizumab IV, a similar price reduction would be needed for vedolizumab SC to remain cost-neutral.

Conclusions

Based on one trial, subcutaneous injection of vedolizumab is more effective than placebo in achieving clinical remission in patients with moderately to severely active CD. The benefits related to other outcomes assessed in the trial are uncertain based on the failure to detect a statistically significant difference between vedolizumab SC and placebo for the secondary outcome (enhanced clinical response), which was ranked higher than other outcomes in the stepwise analysis procedure. The frequency of AEs was similar between placebo and vedolizumab SC, after 52 weeks of treatment.

Based on one sponsor-submitted review of ITCs, [redacted].

Results from an ongoing, open-label, long-term study suggest that the [redacted].

At the submitted price and based on the recommended dosage of 108 mg every 2 weeks, vedolizumab SC has an annual cost of $21,458 per patient in maintenance therapy. This results in cost-neutrality compared to vedolizumab IV on an annual basis; however, the comparative efficacy and safety of vedolizumab SC are uncertain and the exclusion of induction therapy costs underestimates total treatment costs versus other comparators.

Introduction

Disease Background

Crohn disease is a chronic form of IBD that can affect any part of the GI tract, but most commonly affects the ileum (i.e., small intestine), colon (i.e., beginning of the large intestine), and rectum. Common GI symptoms experienced by patients with CD include abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, perianal disease, weight loss, and bloating.[1,2] Inflammation associated with CD can also manifest outside the GI tract, affecting the joints, eyes, and skin of the patient. Complications associated with CD can include fever, malnutrition, weight loss, anemia, bowel obstructions, fistulas, anal fissures, intra-abdominal and other abscesses, and ulcers.[2,3] In addition, patients with colonic CD have been shown to have an increased risk of developing colon cancer.[2] According to the Canadian Gastro-Intestinal Epidemiology Consortium, the predicted prevalence of CD in 2018 was 368 per 100,000 population, thus there are approximately 135,000 Canadians living with CD.[4,5] Based on patient group input for this review, CD has a profound effect on physical, emotional, and social well-being. The classification of disease severity in CD suggested by the American College of Gastroenterology is provided in Table 3.

Table 3: Classification of Disease Severity in Crohn Disease

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

ACG = American College of Gastroenterology; CDAI = Crohn's Disease Activity Index.

Source: American College of Gastroenterology.[10]

Standards of Therapy

Selection of medical therapy is based on the location, extent, phenotype, and severity of disease.[3] Currently there is no cure for CD, and the therapeutic goals include inducing and maintaining clinical and endoscopic remission, reducing the need for long-term corticosteroid use, and preventing the development of colon cancer. Several drug classes are used in the treatment of CD, including aminosalicylates, immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, and 6-mercaptopurine), corticosteroids (e.g., prednisone), TNF alpha antagonists (e.g., infliximab and adalimumab), IL inhibitors, and integrin inhibitors (e.g., vedolizumab).[3,11] With the exception of the TNF alpha antagonists and vedolizumab, all are commonly referred to as conventional therapies. Medical management is based on a stepwise approach, with treatments used sequentially and escalating to either newer therapies or higher doses as patients fail to respond to each step of treatment. Most drugs have important adverse effects that may have short-term or long-

term consequences.[2,11] Surgery, including total colectomy and ileostomy, may be considered for patients with serious complications or for those who do not respond to medical management.[3]

Drug

Vedolizumab is a gut-selective anti-inflammatory biologic. It is a humanized immunoglobin G1 monoclonal antibody that binds exclusively to alpha 4 beta 7 integrin on pathogenic gut-homing lymphocytes and selectively inhibits adhesion of these cells to MAdCAM-1, which is primarily localized to blood vessels within intestinal muscosa and gut-associated lymphoid tissue. Vedolizumab has no known systemic immunosuppressive effects. Vedolizumab is available as powder for solution for IV infusion, 300 mg per vial, or solution for SC injection, 108 mg/0.68 mL pre-filled syringe or pen.[6] Vedolizumab SC has been approved by Health Canada for the treatment of adult patients with CD and received a Notice of Compliance on November 19, 2020.

Vedolizumab has been approved by Health Canada for the use in:

- Treatment of adult patients with moderately to severely active CD who have had an inadequate response, lost response, or were intolerant to immunomodulators or a TNF alpha antagonist; or have had an inadequate response or intolerance to, or demonstrated dependence on, corticosteroids
- Treatment of adult patients with moderately to severely active UC who have had an inadequate response, loss of response, or were intolerant to either conventional therapy or infliximab, a TNF alpha antagonist.[6]

The dosing of vedolizumab IV recommended by Health Canada for CD is 300 mg at 0, 2, and 6 weeks, and then every 8 weeks thereafter. When vedolizumab SC is used as a maintenance treatment following at least 2 IV infusions, the recommended dosing regimen is 108 mg administered by SC injection every 2 weeks The first SC dose should be administered in place of the next scheduled IV dose and every 2 weeks thereafter. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.[6] Vedolizumab IV has been previously reviewed by CADTH, and received CDEC recommendations to reimburse with criteria and conditions for UC in October 2015 and for CD in October 2016. CDEC issued a recommendation to reimburse vedolizumab SC with criteria and conditions for UC in May 2020.

In the current review, the sponsor is seeking reimbursement as per the indication for vedolizumab SC, which is for the maintenance treatment of adults with moderately to severely active CD, following response to induction with vedolizumab IV.

Table 4: Key Characteristics of Vedolizumab, Infliximab, Adalimumab, and Ustekinumab

Characteristic	Vedolizumab	Infliximab	Adalimumab	Ustekinumab
Mechanism	IgG1 monoclonal antibody; binds to the human alpha 4 beta 7 integrin, acting as a gut-selective anti-inflammatory biologic	Anti-TNF. IgG1 kappa monoclonal antibody that neutralizes the biological activity of TNF alpha by specifically binding to its receptors	Anti-TNF. Human IgG1 monoclonal antibody; binds and blocks TNF alpha and its interaction with p55 and p75 cell-surface TNF receptors	Human IgG1 monoclonal antibody; neutralizes cellular responses mediated by IL-12 and IL-23
Indications[a]	**Adult CD** Moderately to severely active CD who have had an inadequate response, lost response, or were intolerant to immunomodulators or a TNF antagonist; or have had an inadequate response or intolerance to, or demonstrated dependence on, a CS	**Adult CD** Reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of CS use in adults with moderately to severely active CD who have had an inadequate response to a CS and/or aminosalicylate **Pediatric CD** Reduction of signs and symptoms and induction and maintenance of clinical remission in pediatrics with moderately to severely active CD who have had an inadequate response to conventional therapy **Fistulizing CD** Adults with fistulizing CD who have not responded despite conventional treatment	**Adult CD** • Reducing signs and symptoms and inducing and maintaining clinical remission in adults with moderately to severely active CD who have had an inadequate response to conventional therapy • Reducing signs and symptoms and inducing clinical remission in adults with moderately to severely active CD who have lost response or are intolerant to infliximab **Pediatric CD** Reducing signs and symptoms and inducing and maintaining clinical remission in patients with severely active CD and/or who have had an inadequate response or were intolerant to conventional therapy and/or a TNF antagonist.	**Adult CD** Moderately to severely active CD who have had an inadequate response, loss of response, or were intolerant to either conventional therapy (CS or immunomodulators) or one or more TNF antagonists, or who were CS-dependent
Administration	IV (induction and maintenance) and SC (maintenance)	IV	SC	IV (induction) and SC (maintenance)
Recommended dose	**Adults (moderate to severe CD)** *IV formulation* • Induction: 300 mg at weeks 0, 2, 6	**Adults (moderate to severe CD)** • Induction: 5 mg/kg at weeks 0, 2, 6	**Adult CD** • Induction: 160 mg at week 0, 80 mg at week 2 • Maintenance: 40 mg q.2.w. beginning at week 4. Dose	• Induction: tiered weight-based dose approximating 6 mg/kg IV at week 0 • Maintenance: 90 mg SC at week 8 and q.8.w. thereafter

Characteristic	Vedolizumab	Infliximab	Adalimumab	Ustekinumab
	• Maintenance: 300 mg q.8.w. following the induction treatment *SC formulation* • Maintenance: 108 mg q.8.w following the induction treatment with IV infusion	• Maintenance: 5 mg/kg q.8.w.; 10 mg/kg for incomplete responders **Adults (fistulizing CD)** • Induction: 5 mg/kg at weeks 0, 2, 6 • Maintenance: 5 mg/kg q.8.w. or 10 mg/kg q.8.w. for those with relapse following an initial response **Pediatrics (moderate to severe CD)** • Induction: 5 mg/kg at weeks 0, 2, 6 • Maintenance: 5 mg/kg q.8.w.	escalation for patients with a disease flare or non-response **Pediatrics CD** • Induction: 160 mg at week 0, 80 mg at week 2 • Maintenance: 20 mg q.2.w. beginning at week 4; 40 mg q.2.w. for patients with a disease flare or non-response	• Alternative maintenance: 90 mg SC at week 12 and q.12.w. thereafter; may switch to q.8.w. for inadequate response
Serious side effects and safety issues	• Contraindicated for patients with active severe infections or opportunistic infections • Infusion reactions and hypersensitivity	• Serious infections • Malignancy • Infusion and serious allergic reactions	• Serious infections • Malignancies, particularly lymphoma • Administration-site reactions	• Infections and reactivation of latent infections • Administration-site reactions • Malignancy

CD = Crohn disease; CS = corticosteroid; IgG1 = immunoglobin G1; IL = interleukin; q.2.w. = every 2 weeks; q.8.w. = every 8 weeks; q.12.w. = every 12 weeks; SC = subcutaneous; TNF = tumour necrosis factor.

[a] Health Canada indication.

Source: Product monographs of vedolizumab (Entyvio),[6] infliximab (Remicade and Inflectra),[12,13] adalimumab (Humira),[14] and ustekinumab (Stelara).[15]

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

Two patient groups submitted input for this review: the Gastrointestinal Society (GI Society) and Crohn's and Colitis Canada (CCC).

The GI Society is a national registered charity that is committed to improving the lives of patients 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 the BadGut Basics pamphlets and a newsletter called *Inside Tract | Du coeur au ventre*. Furthermore, the GI Society informs Canadians through free BadGut lectures given coast to coast, covering various digestive conditions for patients, caregivers and others, and manages a website in both English and French. The society provides additional patient resources, such as responding to information requests and participating in community initiatives. The society has also supported several GI research studies along with its sister charity, the Canadian Society of Intestinal Research.

As a national, volunteer-based charity focused on finding the cures for CD and UC and improving the lives of people affected by these diseases, CCC has a network of volunteer-led chapters in 46 communities across the country, offering information, events, fundraising opportunities, and encouragement. Since its founding in 1974, CCC has invested more than $130 million in CD and colitis research. In addition, the organization provides patient programs, advocacy, and awareness.

None of the patient groups received help from outside their organizations to complete the submissions, or to collect or analyze data used in their submissions. Takeda Inc., the sponsor of Entyvio, provided funding to the GI Society in excess of $50,000 in 2019. Financial payments of more than $50,000 from different pharmaceutical companies, including Takeda, were reported by CCC over the past 2 years.

For the GI Society, patient input used to inform this submission was obtained through 3 surveys: a 2015 survey completed by 423 Canadians with IBD including CD; a 2018 survey completed by 432 Canadians with IBD, 56% of whom had CD; and an ongoing survey, which has had approximately 500 respondents. The GI Society has also had direct contact with patients affected with IBD at BadGut Lectures, patient roundtables, and through telephone calls, emails, and social media.

CCC gathered patient perspectives via its published reports, such as the 2018 *Impact of Inflammatory Bowel Disease (IBD) Report*, and informational brochures found on CCC's website. A series of surveys conducted in June 2020 and interviews with 21 patients who had experience with vedolizumab in treating CD contributed to this submission as well.

Disease Experience

The patient groups described CD as a chronic GI condition that primarily affects the small intestine and/or colon. The most frequent symptoms associated with CD are persistent diarrhea, rectal bleeding, abdominal pain, and weight loss. These symptoms vary from

person to person and may change over time. Patients with CD may also experience symptoms outside of the GI tract that may affect the joints, bones, eyes, skin, and liver. Fever and fatigue are common. Anemia may also present when diarrhea and blood loss are severe. Development of fistula, most commonly around the anal area, is another serious complication of CD. In addition to the physical symptoms, the patient groups stated that CD has a profound effect on patients' emotional and social life. It can affect a person's sense of self, particularly for children and young adults. Both patient groups indicated that patients are constantly concerned with future flare-ups, which can be unpredictable and severely disruptive.

Responses to GI Society surveys included: "It's like I can't control anything. I feel weak and can barely get up. My biggest concerns usually when I see blood and determining at what point to go to the ER" and "The worst part is fear of irreversible permanent damage that will affect your day to day life forever."

Respondents in the CCC survey indicated that pain and frequent unpredictable bowel movements were their top priority concerns. They experienced "a constant urgency to use the bathroom and the malabsorption (of nutrients) that comes from the frequent bowel movements," "horrible cramping," and "the need to wear an adult diaper to bed at night."

Experience With Treatment

The GI Society described treatment of CD as multifaceted as it involves managing symptoms and consequences of the disease, as well as trying to reduce the underlying inflammation. When one medication fails to treat their disease, patients switch to another type. First-line treatments for CD include anti-inflammatory drugs such as 5-aminosalicylic acid and corticosteroids to control disease flare-ups. These drugs can settle acute inflammation and for some, can keep inflammation inactive when taken long-term (maintenance). Corticosteroids in rectal formulations may be used for topical relief; however, these can be ineffective for a patient with significant diarrhea. Immunosuppressants help reduce dependence on steroids and can be used in patients with steroid-resistant disease, although it could take 6 months to see any results. When other medications fail to relieve symptoms, biologics are used. Even though different treatment options are available, many patients still have difficulties obtaining remission and/or adequate symptom relief. For example, in the GI Society submission, 63% of respondents (many of whom had been suffering for years) reported symptom reduction on a biologic and 23% reported confirmed remission. One male patient had experience with Humira and vedolizumab. After losing efficacy with Humira (the patient failed to take Humira consistently when he was feeling well), he received vedolizumab through a clinical trial. The patient noted that his diarrhea was manageable with vedolizumab and the associated pain decreased, although he still experienced some urgency. He also liked the delivery method (SC injection) of vedolizumab. This patient rated his experience with vedolizumab 10 out of 10 in an assessment.

Many respondents from the CCC group have experienced multiple medications over many years. One patient said, "I have tried over 20 different treatments since 1998." Patients reported various side effects associated with the current treatment options, such as kidney damage, skin reactions, or liver damage. In some cases, the side effects led to the discontinuation of treatment. Some patients required invasive surgery due to ineffective treatments as the disease progressed. Among the 21 patients who had experience with vedolizumab, benefits of this treatment were reported. The most commonly reported side effect associated with vedolizumab was fatigue.

The following quotes provide patient perspectives associated with this treatment.

- "… keep me in remission which allowed me to enjoy more events socially."
- "My Crohn's has been under control since I've been under Entyvio without too many side effects."
- "I definitely feel that my symptoms are much better on Entyvio. With that being said I'm not symptom free but I am able to manage life very well … have enough energy/good health days to complete everything that comes up in my life."

The CCC patient group also described the challenge related to the time commitment required for treatment.

Improved Outcomes

Both patient groups emphasized the importance of symptom relief, quality-of-life improvements, and achieving remission in patients with CD.

The GI Society indicated that given that all patients respond differently to treatment, it is important for them to have access to a variety of treatment options. The patient group suggested that vedolizumab has the potential to improve the health and quality of life of many individuals currently suffering from ineffective treatments.

Patients responding through CCC expressed concerns about the challenges in receiving medication for CD via infusion at clinics due to the significant time commitment and time away from work and school. In addition, for patients who are at high risk for coronavirus disease 2019, those who have comorbid conditions, or those experiencing challenges with infusions due to difficulties finding an appropriate IV injection site, a self-administered option, such as the SC formulation of vedolizumab, is desirable.

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 CD.

Based on current standards of practice with existing therapies, the clinical expert consulted by CADTH indicated that there are several areas of unmet need where vedolizumab SC may play a role:

- as primary induction therapy for CD in patients who are primarily non-responsive to either conventional therapy with immunomodulators or TNF alpha antagonists
- in the setting of secondary non-response during maintenance therapy; an important proportion of CD patients will lose response to TNF alpha antagonist therapy during maintenance, either due to formation of anti-drug antibodies or to inflammatory mechanisms that are independent of TNF
- as salvage therapy for patients responding to immunomodulation therapy or TNF alpha antagonists who develop adverse effects to therapy; while immunomodulators such as azathioprine and methotrexate are generally safe medications, well-known side effects include the development of pancreatitis, neutropenia, hepatitis, and neoplasia (e.g.,

skin cancers); in addition, severe allergic reactions, psoriatic skin diseases, neurological complications, congestive heart failure, lupus, and severe infections can be associated with TNF alpha antagonists.

Patients with moderate to severe CD require treatment with biologic therapies (typically starting with the TNF alpha antagonists infliximab and adalimumab) after not meeting treatment goals with aminosalicylates, immunosuppressants, and corticosteroids. Biologic treatments are usually administered in combination with an immunosuppressant such as azathioprine or methotrexate. Patients who respond to this approach may continue with biologic treatment for several years. However, some patients experience a reduction in response over time (e.g., due to the development of antibodies to a particular biologic treatment) or become intolerant of biologic treatment (e.g., due to side effects such as an allergic reaction or other drug-related complications), which necessitates a change in the treatment regimen in order to maintain clinical responsiveness. At present, patients who experience a loss of response to either infliximab or adalimumab can be switched to the other TNF alpha antagonist, although this is often associated with a lower clinical response compared with that in patients who have not been exposed previously to a TNF alpha antagonist. Therefore, there exists an unmet need for patients with moderate to severe CD who are no longer responsive to or intolerant of TNF alpha antagonists.

Vedolizumab is a biologic agent that is an integrin inhibitor, and therefore represents a different class of biologic compared to the TNF alpha antagonists and the IL-12 and IL-23 inhibitor ustekinumab.

There are no barriers to identifying patients for whom vedolizumab treatment would be appropriate in a consistent manner, although a specialized diagnostic test, such as endoscopy, computed tomography scan, abdominal ultrasound, or magnetic resonance enterography, is usually required to assess disease activity and severity for all patients who require biologic therapy, in accordance with standard clinical practice. The following are also advisable to assess prior to initiating treatment:

- assessment for previous TB exposure
- hepatitis B serology
- pregnancy test in women of childbearing age
- immunization history and boosters for low antibody titers.

Sponsor's Summary of the Clinical Evidence

The clinical evidence summarized in this section was prepared by the sponsor in accordance with the CADTH tailored review process.

Pivotal Studies

Table 5: Details of Included Studies

Characteristics		MLN0002SC-3031 (VISIBLE 2)
Designs and Populations	**Study design**	Phase III, multi-centre, multinational, randomized, double-blind, placebo-controlled study
	Locations	Study enrolled patients from [redacted]
	Randomized (N)	410

	Inclusion criteria	• Patient had a diagnosis of CD established at least 3 months before screening by clinical and endoscopic evidence and corroborated by a histopathology report
		• Male or female and aged 18 to 80 years, inclusive
		• Male patients and female patients who were nonsterile with childbearing potential and agreed to use adequate contraception
		• Patient had moderately to severely active CD as determined by a CDAI score of 220 to 450 within 7 days prior to the first dose of the study drug and 1 of the following:
		  ○ CRP level > 2.87 mg/L during the screening period or
		  ○ ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous centimetres of intestine) consistent with CD, within 4 months before screening or
		  ○ fecal calprotectin > 250 mcg/g stool during the screening period in conjunction with computed tomography enterography, magnetic resonance enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing CD ulcerations (aphthae not sufficient), within 4 months before screening
		• The patient had CD involvement of the ileum and/or colon, at a minimum
		• Patients with extensive colitis or pancolitis of > 8 years duration or left-sided colitis > 12 years duration must have had documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (if not performed in previous 12 months, must have been performed during screening)
		• Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, age > 50 years, or other known risk factors must have been up-to-date on colorectal cancer surveillance (may have been performed during screening)
		• Patient had demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents:
		  ○ immunomodulators
		  ○ corticosteroids
		  ○ TNF alpha antagonists

	Exclusion criteria	*GI exclusion criteria* • The patient had evidence of abdominal abscess at the initial screening visit • The patient had extensive colonic resection, subtotal or total colectomy • The patient had a history of > 3 small bowel resections or diagnosis of short bowel syndrome • The patient had received tube feeding, defined formula diets, or parenteral alimentation within 28 days before the administration of the first dose of the study drug • The patient had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine • The patient received any investigational or approved non-biologic therapies, for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever was longer) • The patient had received any investigational or approved biologic or biosimilar agent within 60 days or 5 half-lives of screening (whichever was longer)

Characteristics		MLN0002SC-3031 (VISIBLE 2)

		• The patient had used topical (rectal) treatment with 5-ASA or corticosteroid enemas/ suppositories within 2 weeks of the administration of the first dose of the study drug
		• The patient currently required or was anticipated to require surgical intervention for CD during the study
		• The patient had a history or evidence of adenomatous colonic polyps that had not been removed
		• The patient had a history or evidence of colonic mucosal dysplasia
		• The patient had a suspected or confirmed diagnosis of ulcerative colitis, indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis
		
		Infectious disease exclusion criteria
		• The patient had evidence of an active infection during the screening period
		• The patient had evidence of, or treatment for, *Clostridium difficile* infection or another intestinal pathogen within 28 days before the first dose of the study drug
		• The patient had chronic hepatitis B virus infection or chronic hepatitis C virus infection
		• The patient had active or latent tuberculosis
		• The patient had any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, HIV infection, organ transplantation)
		• The patient had received any live vaccinations within 30 days prior to screening
		• The patient had clinically significant infection (e.g., pneumonia, pyelonephritis) within 30 days prior to screening, or ongoing chronic infection
		
		General exclusion criteria
		• The patient had previous exposure to approved or investigational anti-integrin antibodies (e.g., natalizumab, efalizumab, etrolizumab, abrilumab [AMG 181]), anti-mucosal addressin cell adhesion molecule-1 antibodies or rituximab
		• The patient had previous exposure to vedolizumab
		• The patient had hypersensitivity or allergies to any of the vedolizumab excipients
		• The patient had any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety
		• The patient had any surgical procedure requiring general anesthesia within 30 days prior to screening or was planning to undergo major surgery during the study period
		• The patient had any history of malignancy, except for the following: (a) adequately treated nonmetastatic basal-cell skin cancer; (b) squamous-cell skin cancer that had been adequately treated and that had not recurred for at least 1 year before screening; and (c) history of cervical carcinoma in situ that had been adequately treated and that had not recurred for at least 3 years before screening; patients with remote history of malignancy (e.g., > 10 years since completion of curative therapy without recurrence) were to be considered based on the nature of the malignancy and the therapy received and must have been discussed with the sponsor on a case-by-case basis before screening
		• The patient had a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumour, or neurodegenerative disease
		• The patient had a positive PML subjective symptom checklist at screening (or before the administration of the first dose of the study drug at week 0)
		• The patient had any of the following laboratory abnormalities during the screening period:
		  ○ hemoglobin level < 8 g/dL
		  ○ white blood cell count < 3×10^9/L
		  ○ lymphocyte count < 0.5×10^9/L
		  ○ platelet count < 100×10^9/L or > $1,200 \times 10^9$/L
		  ○ alanine aminotransferase or aspartate aminotransferase > 3 × the upper limit of normal
		  ○ alkaline phosphatase > 3 × the upper limit of normal
		  ○ serum creatinine > 2 × the upper limit of normal
		• The patient had a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year before screening

Characteristics		MLN0002SC-3031 (VISIBLE 2)
		• The patient had an active psychiatric problem that, in the investigator's opinion, may have interfered with compliance with study procedures • The patient or caregiver was unable to attend all the study visits or comply with study procedures • The patient was required to take excluded medications • The patient was unwilling or unable to self-inject, or did not have a caregiver (defined as a legal adult) to inject the study medication • Female patients who were lactating or had a positive serum pregnancy test during the screening period or a positive urine pregnancy test at week 0, before study drug administration • If female, the patient was intending to become pregnant before, during, or within 18 weeks after participating in this study; or intended to donate ova during such time period • If male, the patient intended to donate sperm during the course of this study or for 18 weeks thereafter • The patient was an immediate family member, study-site employee, or was in a dependent relationship with a study-site employee who was involved in conducting this study (e.g., spouse, parent, child, sibling) or may have consented under duress
DRUGS	**Intervention**	Vedolizumab, 108 mg, SC injection, every 2 weeks
	Comparator(s)	Placebo, SC, every 2 weeks
DURATION	**Phase**	III
	Run-in	4-week screening period 6-week induction phase (open-label)
	Double-blind	46 weeks
	Follow-up	18 weeks (final safety visit)
OUTCOMES	**Primary end point**	Proportion of patients with clinical remission, defined as a CDAI score ≤ 150, at week 52
	Secondary and exploratory end points	*Secondary end points* • Proportion of patients with enhanced clinical response, defined as a ≥ 100-point decrease in CDAI score from baseline (week 0), at week 52 • Proportion of patients with corticosteroid-free remission, defined as patients using oral corticosteroids at baseline (week 0) who have discontinued oral corticosteroids and are in clinical remission at week 52 • Proportion of TNF alpha antagonist–naive patients who achieved clinical remission, defined as CDAI score ≤ 150, at week 52 *Patient-reported outcome end points* • Changes in IBDQ total score and subscores, from baseline (week 0) to week 52 and from week 6 to week 52 • Changes in EQ-5D utility scores and EQ-5D VAS score from baseline (week 0) to week 52 and from week 6 to week 52 • Changes in WPAI-CD instrument end points (percent of work time missed, impairment while working, overall work impairment, and activity impairment) from baseline (week 0) to week 52 and from week 6 to week 52 *Exploratory end points* • Other efficacy end points: ○ [redacted] ○ [redacted] ○ Proportion of patients with an elevated CRP level at baseline (week 0) who have reduction in CRP level at week 52 ○ [redacted] ○ [redacted]

Characteristics		MLN0002SC-3031 (VISIBLE 2)
		[redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ [redacted] ○ Pharmacokinetic end points: [redacted] • Immunogenicity end points: ○ Proportion of patients with positive AVA during the study ○ Proportion of patients with positive neutralizing AVA during the study ○ Proportion of patients with clinical remission at week 52 by positive AVA ○ Proportion of patients with clinical response at week 52 by positive AVA ○ Proportion of patients with infusion-related reactions by positive AVA ○ Proportion of patients with injection-site reactions by positive AVA ○ Proportion of patients with hypersensitivity reactions by positive AVA • [redacted] ○ [redacted] ○ [redacted] • Health care resource utilization and patient-reported outcome end points: ○ Proportion of patients with clinical remission at week 6 and at week 52, defined based on patient-reported items from CDAI diary ○ Proportion of patients with clinical response at week 6 and at week 52, defined based on patient-reported items from CDAI diary [redacted] • Safety assessments: ○ Safety for maintenance therapy as assessed by AEs, AEs of special interest (including serious infections including opportunistic infection such as PML, liver injury, malignancies, infusion-related or injection-site reactions, or systemic reactions and hypersensitivity), SAEs, vital signs, results of standard laboratory tests (clinical chemistry, hematology, coagulation, urinalysis), and results of 12-lead ECGs
NOTES	**Publications**	NCT02611817

5-ASA = 5-aminosalicylic acid; AE = adverse event; AVA = anti-vedolizumab antibodies; CD = Crohn disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; ECG = electrocardiogram; EQ-5D = EuroQol 5-Dimensions questionnaire; GI = gastrointestinal; IBDQ = Inflammatory Bowel Disease Questionnaire; PML = progressive multifocal leukoencephalopathy; SAE = serious adverse event; SC = subcutaneous; TNF = tumour necrosis factor; [redacted] VAS = Visual Analogue Scale; WPAI-CD = Work Productivity and Activity Impairment–Crohn's disease.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Description of Studies

Study SC-3031 was a pivotal, phase III, multi-centre, multinational, randomized, double-blind, placebo-controlled study, designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC injection in adult patients with moderately to severely active CD who achieved a clinical response at week 6 with open-label therapy with 300 mg vedolizumab IV infusion at weeks 0 and 2.

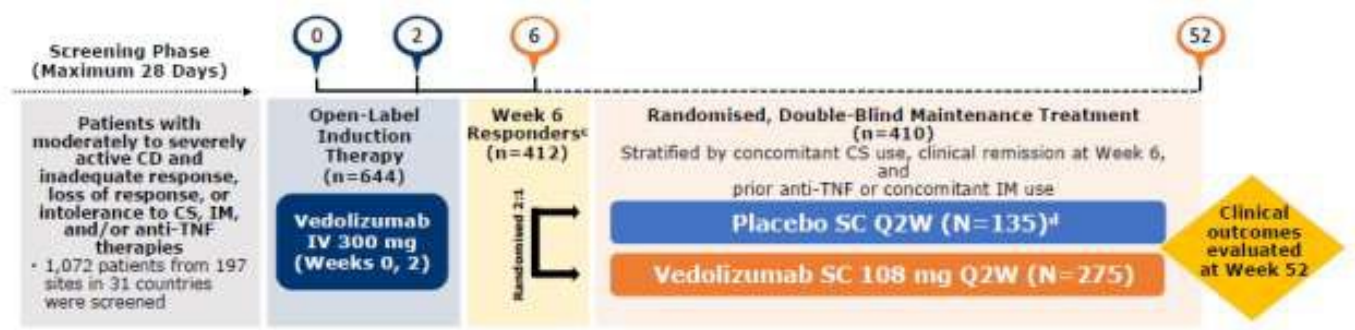
A total of 169 sites enrolled patients into the open-label induction phase, of which [redacted] enrolled patients into the double-blind maintenance phase. Five of the sites were in Canada.

The primary objective was to assess the effect of vedolizumab SC maintenance treatment on clinical remission at week 52 in patients with moderately to severely active CD who achieved clinical response at week 6 following administration of vedolizumab IV at weeks 0 and 2. Secondary objectives were to determine the effect of vedolizumab SC maintenance treatment on enhanced clinical response at week 52, corticosteroid-free remission at week 52, and clinical remission at week 52 in patients who are naive to TNF alpha antagonist exposure.

Following a 4-week (28-day) screening period, 644 patients were enrolled and treated in a 6-week open-label induction phase with vedolizumab IV. These patients received open-label infusions of vedolizumab IV 300 mg at weeks 0 and 2, and were assessed for clinical response by CDAI at week 6 (defined as a ≥ 70-point decrease in CDAI score from baseline [week 0]). Of the patients who entered the induction phase, 412 (64%) achieved a clinical response at week 6 and were eligible for randomization into the double-blind maintenance phase of the study. A total of 410 patients were randomized in a 2:1 ratio to double-blind treatment with vedolizumab SC administered every 2 weeks or placebo SC every 2 weeks

Randomization was stratified by concomitant use of oral corticosteroids, clinical remission status at week 6, and previous treatment failure with or exposure to TNF alpha antagonists or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use.

Figure 1: Study Design for SC-3031



CD = Crohn disease; CS = corticosteroid; IM = immunomodulators; Q2W = every 2 weeks; SC = subcutaneous; TNF = tumour necrosis factor.
Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Populations

Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Patient had a diagnosis of CD established at least 3 months before screening by clinical and endoscopic evidence and corroborated by a histopathology report.
- Male or female and aged 18 to 80 years, inclusive.
- Patient had moderately to severely active CD as determined by a CDAI score of 220 to 450 within 7 days prior to the first dose of the study drug and 1 of the following:
  - CRP level greater than 2.87 mg/L during the screening period or
  - ileocolonoscopy with photographic documentation of a minimum of 3 nonanastomotic ulcerations (each > 0.5 cm in diameter) or 10 aphthous ulcerations (involving a minimum of 10 contiguous centimetres of intestine) consistent with CD, within 4 months before screening or
  - fecal calprotectin > 250 mcg/g stool during the screening period in conjunction with computed tomography enterography, magnetic resonance enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy revealing CD ulcerations (aphthae not sufficient), within 4 months before screening.
- Patient had CD involvement of the ileum and/or colon, at a minimum.
- Patients with extensive colitis or pancolitis of more than 8 years duration or left-sided colitis more than 12 years duration must have had documented evidence that a surveillance colonoscopy was performed within 12 months of the initial screening visit (if not performed in previous 12 months, must have been performed during screening).
- Patients with a family history of colorectal cancer, personal history of increased colorectal cancer risk, older than 50 years, or other known risk factors must have been up-to-date on colorectal cancer surveillance (may have been performed during screening).
- Patient had demonstrated an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents:
  - immunomodulators
  - corticosteroids
  - TNF alpha antagonists.

Key Exclusion Criteria

GI Exclusion Criteria

- The patient had evidence of abdominal abscess at the initial screening visit.
- The patient had extensive colonic resection, subtotal or total colectomy.
- The patient had a history of more than 3 small bowel resections or diagnosis of short bowel syndrome.
- The patient had received tube feeding, defined formula diets, or parenteral alimentation within 28 days before administration of the first dose of the study drug.
- The patient had ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine.

- The patient received any investigational or approved non-biologic therapies for the treatment of underlying disease within 30 days or 5 half-lives of screening (whichever was longer).
- The patient had received any investigational or approved biologic or biosimilar agent within 60 days or 5 half-lives of screening (whichever was longer).
- The patient had used topical (rectal) treatment with 5-aminosalicylic acid or corticosteroid enemas/suppositories within 2 weeks of administration of the first dose of the study drug.
- The patient currently required or was anticipated to require surgical intervention for CD during the study.
- The patient had a history or evidence of adenomatous colonic polyps that had not been removed.
- The patient had a history or evidence of colonic mucosal dysplasia.
- The patient had a suspected or confirmed diagnosis of UC, indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, or microscopic colitis.

Infectious Disease Exclusion Criteria

- The patient had evidence of an active infection during the screening period.
- The patient had evidence of, or treatment for, *Clostridium difficile* infection or another intestinal pathogen within 28 days before the first dose of the study drug.
- The patient had chronic hepatitis B virus infection or chronic hepatitis C virus infection.
- The patient had active or latent tuberculosis.
- The patient had any identified congenital or acquired immunodeficiency (e.g., common variable immunodeficiency, HIV infection, organ transplantation).
- The patient had received any live vaccinations within 30 days prior to screening.
- The patient had clinically significant infection (e.g., pneumonia, pyelonephritis) within 30 days prior to screening, or ongoing chronic infection.

General Exclusion Criteria

- The patient had previous exposure to approved or investigational anti-integrin antibodies (e.g., natalizumab, efalizumab, etrolizumab, abrilumab [AMG 181]), MAdCAM-1 antibodies, or rituximab.
- The patient had previous exposure to vedolizumab.
- The patient had hypersensitivity or allergies to any of the vedolizumab excipients.
- The patient had any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the investigator, would confound the study results or compromise patient safety.
- The patient had any surgical procedure requiring general anesthesia within 30 days prior to screening or was planning to undergo major surgery during the study period.
- The patient had any history of malignancy, except for the following: (a) adequately treated nonmetastatic skin cancer; (b) squamous-cell skin cancer that had been adequately treated and that had not recurred for at least 1 year before screening; and (c) history of cervical carcinoma in situ that had been adequately treated and that had not recurred for at least 3 years before screening. Patients with remote history of

malignancy (e.g., > 10 years since completion of curative therapy without recurrence) were to be considered based on the nature of the malignancy and the therapy received and must have been discussed with the sponsor on a case-by-case basis before screening.

- The patient had a history of any major neurological disorders, including stroke, multiple sclerosis, brain tumour, or neurodegenerative disease.
- The patient had a positive progressive multifocal leukoencephalopathy subjective symptom checklist at screening (or before the administration of the first dose of the study drug at week 0).
- The patient had any of the following laboratory abnormalities during the screening period:
  - hemoglobin level less than 8 g/dL
  - white blood cell count less than 3 × 10^9/L
  - lymphocyte count less than 0.5 × 10^9/L
  - platelet count less than 100 × 10^9/L or > 1,200 × 10^9/L
  - alanine aminotransferase or aspartate aminotransferase greater than 3 × the upper limit of normal (ULN)
  - alkaline phosphatase greater than 3 × ULN
  - serum creatinine greater than 2 × ULN.

Baseline Characteristics

Overall, baseline demographics were similar for vedolizumab SC and placebo patients in the full analysis set (FAS) and safety analysis set (SAF). One randomized patient was not treated in the maintenance phase.

Among the patients who were randomized and received blinded treatment in the maintenance phase of the study (FAS), there was a higher proportion of male patients than female patients (54.5% and 45.5%, respectively). Most patients (91.4%) were White. The [redacted] and few patients were 65 years of age or older (3.9%). The mean body weight was 69.8 kg in the placebo arm and 74.1 kg in the vedolizumab SC arm. With respect to geographic distribution, [redacted] of patients in the placebo arm and vedolizumab SC arm, respectively, were enrolled at sites in North America.

Table 6: Summary of Baseline Characteristics

Characteristic	Placebo N = 134[a]	Vedolizumab SC N = 275
Age (years), mean (SD)	36.1 (12.9)	38.2 (13.9)
Male gender, n (%)	66 (49.3)	157 (57.1)
Body weight (kg), mean (SD)	69.8 (18.1)	74.1 (19.0)
[redacted]	[redacted]	[redacted]
Duration of CD (years), mean (SD)	8.2 (8.4)	9.5 (8.3)
Prior anti–TNF alpha use (yes), n (%)	71 (53.0)	168 (61.1)
Concomitant medications at week 0, n (%)		
IMM only	34 (25.4)	51 (18.5)
Oral corticosteroids only	31 (23.1)	64 (23.3)
Oral corticosteroids + IMM	13 (9.7)	31 (11.3)
Ileal disease only	21 (15.7)	66 (24.0)
C-reactive protein > 5 mg/mL, n (%)	80 (59.7)	168 (61.1)
Fecal calprotectin (mcg/g), median (range)	871 (10 to 15,050)	736 (10 to 14,570)
Severe disease (CDAI > 330), n (%)	53 (39.6)	115 (41.8)

CD = Crohn disease; CDAI = Crohn's Disease Activity Index; IMM = immunomodulator; SD = standard deviation; TNF alpha = tumour necrosis factor alpha.

[a] One randomized patient was not treated in the maintenance phase.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Interventions

- Vedolizumab, 108 mg, SC injection, every 2 weeks for 46 weeks.
- Placebo, subcutaneous injection, every 2 weeks for 46 weeks.

A total of 139 patients (44 patients in the placebo group and 95 patients in the vedolizumab SC group) had concomitant oral corticosteroid (i.e., prednisone or equivalent and budesonide or equivalent) use at baseline. These patients continued on the same dose of corticosteroids until week 6, when they began a mandatory corticosteroid-tapering regimen. For patients who could not tolerate the corticosteroid taper without recurrence of clinical symptoms, corticosteroids may have been increased up to the original dose at the start of induction therapy (not to have exceeded the baseline dose). Patients who required consistently higher doses of corticosteroids were to be withdrawn from the study.

In this study, any new medication or any increase in the dose of a baseline medication required to treat new or unresolved CD symptoms (other than antidiarrheals for control of chronic diarrhea) was considered a rescue medication. An increase in corticosteroid dose back to baseline for patients undergoing corticosteroid tapering was not considered rescue medication. Administration of rescue medications, approved or investigational, constituted treatment failure. Rescue medications should not have been withheld if, in the opinion of the investigator, failure to prescribe them would have compromised patient safety.

Patients were trained by the health care provider (HCP), either an investigator or designee, on the proper SC injection technique and how to manage hypersensitivity reactions potentially associated with the injection. Patients or their caregivers injected vedolizumab SC or placebo SC under the supervision of the HCP during clinic visits to ensure proper

injection technique and to allow the HCP to monitor AEs and potential hypersensitivity or injection-site reactions associated with SC injection.

Outcomes

Primary End Point

- The proportion of patients with clinical remission, defined as a CDAI score of at least 150, at week 52.

Secondary End Points

- The proportion of patients with enhanced clinical response, defined as a decrease of at least 100 points in CDAI score from baseline, at week 52.
- The proportion of patients with corticosteroid-free remission, defined as patients using oral corticosteroids at baseline who have discontinued oral corticosteroids and are in clinical remission at week 52.
- The proportion of TNF alpha antagonist–naive patients who achieved clinical remission, defined as a CDAI score of least 150, at week 52.

The CDAI consists of an 8-item list (soft or liquid stools, abdominal pain, general well-being, symptoms manifested, antidiarrheal use, abdominal mass, hematocrit, body weight), each with an individual score and weighting factor.[ii] The CDAI score is calculated as a weighted product of the scores of each item and their respective weighting factors. Index scores of 150 and below are associated with non-active disease (remission), while values above that indicate active disease; values above 450 indicated extremely severe disease.[iii]

Statistical Analysis

All statistical testing was performed at a 2-sided 0.05 level of significance. To control the overall type I error rate for the comparison between vedolizumab SC and placebo groups for the primary and secondary end points, a hierarchical approach was applied to the statistical testing. The statistical inference for the first secondary end point of enhanced clinical response at week 52 was only performed if the primary end point, the proportion of patients with clinical remission at week 52, was statistically significant ($P < 0.05$). The second secondary end point of corticosteroid-free remission at week 52 was only tested if the first secondary end point was statistically significant ($P < 0.05$). The third secondary end point of clinical remission at week 52 among TNF alpha antagonist–naive patients was only tested if the second secondary end point was statistically significant ($P < 0.05$). Multiplicity was not adjusted across exploratory end points.

Data Imputation Methods

Missing data for dichotomous (i.e., proportion-based) end points were handled using the nonresponder imputation method in which any patient with missing information for determination of end-point status was considered a treatment failure/nonresponder in the analysis. A sensitivity analysis was conducted to assess the impact of dropouts for different missing mechanisms using a hybrid approach in which discontinuation due to an AE or lack of efficacy was imputed as nonresponder and other discontinuation/missing data were imputed using multiple imputation for primary and all secondary efficacy end points. Missing data for continuous end points were imputed using the last available post-baseline observation carried forward method. For patients with all post-baseline measurements missing, the missing data were imputed using the baseline observation carried forward method.

Primary Outcome(s) of the Studies

Power Calculation

Assuming a clinical remission rate of 38% for vedolizumab and 22% for placebo at week 52, a sample size of 258 patients in the vedolizumab group and 129 patients in the placebo group was needed to provide 90% power at a 2-sided 0.05 level of significance. To ensure a randomized sample size of 387 patients, and assuming 47% of the patients entering induction would achieve clinical response at week 6, approximately 824 patients were needed to be enrolled into the study.

Statistical Test or Model

The proportion of patients with clinical remission at week 52 was summarized descriptively by treatment group. Count, percentage, and associated 95% CI using the Clopper-Pearson method was provided for each treatment group. The primary end point was analyzed using Cochran-Mantel-Haenszel (CMH) test, stratified by randomization stratification factors reported in an interactive web response system (IWRS). Respondents were asked about concomitant use of oral corticosteroids (yes or no), clinical remission status at week 6 (yes or no), and previous TNF alpha antagonist failure/exposure or concomitant immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) use (yes or no). The P value and the point estimate of the treatment difference based on the CMH method adjusted for stratification factors along with a 95% CI were presented. If the number of remitters or nonremitters in either treatment arm was too small (5 or fewer), Fisher exact method with exact unconditional confidence limits was to be used instead. All patients with missing data for determination of clinical remission status at week 52 were considered nonremitters in the analysis.

Secondary Outcomes of the Study

Enhanced clinical response at week 52 was analyzed in the FAS patients. Corticosteroid-free remission at week 52 was analyzed in a subset of the FAS patients with baseline concomitant oral corticosteroid use (based on data reported in the concomitant medications electronic case report form), where corticosteroid use was defined as prednisone or equivalent and/or budesonide or equivalent. The proportion of TNF alpha antagonist–naive patients who achieved clinical remission was analyzed in a subset of the FAS patients who were TNF alpha antagonist–naive (based on data reported in the prior therapy electronic case report form).

All secondary end points were analyzed in a manner similar to that of the primary efficacy end point, using CMH tests for treatment differences, stratified by randomization stratification factors reported in the IWRS (except for corticosteroid-free remission, for which concomitant use of the oral corticosteroid stratification factor was not considered). All patients with missing data for determination of the status of secondary efficacy end points at week 52 were considered nonresponders/nonremitters in the analysis. The exact method would be performed if the number of observations in either treatment arm was 5 or fewer.

Subgroup Analyses

Descriptive analyses were performed on the primary and all secondary end points to evaluate the treatment effect across subpopulations. The treatment effect in proportions in vedolizumab SC and placebo and associated 95% CI using the Clopper-Pearson method are provided for each subgroup. The point estimate of the absolute treatment difference between vedolizumab SC and placebo based on the crude estimate and associated 95% CI (using the normal approximation method) are presented. If the number of observations was

too small (i.e., 5 or fewer) in either treatment arm, the exact method would be performed instead.

For subgroup analysis by prior use of TNF alpha antagonist only, nominal P values were obtained by the CMH test stratified by randomization stratification factors reported in the IWRS, or Fisher's exact test in the event of small number of responders/remitters or nonresponders/nonremitters (i.e., 5 or fewer).

Subpopulations were defined by the following baseline characteristics:

- age (< 35 years, ≥ 35 to < 65 years, ≥ 65 years)
- gender
- race (Asian, Black or African-American, White, other)
- duration of CD (< 1 year, ≥ 1 year to < 3 years, ≥ 3 years to < 7 years, ≥ 7 years)
- geographic region (North America, South America, Western/Northern Europe, Central Europe, Eastern Europe, East Asia, Africa/Australia)
- baseline disease activity (moderate [CDAI ≤ 330], severe [CDAI > 330])
- baseline fecal calprotectin (≤ 250 mcg/g, > 250 to ≤ 500 mcg/g, > 500 mcg/g)
- baseline CRP (≤ 5 mg/L, > 5 mg/L to ≤ 10 mg/L, > 10 mg/L)
- baseline fistula status (draining, all closed, none)
- disease localization (ileum only, colon only, ileocolonic, other)
- clinical remission status at week 6
- prior TNF alpha antagonist therapy (naive, exposed but not failure, failure; failure was further categorized by type: inadequate response, loss of response, intolerance)
- prior immunomodulator and TNF alpha antagonist failure (yes or no)
- prior corticosteroids failure (yes or no)
- prior immunomodulator failure (yes or no)
- baseline concomitant therapies: corticosteroids and immunomodulators (concomitant corticosteroids only, concomitant immunomodulators only, concomitant 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 but not TNF alpha antagonist or immunomodulator failure).

If the value of the grouping variable could not be determined, the patient would be excluded from the corresponding subgroup analysis (e.g., if the age was missing for a particular patient, then that patient was not included in the age-related subgroup analysis). If the number of patients in any subgroup across the 2 treatment groups was fewer than 10, that subgroup would not be presented.

[redacted]

Sensitivity Analyses

The following pre-specified sensitivity and additional analyses were performed for primary and all secondary end points:

- The primary analysis was repeated for primary and secondary efficacy end points using the intention-to-treat (ITT) population for additional analysis.
- The primary analysis was repeated for primary and secondary efficacy end points using the per-protocol set (PPS) for sensitivity analysis.
- To assess the impact of dropouts for different missing mechanisms for primary and all secondary end points, 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 and other discontinuation/missing data were imputed using multiple imputations. [redacted]
- If any clinical site had detected or reported significant noncompliance with regulatory requirements during the study, a sensitivity analysis was to be conducted for the primary efficacy end point in the FAS, excluding all patients from that particular site.

Analysis Populations

Full Analysis Set

- The FAS included all randomized patients who received at least 1 dose of the study SC drug (placebo or vedolizumab). Patients who only received induction IV therapy and were not randomized into the maintenance phase were not included in the FAS. Patients in this set were analyzed according to the treatment they were randomized to receive.
- The FAS was used for the efficacy analysis, except for: corticosteroid-free remission, clinical remission in TNF alpha antagonist–naive patients, [redacted].

ITT Set

- The ITT population included all randomized patients. Patients in this set were analyzed according to the treatment they were randomized to receive. Analyses of primary and secondary efficacy end points were performed in the ITT population as additional analyses.

Per-Protocol Set

- The PPS is a subset of the FAS. The PPS consisted of all patients who did not violate the terms of the protocol in a way that would affect the study output significantly. All decisions to exclude patients from the PPS were made before study unblinding.
- Analyses of primary and secondary efficacy end points were performed using the PPS as a sensitivity analysis.

Safety Analysis Set

- The SAF included all patients who received at least 1 dose of the study SC drug. Patients in this set were analyzed according to the treatment they actually received. The SAF-induction included all patients who received at least 1 induction dose but were not dosed in the maintenance phase. The SAF-combined included all patients who received at least 1 dose of vedolizumab IV.

Pharmacokinetic Evaluable Set

- The pharmacokinetic evaluable population was defined as all patients who received at least 1 dose of the study SC drug and had sufficient blood sampling to allow for pharmacokinetic evaluation.

[redacted]

Sponsor's Summary of the Results

Patient Disposition

A total of 1,072 patients were screened for enrolment in the study; of these, 428 patients failed screening [redacted] and 644 patients were enrolled into the open-label induction phase. Patients who achieved a clinical response at week 6 following 2 doses of open-label vedolizumab IV infusions (at weeks 0 and 2), as assessed by CDAI score (defined as a ≥ 70-point decrease from baseline [week 0]) at week 6), were randomized into the double-blind maintenance phase. Patients who did not exhibit a clinical response at week 6 were not randomized into the maintenance phase and instead received a third IV dose of vedolizumab at week 6. Clinical response of these patients was assessed again at week 14 by CDAI score. Patients who achieved a clinical response at the week 14 assessment (defined as a ≥ 70-point decrease in CDAI score from baseline [week 0] at week 14) were eligible to participate in the OLE, Study SC-3030.

Of the 644 patients enrolled in the open-label vedolizumab IV induction period, 412 patients (64%) achieved a clinical response at week 6 based on a ≥ 70-point decrease from baseline in CDAI score. These 412 patients were eligible for randomization into the double-blind maintenance phase of the study. A total of 410 patients were randomized into the double-blind maintenance phase (ITT = 410 patients). One patient was randomized to the placebo group but did not receive any blinded treatment [redacted] (FAS = 409 patients). A total of 107 patients (38.9%) in the vedolizumab SC group and 61 patients (45.2%) in the placebo group discontinued the study drug during the maintenance phase.

Table 7: Disposition of Patients – All Enrolled, Induction Phase

Patients	Induction phase Vedolizumab IV
Screened, N	1,072
Enrolled and treated in open-label induction phase, N	644
Achieved clinical response at week 6, N	412

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Table 8: Disposition of Patients – Maintenance Phase

Patients	Maintenance phase		
	Placebo	Vedolizumab SC	Total
Randomized, n	**135**	**275**	**410**
Randomized but not treated	1	0	1
Discontinued study drug during maintenance phase, n (%)	**61 (45.2)**	**107 (38.9)**	**168 (41.0)**
Reason for discontinuation, n (%)			
Lack of efficacy	43 (70.5)	78 (72.9)	121 (72.0)
Adverse event	12 (19.7)	11 (10.3)	23 (13.7)
Other	1 (1.6)	2 (1.9)	3 (1.8)
Voluntary withdrawal	5 (8.2)	14 (13.1)	19 (11.3)
Lost to follow-up	0	1 (0.9)	1 (0.6)
Pregnancy	0	1 (0.9)	1 (0.6)
FAS, N (%)	**134 (99.3)**	**275 (100)**	**409 (99.8)**
ITT, N (%)	**135 (100)**	**275 (100)**	**410 (100)**
[redacted]			
[redacted]			
[redacted]			

FAS = full analysis set; ITT = intention-to-treat; [redacted]; SC = subcutaneous.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Exposure to Study Treatments

Study Treatments

Exposure to study medication and study drug compliance for the SAF population are presented in Table 9. Exposure was [redacted]

Table 9: [redacted]

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

SC = subcutaneous; SD = standard deviation.

[redacted]

[b] Duration of exposure = (date of last dose of study drug – date of first dose of study drug) + 12.7. If last dose was missing, 127 was imputed as the treatment period.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Concomitant Medications

Concomitant medication was defined as a medication that started on or was ongoing as of day 1 and no later than 126 days after the last dose of the study drug. Table 10 summarizes concomitant IBD medications taken by patients in the maintenance phase (SAF). Concomitant IBD medications used during the maintenance phase of this study were generally similar between the 2 arms.

Table 10: [redacted]

[redacted]	Placebo N = 134	Vedolizumab SC N = 275
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

IBD = inflammatory bowel disease; SC = subcutaneous.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Efficacy

Clinical Remission at Week 52

Results of the primary end point analysis (FAS) showed a statistically significant treatment difference in favour of the vedolizumab SC arm (P = 0.008). A total of 132 of 275 vedolizumab SC–treated patients (48.0%) achieved clinical remission (defined as CDAI score ≤ 150) at week 52 compared with 46 of 134 patients who received placebo (34.3%). The adjusted treatment difference between treatment arms was 13.7% (95% CI, 3.8 to 23.7). [redacted].

Table 11: Clinical Remission at Week 52 – FAS

VISIBLE 2	Total N	Number of patients achieving clinical remission[a]		
		n (%)	Treatment difference (95% CI)[b]	P value[c]
Vedolizumab SC	275	132 (48.0)	13.7 (3.8 to 23.7)	0.008
Placebo	134	46 (34.3)	—	—

CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = full analysis set; SC = subcutaneous.

[a] Clinical remission, defined as CDAI score of no more than 150, at week 54 was the primary efficacy end point.

[b] The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.

[c] Within statistical testing hierarchy.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Enhanced Clinical Response at Week 52

Enhanced clinical response was defined as a decrease of at least 100 points in the CDAI score from baseline (week 0) at week 52. A greater proportion of patients (FAS) in the vedolizumab SC group (52.0%) compared with the placebo group (44.8%) achieved enhanced clinical response at week 52; however, the treatment difference of 7.3% was not

statistically significant (95% CI, −3.0 to 17.5; P = 0.167).

[redacted]

Table 12: Enhanced Clinical Response at Week 52 – FAS

VISIBLE 2	Total N	Number of patients achieving clinical remission[a]		
		n (%)	Treatment difference (95% CI)[b]	P value[c]
Vedolizumab SC	275	143 (52.0)	7.3 (−3.0 to 17.5)	0.167
Placebo	134	60 (44.8)	—	—

CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = full analysis set; SC = subcutaneous.

[a] Enhanced clinical response, defined as a decrease in CDAI score of at least 100 from baseline, at week 54 was the first secondary efficacy end point.

[b] The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.

[c] Within statistical testing hierarchy.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Corticosteroid-Free Remission at Week 52

A total of 139 patients (44 patients in placebo group, 95 patients in vedolizumab SC group) had concomitant oral corticosteroid (i.e., prednisone or equivalent and budesonide or equivalent) use at baseline and were included in this analysis. Among the patients (FAS) who were receiving corticosteroid or budesonide treatment at baseline, a greater proportion of patients treated with vedolizumab SC (43 of 95 patients; 45.3%) achieved corticosteroid-free remission at week 52 compared with patients who received placebo (8 of 44 patients; 18.2%). The treatment difference was 27.1% (95% CI, 11.9 to 42.3) with a nominal P value of 0.002. Results of the analyses with the

[redacted]

Table 13: Corticosteroid-Free Remission at Week 52 – FAS

VISIBLE 2	Total N	Number of patients achieving clinical remission[a]		
		n (%)	Treatment difference (95% CI)[b]	P value[c]
Vedolizumab SC	95	43 (45.3)	27.1 (11.9 to 42.3)	0.002
Placebo	44	8 (18.2)	—	—

CI = confidence interval; FAS = full analysis set; SC = subcutaneous.

[a] Corticosteroid-free remission defined as subjects using oral corticosteroids at baseline (week 0) who had discontinued oral corticosteroids and were in clinical remission at week 52, was the first secondary efficacy end point.

[b] The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.

[c] Within statistical testing hierarchy.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Clinical Remission in Patients Who Were Naive to TNF Alpha Antagonists

In the FAS population, 170 patients (41.6%) did not have prior exposure to TNF alpha antagonist therapy. In TNF alpha antagonist–naive patients, a slightly higher proportion of patients treated with vedolizumab SC (48.6%) achieved clinical remission at week 52 compared with those treated with placebo (42.9%). The treatment difference was 4.3% (95% CI: −11.6 to 20.3; P = 0.591). [redacted]

[redacted]

Table 14: Clinical Remission at Week 52 in Patients Naive to TNF Alpha Antagonists – FAS

VISIBLE 2	Total N	Number of patients achieving clinical remission[a]		
		n (%)	Treatment difference (95% CI)[b]	P value[c]
Vedolizumab SC	107	52 (48.6)	4.3 (−11.6 to 20.3)	0.591
Placebo	63	27 (42.9)	—	—

CDAI = Crohn's Disease Activity Index; CI = confidence interval; FAS = full analysis set; SC = subcutaneous; TNF alpha = tumour necrosis factor alpha.

[a] Clinical remission, defined as a CDAI score of no more than 150, at week 52 in subjects who were TNF alpha antagonist–naive was the third secondary efficacy end point.

[b] The 95% CIs of the percentages for each treatment group were based on the Clopper-Pearson method.

[c] Within statistical testing hierarchy.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Health-Related Quality of Life

Assessment of HRQoL was conducted using the IBDQ and EQ-5D. Work productivity was assessed by the Work Productivity and Activity Impairment–Crohn's disease (WPAI-CD) instrument.

IBDQ

A total score of 170 or higher is representative of clinical remission. A 16-point change in IBDQ total score is considered clinically meaningful.

The total IBDQ scores improved after the open-label induction phase and were similar at week 6 between the 2 treatment groups (mean [standard deviation]: 161.2 [redacted] for placebo; 162.7 [redacted] for vedolizumab SC). In the maintenance phase, patients who received vedolizumab SC showed further improvements in IBDQ total score and in all IBDQ domain scales compared with the placebo group. The greater improvements on the total IBDQ score and all domain scales for the vedolizumab SC treatment group at week 52 were clinically meaningful.

EuroQol 5-Dimensions Questionnaire

The EQ-5D index and VAS scores improved (increased values) after the open-label vedolizumab IV induction phase and were similar at week 6 in the 2 treatment groups (mean [standard deviation]: 0.8 [redacted] for placebo, 0.8 [redacted] for vedolizumab SC). In the maintenance phase, at week 52, patients in the vedolizumab SC treatment group had greater improvements in the EQ-5D index score and EQ-5D VAS score compared with the placebo group. Similarly, for all subscores of the EQ-5D assessment tool, vedolizumab SC treatment resulted in a greater improvement (change from baseline) at week 52 compared with placebo treatment.

WPAI-CD

WPAI-CD outcomes are expressed as impairment percentages, with higher values indicating greater impairment and less productivity.

Patients treated with vedolizumab SC had greater improvement in all subscores of the WPAI-CD (absenteeism, presenteeism, overall work productivity loss, activity impairment) compared with placebo at week 52.

Harms

Safety Evaluation Plan

All safety analyses were performed using the SAF. Data were summarized by treatment group. No statistical inference was made for safety analyses.

All AEs were coded using version 22.0 of the Medical Dictionary for Regulatory Activities. The number and percentage of patients with TEAEs, defined as an AE that started or worsened on or after study day 1, adverse events of special interest (AESIs), and SAEs that occur on or after the first dose date and up to 18 weeks after the last dose date of the study drug and the day before the first dose of the OLE study, SC-3030, were summarized by system organ class (SOC), high-level term and preferred term overall, by severity, and by relationship to study drug for each treatment group.

Overview of Safety

In the SAF population, the percentage of randomized patients who experienced at least 1 TEAE were comparable between the placebo (76.1%) and vedolizumab SC (73.5%) groups. [redacted] The percentage of placebo patients who had AEs leading to study discontinuation was more than twice that of the vedolizumab SC group (8.2% and 4.0%). Within the placebo group, 10.4% of patients experienced an SAE compared with 8.4% in the vedolizumab SC group. Most of these SAEs were assessed by the investigator as not related to study medication. No deaths occurred during the study.

Table 15: Overview of TEAEs Including SAEs – SAF

Adverse events, n (%)	Placebo N = 134	Vedolizumab SC N = 275
TEAEs, n (%)	**102 (76.1)**	**202 (73.5)**
Related	20 (14.9)	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Severe	12 (9.0)	14 (5.1)
Leading to discontinuation	11 (8.2)	11 (4.0)
SAEs, n (%)	**14 (10.4)**	**23 (8.4)**
Related	2 (1.5)	4 (1.5)
Leading to discontinuation	5 (3.7)	5 (1.8)
Deaths	**0**	**0**

SAE = serious adverse event; SAF = safety analysis set; SC = subcutaneous; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

AEs

In the SAF population, the SOCs with the highest frequency of AEs were GI disorders ([redacted]) and infections and infestations (34.3% and 31.3%, respectively). In the GI disorders SOC, most of the events were exacerbation or worsening of CD (19.4% and 15.3% for placebo and vedolizumab SC, respectively).

The most common AEs (occurring in at least 5% of patients in any treatment group) are summarized by frequency for the maintenance study SAF population in Table 16. The overall percentage of most-frequently reported (at least 5%) AEs was similar in the placebo and vedolizumab SC groups (41.8% and 39.3%, respectively). The condition under study was the most commonly reported AE in the SAF population, with CD reported in 19.4% and 15.3% of the placebo and vedolizumab SC groups, respectively. The next most common AEs were abdominal pain, nasopharyngitis, arthralgia, and upper respiratory tract infection. Nasopharyngitis, upper respiratory tract infection, and headache were more common in the vedolizumab SC treatment group than in the placebo group, while nausea, vomiting, and abdominal pain were more common in placebo group than in the vedolizumab SC group.

Table 16: Most Frequent (≥ 5%) TEAEs by SOC and PT – SAF

SOC, n (%) PT, n (%)	Placebo N = 134	Vedolizumab SC N = 275
Patients with any most frequent TEAEs	**56 (41.8)**	**108 (39.3)**
Gastrointestinal disorders	[redacted]	[redacted]
Crohn disease	26 (19.4)	42 (15.3)
Abdominal pain	11 (8.2)	21 (7.6)
Nausea	7 (5.2)	11 (4.0)
Vomiting	7 (5.2)	6 (2.2)
Infections and infestations	[redacted]	[redacted]
Nasopharyngitis	6 (4.5)	25 (9.1)
Upper respiratory tract infection	5 (3.7)	17 (6.2)
Musculoskeletal and connective tissue disorders	**9 (6.7)**	**18 (6.5)**
Arthralgia	9 (6.7)	18 (6.5)
Nervous system disorders	**5 (3.7)**	**15 (5.5)**
Headache	5 (3.7)	15 (5.5)

PT = preferred term; SAF = safety analysis set; SC = subcutaneous; SOC = system organ class; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

SAEs

Overall, 9.0% of patients experienced at least 1 SAE (10.4% and 8.4% in placebo and vedolizumab SC groups, respectively). The incidence of SAEs was generally comparable between the treatment groups. The highest frequency of SAEs occurred in the GI disorders SOC and were more frequent in the placebo group ([redacted]) than in the vedolizumab SC group ([redacted]). The incidence of SAEs in the infections and infestations SOC was also greater in the placebo group ([redacted]) than in the vedolizumab SC ([redacted]) group. The overall incidences of SAEs in the other SOCs were less than 2%. Two events in the placebo-treated group, small intestinal obstruction and gastroenteritis, were considered by the investigator to be related to the study drug. Five events in the vedolizumab SC group were assessed as related to

treatment with the study drug. These included ileal stenosis and abscess intestinal (both in 1 patient), and small intestinal obstruction, pneumonia, and exacerbation of CD (1 patient each). The SAEs in the SAF population are summarized in Table 17, in which SAEs in the GI and infections and infestations SOC are broken out by preferred term.

Table 17: Serious TEAEs by SOC and PT – SAF

SOC, n (%) PT, n (%)	Placebo N = 134	Vedolizumab SC N = 275
Patients with any serious TEAEs	**14 (10.4)**	**23 (8.4)**
Blood and lymphatic system disorders		**1 (0.4)**
Anemia	1 (0.7)	1 (0.4)
Leukocytosis	1 (0.7)	0
Cardiac disorders	**0**	
Angina pectoris	0	1 (0.4)
Atrial fibrillation	0	2 (0.7)
Gastrointestinal disorders		
Pancreatitis	1 (0.7)	0
Crohn disease	5 (3.7)	6 (2.2)
Small intestinal obstruction	2 (1.5)	1 (0.4)
Ileal stenosis	0	1 (0.4)
Anal fistula	1 (0.7)	1 (0.4)
Enterovesical fistula	1 (0.7)	0
Intestinal obstruction	0	2 (0.7)
Subileus	0	1 (0.4)
General disorders and administration-site conditions	**0**	**1 (0.4)**
General physical health deterioration		
Infections and infestations		
Anal abscess	1 (0.7)	1 (0.4)
Abdominal wall abscess	1 (0.7)	0
Abscess intestinal	0	1 (0.4)
Appendicitis	1 (0.7)	0
Appendicitis	1 (0.7)	0
Rectal abscess	0	1 (0.4)
Dengue fever	1 (0.7)	0
Bronchitis	1 (0.7)	0
Pneumonia	0	1 (0.4)
Injury, poisoning and procedural complications	**0**	
Gastrointestinal anastomotic stenosis	0	1 (0.4)
Incisional hernia	0	1 (0.4)
Investigations	**0**	**1 (0.4)**
White blood cell count increased	0	1 (0.4)
Metabolism and nutrition disorders	**1 (0.7)**	**0**
Poor weight gain	1 (0.7)	0
Musculoskeletal and connective tissue disorders	**0**	**1 (0.4)**

SOC, n (%) PT, n (%)	Placebo N = 134	Vedolizumab SC N = 275
Arthralgia	0	1 (0.4)
Neoplasms benign, malignant, and unspecified	**0**	**1 (0.4)**
Intraductal papilloma of breast	0	1 (0.4)
Nervous system disorders	**1 (0.7)**	**1 (0.4)**
Hemorrhagic stroke	0	1 (0.4)
Intraventricular hemorrhage	1 (0.7)	0
Psychiatric disorders	**0**	[redacted]
Alcoholism	0	1 (0.4)
Suicidal ideation	0	1 (0.4)

PT = preferred term; SAF = safety analysis set; SC = subcutaneous; SOC = system organ class; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Withdrawals Due to Adverse Event

The overall incidence of AEs leading to study discontinuation was 22 of 409 patients (5.4%; 8.2% and 4.0% in the placebo and vedolizumab SC groups, respectively); of these 22 patients, [redacted]

Table 18: Adverse Events Leading to Study Discontinuation by SOC and PT – SAF

SOC, n (%) PT, n (%)	Placebo N = 134	Vedolizumab SC N = 275
Patients with any TEAEs leading to study drug discontinuation	**11 (8.2)**	**11 (4.0)**
[redacted]		

SOC, n (%) PT, n (%)	Placebo N = 134	Vedolizumab SC N = 275
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

PT = preferred term; SAF = safety analysis set; SC = subcutaneous; SOC = system organ class; TEAE = treatment-emergent adverse event.

Source: Clinical Study Report for VISIBLE 2 (Study SC-3031).[7]

Adverse Events of Special Interest

Infections

Overall, infections were reported in 132 of 409 patients (32.3%). A slightly higher number of infections was reported in the placebo-treated patients (34.3%) than in the vedolizumab SC–treated patients (31.3%).

[redacted]

[redacted]

Hypersensitivity

[redacted]

Injection-Site Reactions

Overall, 10 of 409 patients (2.4%) reported an injection-site reaction, and these reports were more frequent in the vedolizumab SC group (8 patients, 2.9%) than in the placebo group (2 patients, 1.5%). [redacted]

[redacted]

Infusion Reactions

[redacted]

Malignancies

Five malignancy TEAEs were reported (1.2%) overall. These included 3 in placebo-treated patients (2.2%) and 2 in vedolizumab SC–treated patients (0.7%).

[redacted]

Liver Injury

There were 15 patients overall with liver injury AESIs (3.7%), which included a greater proportion of the placebo group (7 patients, 5.2%) than of the vedolizumab SC group (8 patients, 2.9%). [redacted]

Progressive Multifocal Leukoencephalopathy

[redacted]

Bioequivalence

Study SC-101

This study was designed primarily to assess the absolute bioavailability and pharmacokinetics of vedolizumab (liquid formulation) following a single SC injection in healthy individuals. The study was a phase I, open-label, parallel-group design. A total of 48 individuals were randomized in a ratio of 1:1:1:1 to 1 of 4 treatment groups (12 per treatment). [redacted] (Japanese and non-Japanese). All individuals received drug on day 1. The 4 treatment groups were:

- vedolizumab (lyophilized) IV 300 mg by infusion over approximately 30 minutes
- vedolizumab (liquid) SC 54 mg by SC injection ([redacted])
- vedolizumab (liquid) SC 108 mg by SC injection ([redacted])
- vedolizumab (liquid) SC 160 mg by SC injection ([redacted]).

[redacted]

[redacted]

Table 19: Summary of Pharmacokinetic Parameters Following a Single IV Infusion or a Single SC Injection of Vedolizumab

Pharmacokinetics	Vedolizumab SC 108 mg, [redacted]	Vedolizumab IV 300 mg, N = 12
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted] SC = subcutaneous; [redacted].

[redacted].

Source: Clinical Study Report for Study SC-101.[iv]

CADTH Critical Appraisal

Internal Validity

VISIBLE 2 was the only pivotal study included in this review. The investigators adequately produced a randomization sequence, with a 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. Differences were noted in the baseline characteristics of patients, such as prior anti–TNF alpha use, concomitant medications with immunomodulators only at week 0 and ileal disease. These differences were small and less likely to have a meaningful impact on the validity of the results; however, the higher proportion of patients with prior anti–TNF alpha use and ileal disease only, and the fewer patients who received concomitant immunomodulators only at baseline in the vedolizumab SC group compared to placebo may suggest that patients in the vedolizumab group would be more difficult to treat, which could result in a more conservative estimate of the treatment effect. 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 on the double-dummy

design of the trial. Patients who stopped or deviated from the interventions were properly accounted for and analyzed in an FAS, which was close to the ITT population in the study.

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

During the maintenance phase, 41% of the participants prematurely discontinued the study drug, 45% in the placebo group and 39% in the vedolizumab SC group. The main reason for treatment discontinuation in the maintenance phase was lack of efficacy (with 71% and 73% on placebo and vedolizumab SC among those who discontinued, respectively), followed by voluntary withdrawal and AEs. This difference in missing data could bias the results. Sensitivity analyses were conducted to examine the robustness of study findings to missing data assumptions, [redacted].

Outcomes were objectively obtained with validated tools (see Appendix 1) 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 selection of the reported results. A protocol was well described, and the presented results follow the pre-specified analysis plan. Amendments made during the study were well addressed and unlikely to affect the end results or imply bias due to selection of participants.

Subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary and all secondary outcomes based on age, gender, race, duration of CD, 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. However, conclusions in regard to these subgroups are uncertain due to the small sample sizes in the subgroups. In addition, subgroup analyses were exploratory in VISIBLE 2, and there was also a lack of adjustment for multiplicity. All of these increase the uncertainty in interpreting the results in the subgroups. Appendix 2 presents the efficacy outcomes by prior TNF alpha antagonist therapy (patients without prior exposure to TNF alpha antagonist therapy versus patients who had prior exposure to TNF alpha antagonist therapy but did not fail this treatment versus patients who had prior failure to TNF alpha antagonist therapy).

The VISIBLE 2 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 all secondary end points, such as enhanced clinical response and corticosteroid-free clinical remission.

External Validity

The populations included in VISIBLE 2 are, to an extent and within the limitations of a controlled setting of a clinical trial, similar to what it is encountered in clinical practice and relevant to the population of interest for this review, which focuses on SC administration and specific doses that are in accordance with what is approved by Health Canada and planned to be used in real-life practice. However, adherence could be overstated as it is usual in controlled randomized trials, and generalizability may be an issue when the medication is applied in real clinical settings.

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 training to apply the SC vedolizumab doses and the study participants reportedly performed well in this sense. It is likely this training would be similar to real clinical practice.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

As there was no direct evidence comparing vedolizumab SC to other active treatments for moderately to severely active CD, a review of indirect evidence was undertaken. The aim of this section is to provide an overview and critical appraisal of the published and unpublished indirect evidence available for the assessment of the comparative efficacy and safety of vedolizumab SC to the currently available biologic treatments for adult patients with CD.

CADTH conducted a literature search to identify potentially relevant ITCs in patients with moderately to severely active CD, in addition to reviewing the sponsor's CADTH Common Drug Review submission. No potentially relevant ITCs were identified in the literature search. One sponsor-submitted ITC was included in this review.[8]

Description of the Indirect Comparison

The sponsor-submitted ITC included a systematic review of the literature and an NMA that compared vedolizumab SC to the other biologic treatments available in Canada for patients with moderate to severe CD.

Methods of the Sponsor-Submitted NMA

Objectives

The objective of the sponsor-submitted report was to perform an ITC or NMA to obtain estimates of the comparative efficacy and safety of vedolizumab SC and competing interventions for the treatment of CD. The NMA was used to inform the health economic models for vedolizumab SC.

Study Selection Methods

The RCTs that were used to inform the ITC were identified through a systematic literature search conducted by the sponsor. Multiple databases were searched to identify RCTs that evaluated the efficacy of relevant biologic treatments for the treatment of CD. [redacted]

[redacted]

[redacted]

[redacted]

The inclusion criteria for the sponsor submitted NMA are summarized in Table 20.

Table 20: Study Selection Criteria and Methods for the Sponsor-Submitted NMA

	SLR	NMA
Population	[redacted]	[redacted]
Intervention and comparators	[redacted]	[redacted]
Outcome	[redacted]	[redacted]

	SLR	NMA
Study design	[redacted]	[redacted]
Publication characteristics	[redacted]	[redacted]
Exclusion criteria	[redacted]	[redacted]
Databases searched	[redacted]	
Selection process	[redacted]	
Data extraction process	[redacted]	
Quality assessment	[redacted]	

CD = Crohn disease; IBD = inflammatory bowel disease; NMA = network meta-analysis; RCT = randomized controlled trial; SLR = systematic literature review; [redacted]

Source: Sponsor-submitted NMA.[8]

ITC Analysis Methods

[redacted]

Results of the Sponsor-Submitted NMA

Summary of Included Studies

[redacted]

[redacted]

Figure 2: [redacted]

Figure 2 contained confidential information and was removed at the request of the sponsor.

[redacted]; PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w = every 8 weeks; SC = subcutaneous; VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

Figure 3: [redacted]

Figure 3 contained confidential information and was removed at the request of the sponsor.

PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w = every 8 weeks; SC = subcutaneous; VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

Figure 4: [redacted]

Figure 4 contained confidential information and was removed at the request of the sponsor.

[redacted] PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w = every 8 weeks; [redacted] SC = subcutaneous; VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

Figure 5: [redacted]

Figure 5 contained confidential information and was removed at the request of the sponsor.

[redacted] PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w = every 8 weeks; SC = subcutaneous; VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

Figure 6: [redacted]

Figure 6 contained confidential information and was removed at the request of the sponsor.

[redacted]; PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w = every 8 weeks; SC = subcutaneous; VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

Figure 7: [redacted]

Figure 7 contained confidential information and was removed at the request of the sponsor.

[redacted]; PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w = every 8 weeks; SC = subcutaneous; VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

Figure 8: [redacted]

Figure 8 contained confidential information and was removed at the request of the sponsor.

[redacted]; PBO = placebo; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; SC = subcutaneous; [redacted]

[redacted] VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

[redacted]

Table 21: [redacted]

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

IQR = interquartile range; NR = not reported; SC = subcutaneous; SD = standard deviation; wk = week.

Source: Sponsor-submitted network meta-analysis.[8]

Table 22:

IQR = interquartile range; NR = not reported; SC = subcutaneous; SD = standard deviation; TNF = tumour necrosis factor.

Source: Sponsor-submitted network meta-analysis.[8]

Table 23: [redacted]

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

e.o.w = every other week; IQR = interquartile range; NR = not reported; SC = subcutaneous; SD = standard deviation; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; TNF = tumour necrosis factor.

Source: Sponsor-submitted network meta-analysis.[8]

Results

[redacted]

[redacted]

Results of the NMA on various efficacy and safety outcomes are summarized in Table 24.

Table 24: [redacted]

Comparison between VDZ SC and comparators	[redacted]							
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

[redacted] IV = intravenous; [redacted]; OR = odds ratio; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; q.8.w. = every 8 weeks; [redacted]; SC = subcutaneous; [redacted] VDZ = vedolizumab.

Source: Sponsor-submitted network meta-analysis.[8]

CADTH Critical Appraisal of the Sponsor-Submitted NMA

A number of RCTs were included in the sponsor-submitted NMA to evaluate the comparative effectiveness and safety of vedolizumab SC relative to other biologics. However, only a limited number of trials were relevant to the use of vedolizumab SC as maintenance treatment in patients with CD. [redacted]. However, due to limitations of the submitted NMA, the results comparing vedolizumab SC to other active treatments 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 limited size of the evidence base (for example, only 4 trials contributed to the analysis of [redacted]) and heterogeneity across trials in both design and patient baseline characteristics.

Even though quality of the included trials was examined using [redacted].

A significant concern with the NMA presented is that studies included in the analyses were [redacted]

[redacted].

Summary

Based on the results of the sponsor-submitted NMA, vedolizumab SC was not clearly favoured relative to other comparators of interest for either efficacy or safety. Little should be inferred regarding the comparative efficacy or safety to other products based solely on this submitted NMA. The applicability of sponsor's NMA is undermined by the limited size of the evidence base (i.e., [redacted]), potential limitations in the submitted analysis, and heterogeneity in trial design and patient populations across trials. These limitations make it difficult to draw firm conclusions based on the results of this NMA.

Other Relevant Evidence

This section deals with 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 found in the systematic review.

Long-Term Extension Studies

An OLE study to determine the long-term safety and efficacy of vedolizumab SC in patients with CD and UC was ongoing at the time of this review (SC-3030; NCT02620046; estimated completion date of February 2022).[9] This study is intended to collect long-term safety data for vedolizumab SC dosing to complement the safety data gathered by VISIBLE 2 in CD patients. [redacted].[9]

Methods

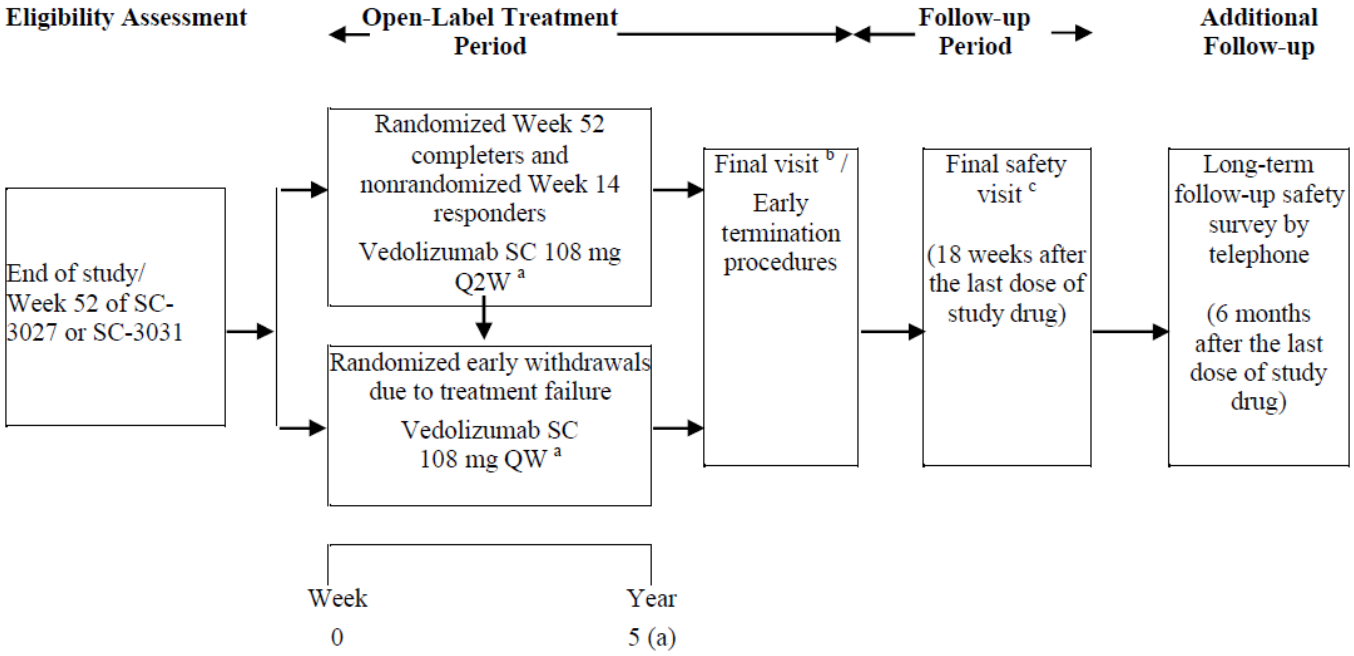
Patients are eligible to enter this OLE study if they participated in the SC-3027 (UC) or SC-3031 (CD) study, and are:

- Patients with UC or CD who completed the maintenance phase (week 52) and received vedolizumab SC 108 mg every 2 weeks
- Patients with UC or CD who withdrew early from the maintenance phase due to disease worsening or need for rescue medications received vedolizumab SC 108 mg weekly

- Patients with UC or CD who did not achieve a clinical response at week 6, but after receiving a third vedolizumab IV infusion at week 6 achieved a clinical response at week 14 and received vedolizumab SC 108 mg every 2 weeks.

Patients entered in the extension study received open-label vedolizumab SC 108 mg either weekly or every 2 weeks. Participants continue the study drug for up to 5 years. Participants complete a final safety visit 18 weeks after the last dose of vedolizumab SC on the study, followed by a 6-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 9, and details of the study can be found in Table 25.[9]

Figure 9: Study Design of SC-3030



Source: Interim Clinical Study Report for SC-3030, including patients with Crohn disease or ulcerative colitis.[9]

Table 25: Details of the Long-Term Extension Study SC-3030

Characteristics		Details
Designs and Populations	**Study design**	Open-label long-term extension study
	Locations	[redacted]
	Sample size	[redacted]
	Inclusion criteria	• Patients with CD who had previously participated in VISIBLE 2 including: ○ Participants who withdrew early from VISIBLE 2 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 into 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 CD during or after participation in VISIBLE 2 or are anticipated to require surgical intervention for CD during this study • Patients who withdrew from VISIBLE 2 due to a study drug–related AE
Drugs	**Intervention**	1. **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. 2. **Randomized early terminators:** vedolizumab SC 108 mg q.w. 3. **Nonrandomized late responders:** vedolizumab SC 108 mg q.2.w.
Duration	**Treatment phase**	Up to 5 years
	Safety follow-up	18 weeks and 6 months post–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 using HBI scores (defined as a decreased in HBI score of ≥ 3 points from baseline) • Proportion of patients achieving clinical remission (defined as an HBI score of ≤ 4 points) • Change from baseline in IBDQ total and subscale scores • Change from baseline in EQ-5D utility [redacted] • [redacted] • [redacted] • [redacted]

AE = adverse event; AESI = adverse event of special interest; CD = Crohn disease; EQ-5D = EuroQol-5-Dimensions questionnaire; HBI = Harvey-Bradshaw Index; IBDQ = Inflammatory Bowel Disease Questionnaire; q.w. = every week; q.2.w. = every 2 weeks; SAE = serious adverse event; SC = subcutaneous; TEAE = treatment-emergent adverse event; UC = ulcerative colitis.

Source: Interim Clinical Study Report for SC-3030 (focused on patients with CD).[9]

Populations

The following 3 groups of patients were eligible for the VISIBLE 2 long-term extension study:

- **Randomized study completers:** patients with CD who completed the maintenance phase of the VISIBLE 2 up to week 52
- **Randomized early terminators:** patients with CD who withdrew early from the maintenance phase of the VISIBLE 2 due to disease worsening or need for rescue medications
- **Nonrandomized late responders:** patients with CD who did not achieve a clinical response at week 6 in the induction phase of the VISIBLE 2 but achieved a clinical response at week 14 after receiving a third vedolizumab IV induction dose at week 6.

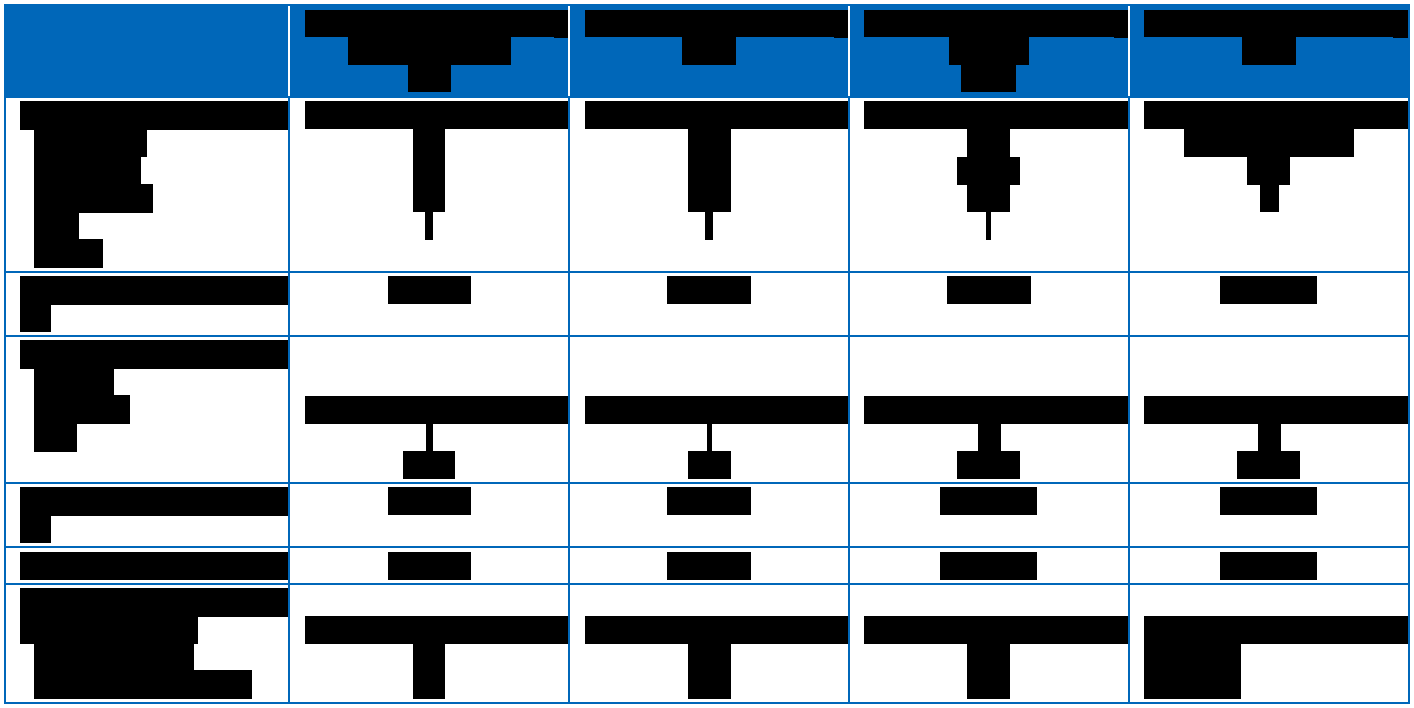
Patients who withdrew from VISIBLE 2 due to a drug-related AE were not eligible to enter the extension study. Additionally, patients who required surgical intervention for CD during or after participation in the VISIBLE 2 or were anticipated to require surgical intervention for CD during this study were not eligible to enter the extension study.[9]

Baseline and Demographic Characteristics

[redacted]

Table 26: [redacted]

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



CD = Crohn disease; [redacted]; IBD = inflammatory bowel disease; IV = intravenous; SAF = safety analysis set; SC = subcutaneous; SD = standard deviation.

Source: Interim Clinical Study Report for SC-3030.[9]

Interventions

All patients enrolled in the extension study were administered open-label vedolizumab SC 108 mg every 2 weeks, with the exception of the early terminators who were administered vedolizumab SC 108 mg weekly. Patients who experienced treatment failure (i.e., disease worsening or need for rescue medication) while receiving vedolizumab SC 108 mg every 2 weeks during the OLE study were permitted a dose escalation to vedolizumab SC 108 mg weekly. Patients who completed VISIBLE 2 or terminated VISIBLE 2 (i.e., early terminators) received their first dose of open-label vedolizumab SC 4 weeks after the last dose of the study drug or placebo in VISIBLE 2. For the late responders, patients received vedolizumab SC 108 mg every 2 weeks. Disease activity was assessed by Harvey-Bradshaw Index for CD patients.

Outcomes

The primary objective of the VISIBLE 2 OLE study was to obtain data on the long-term safety and tolerability of vedolizumab SC. The primary end point was patient-year-adjusted TEAEs. Secondary efficacy outcomes include patient-year-adjusted AESIs, clinical responses, and clinical remissions. Additional secondary end points include changes from baseline in IBDQ total and subscale scores, EQ-5D utility [redacted]

Statistical Analysis

[redacted]

Analysis Sets

[redacted]

Patient Disposition

[redacted]

Table 27: Patient Disposition of SC-3030

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

AE = adverse event; ET = early termination; NR = nonrandomized; SC = subcutaneous.

[redacted]

Source: Interim Clinical Study Report for SC-3030.[9]

Exposure to Study Treatments

[redacted]

Table 28: Extent of Exposure in SC-3030

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

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

NR = nonrandomized; SC = subcutaneous.

[redacted]

Source: Interim Clinical Study Report for SC-3030.[9]

Efficacy

[redacted]

Harms

[redacted]

Table 29: [redacted]

[redacted]	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
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Source: Interim Case Study Report for SC-3030.[9]

Critical Appraisal

As with most long-term extension studies, the VISIBLE 2 long-term extension study was limited by the open-label administration of the study drug, the absence of an active or placebo comparator group, and the reporting of descriptive summary statistics. Additionally, given that the study is ongoing, results were limited to the interim analyses, [redacted]. Open-label administration can bias the reporting of end points, specifically subjective end points in the Harvey-Bradshaw Index and reporting of AEs. The lack of a comparator such as a placebo may result in an overestimate of the magnitude of clinical benefit reported to date. All efficacy and safety end points were descriptively summarized. Furthermore, [redacted]. Therefore, long-term benefit of vedolizumab on the treatment effect and harm remains uncertain. [redacted]; this allows for a comparison to the randomized study population, or to those in clinical practice. It is important to note, however, that patients enrolled in the OLE study had highly different [redacted]. Furthermore, the early terminators were dosed more frequently than the other 2 groups, and dose escalation to weekly was allowed in the randomized study completers for patients who experience treatment failure.

The [redacted], which is representative of the Canadian population with CD. 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.

[redacted]. These factors may limit the applicability of the preliminary results.

Summary

A long-term extension study of the VISIBLE 2 study to assess the long-term safety and tolerability of vedolizumab SC in the treatment of CD is currently ongoing. The results of the second interim analysis [redacted]. The available efficacy results to date were limited by their descriptive nature and [redacted] of evaluable patients. Results from this extension study to inform long-term durability of response of vedolizumab SC in responders on maintenance therapy should be interpreted with caution.

Sponsor's Summary of the Cost Information

Figure 10: Sponsor's Submitted Cost Comparison[16]

Generic Name (Brand Name)	Strength, Dosage Form	Price[a] ($)	Recommended Dosage Regimen	Annual[c] Drug Cost ($)	Difference in Annual[c] Cost
Vedolizumab SC (ENTYVIO®)	108 mg, pre-filled syringe or pen	$822.5000	108 mg, Q2W	$21,458.44	-
Comparators					
Vedolizumab IV (ENTYVIO®)	300 mg, vial	$3,290.0000	300 mg, Q8W	$21,458.44	$0.00
Adalimumab (HUMIRA®)	40 mg, vial	$769.9700	40 mg, Q2W	$20,087.97	$1,370.47
Infliximab (INFLECTRA®)	100 mg, vial	$525.0000	5 mg/kg, Q8W	$12,683.31	$8,775.13
Infliximab (REMICADE®)	100 mg, vial	$987.5600	5 mg/kg, Q8W	$23,858.14	($2,399.70)
Infliximab (RENFLEXIS™)	100 mg, vial	$493.0000	5 mg/kg, Q8W	$11,910.23	$9,548.21
Ustekinumab (STELARA®)	90 mg, vial	$4,593.1400	90 mg, Q8W	$29,957.93	($8,499.49)

IV, intravenous; Q2W, every two weeks; Q8W, every eight weeks; SC, subcutaneous.
[a] Price of vedolizumab SC provided by Takeda Canada Inc. Prices for comparators referenced from Ontario, as a proxy.[5,6] Excludes mark-up and dispensing fees.
[b] Recommended dosage regimens referenced from each product's respective product monograph.[7-12]
[c] Annual cost provided assuming maintenance treatment of CD. For treatments with weight-based dosing (infliximab), the average patient weight for patients receiving vedolizumab SC in the VISIBLE 2 trial was used.[1]

Healthcare Resource	Frequency per year	Unit Cost[a]	Treatment(s)
Administration costs associated with intravenously infused products.	Based on recommended dosing regimens, infused comparators are to be administered 6.5 times per year. Administration costs are applied once per product administration.	$288.36	Vedolizumab IV (ENTYVIO®), infliximab (INFLECTRA®, REMICADE®, RENFLEXIS™)

[a] Costs referenced from Ontario, as a proxy.[14,15]

The sponsor assessed the cost of vedolizumab as an SC injection for the maintenance treatment of adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant of immunomodulators or a TNF alpha antagonist, or have had an inadequate response or intolerance to, or demonstrated dependence on, corticosteroids.[16] Vedolizumab SC is a new formulation of vedolizumab that can be self-administered in an at-home setting, removing the need to travel to a hospital or clinic for maintenance therapy, compared with vedolizumab IV infusion, which requires administration in a hospital or infusion clinic. The cost comparison was undertaken from the public drug plan perspective and included drug acquisition costs, with a scenario analysis conducted from the health care payer perspective that included administration costs for IV treatments.

The drug acquisition cost of vedolizumab SC is $822.50 per 108 mg pre-filled pen, while the cost per 300 mg vial of vedolizumab IV is $3,290.00. The recommended maintenance dose for vedolizumab SC is 108 mg every 2 weeks and 300 mg every 8 weeks for vedolizumab IV; an IV induction phase is required for both IV and SC vedolizumab. The average annual maintenance cost of both vedolizumab SC and vedolizumab IV is $21,458 after year 1, suggesting cost-neutrality if vedolizumab SC is reimbursed. Other relevant comparators included in this comparison were adalimumab (Humira), infliximab (Inflectra, Remicade, and Renflexis), and ustekinumab (Stelara). The average annual maintenance costs for the comparators ranged from $11,910 to $29,958 (Figure 10); however, the sponsor noted that, while ustekinumab is indicated for the treatment of CD, it is currently only reimbursed in Saskatchewan.

From a health care payer perspective, the sponsor estimated a total cost of $288.36 per IV administration ($200.06 chair time; $75.00 complex single or multi-agent therapy; $13.30 monthly telephone supervision of chemotherapy) for vedolizumab IV and infliximab. Based on the assumption that patients would receive vedolizumab IV and infliximab an average of 6.5 times per year, the sponsor estimated annual administration costs of $1,874 for IV treatments in Canada.

Critical Appraisal of Cost Information

- **Comparative efficacy of vedolizumab SC is uncertain:** Due to the lack of direct evidence for comparisons between vedolizumab SC and vedolizumab IV or other comparators, the sponsor submitted an ITC to inform relative clinical efficacy (i.e., clinical remission and enhanced clinical response) and safety.
[redacted].
- **Consideration of induction costs:** The sponsor did not include costs associated with the induction of IV therapies in its cost comparison. In the 2016 review of vedolizumab IV, CADTH noted that the costs associated with the first year of induction therapy were more than in subsequent maintenance years; therefore, the sponsor's consideration of maintenance treatment likely underestimates total treatment costs for the introduction of vedolizumab SC.[17] The costs for induction treatment with the comparators included in this review were $26,320 for vedolizumab IV, $23,564 for adalimumab, $31,264 for infliximab (Remicade), $15,776 for subsequent entry biologic (SEB) infliximab (Renflexis), $16,800 for SEB infliximab (Inflectra), and $36,745 for ustekinumab in the first year of treatment (Table).

CADTH Reanalyses

Based on the assumption that vedolizumab SC would only replace vedolizumab IV upon reimbursement, funding of vedolizumab SC would likely be cost-neutral from the public drug plan perspective as both formulations result in an average annual drug cost of $21,458 (Table).

When considering the other comparators included by the sponsor, the difference in annual maintenance costs compared to vedolizumab SC range from a savings of $8,499 versus ustekinumab to increased costs of $8,596 versus SEB infliximab (Renflexis). The difference in annual induction costs compared to vedolizumab SC range from a savings of $10,425 versus ustekinumab to increased costs of $10,544 versus SEB infliximab (Renflexis).

If a health care payer perspective is adopted, vedolizumab SC would be associated with a cost savings of approximately $1,874 annually per patient for maintenance therapy when compared with vedolizumab IV due to reduced treatment administration costs.

Table 30: CADTH Cost Comparison Table – New Formulation of Vedolizumab

Drug and comparator	Strength	Dosage form	Price ($)	Recommended dose[a]	Average annual drug cost ($)		Relative difference in annual drug costs ($) compared to new formulation	
					Year 1 (induction + maint.)	Year 2 (maint. only)	Year 1 (induction + maint.)	Year 2 (maint. only)
New formulation								
Vedolizumab SC (Entyvio)	108 mg/ 0.68 mL	Pre-filled syringe	822.5000[b]	300 mg (IV) at weeks 0 and 2, followed by 108 mg (SC) every 2 weeks thereafter	26,320	21,458	—	—
Reference formulation								
Vedolizumab IV (Entyvio)	300 mg	Vial	3,290.0000[b]	300 mg at weeks 0, 2, and 6, followed by every 8 weeks thereafter	26,320	21,458	0% (0)	0% (0)
Relevant comparators								
Adalimumab (Humira)	40 mg/0.8 mL; 10 mg/0.1 mL; 20 mg/0.2 mL; 40 mg/0.4 mL; and 80 mg/0.8 mL	Pre-filled syringe	785.4500; NA; 392.7250[c];NA; and NA	160 mg week 0, 80 mg week 2, followed by 40 mg every 2 weeks thereafter	23,564	20,492	−10.5% (−2,757)	−4.50% (−967)
Infliximab (Inflectra)	100 mg	Vial	525.0000	5 mg/kg at weeks 0, 2, and 6, followed by every 8 weeks thereafter[d]	16,800	13,697	−36.2% (−9,520)	−36.2% (−7,762)
Infliximab (Remicade)	100 mg	Vial	977.0000[c]	5 mg/kg at weeks 0, 2, and 6, followed by every 8 weeks thereafter[d]	31,264	25,489	18.8% (4,944)	18.8% (4,031)
Infliximab (Renflexis)	100 mg	Vial	493.0000	5 mg/kg at weeks 0, 2, and 6, followed by every 8 weeks thereafter[d]	15,776	12,862	−40.1% (−10,544)	−40.1% (−8,596)

Drug and comparator	Strength	Dosage form	Price ($)	Recommended dose[a]	Average annual drug cost ($)		Relative difference in annual drug costs ($) compared to new formulation	
					Year 1 (induction + maint.)	Year 2 (maint. only)	Year 1 (induction + maint.)	Year 2 (maint. only)
Ustekinumab (Stelara)	130 mg/ 26 mL	Vial	2,080.0000[c]	260 mg to 520 mg (IV) depending on body weight followed by 90 mg (SC) every 8 weeks[e]	34,118 to 38,278	29,958	7,798 (29.6%) to 11,958 (45.4%)	39.6% (8,499)
	45 mg/ 0.5 mL and 90 mg/ 1.0 mL	Pre-filled syringe or vial	4,593.1400					

maint. = maintenance; SC = subcutaneous.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed October 2020)[18] unless otherwise indicated and do not include dispensing fees. Annual cost calculations based on 365.25 days per year.

[a] Based on doses recommended in the appropriate product monographs: adalimumab,[14] Infliximab (Inflectra),[13] Infliximab (Remicade),[12] Infliximab (Renflexis),[19] and ustekinumab.[15]

[b] Sponsor's submitted price.[16]

[c] Saskatchewan drug formulary (accessed October 2020).[20]

[d] Average patient weight of 74.1 kg from VISIBLE 2 trial used to calculate dosage/cost.[16] No vial sharing was assumed.

[e] For patients weighing up to 55 kg, more than 55 kg up to 85 kg, and more than 85 kg, the recommended initial dosing of ustekinumab IV was 260 mg, 390 mg, and 520 mg, respectively.[15]

Issues for Consideration

- **Use of ustekinumab**: In 2017, CADTH reviewed ustekinumab for induction and maintenance treatment of CD, and issued a positive recommendation on the condition that the cost of ustekinumab should not exceed the drug plan cost of the least-costly alternative biologic treatment option.[21] However, negotiations for ustekinumab for CD by the pCPA and the sponsor were concluded without agreement in March 2019, indicating there may be limited uptake of this treatment for CD by the participating public drug plans.[22]
- **Impact of health care resource utilization**: The introduction of vedolizumab SC as maintenance treatment will lead to a reduced need for IV infusions. However, there may be additional dispensing fees associated with vedolizumab SC given the frequent dosing regimen (i.e., every 2 weeks) compared to vedolizumab IV (i.e., every 8 weeks).
- **Price reduction of vedolizumab SC:** CADTH reviewed vedolizumab IV in 2016, and recommended vedolizumab with a pricing condition in which the cost of treatment with vedolizumab IV should not exceed the drug plan cost of the least-costly alternative biologic treatment option (infliximab [Inflectra] at the time).[23] Comparing current treatment costs between vedolizumab IV ($21,458 annual costs) and infliximab (Inflectra; $13,697) would suggest a price reduction of 36% for vedolizumab IV to meet this condition. Additionally, following the 2016 review SEB infliximab (Renflexis) was introduced at a lower treatment cost compared to infliximab (Inflectra); therefore, a greater price reduction of 40% is required to achieve cost-neutrality. Where participating drug plans were able to negotiate a price reduction for vedolizumab IV, a similar price reduction would be needed for vedolizumab SC to remain cost-neutral relative to vedolizumab IV.

Discussion

Summary of Available Evidence

The body of evidence comprising this review includes a phase III, double-blind, placebo-controlled RCT (VISIBLE 2) (N = 410),[7] an ITC (NMA),[8] and an OLE study (SC-3030, currently ongoing).[9] The data were provided by the sponsor and critically appraised by CADTH reviewers.

VISIBLE 2 was designed to evaluate the efficacy and safety of maintenance treatment with vedolizumab SC injections in adult patients with moderately to severely active CD who achieved a clinical response at week 6 with open-label therapy of 300 mg vedolizumab IV infusion at weeks 0 and 2. Patients with a clinical response at week 6 were randomized to maintenance treatment with vedolizumab SC (108 mg vedolizumab SC every 2 weeks), or placebo in a 2:1 ratio. The primary outcome was the proportion of patients with clinical remission, defined as a CDAI score of at least 150 at week 52. Outcomes were obtained with validated tools. To control for an overall type I error rate in the comparison between vedolizumab SC and the placebo for the primary and secondary end points, a hierarchical approach was applied to the statistical testing.

During the maintenance phase, 59% of the study participants completed treatment, 61% in the vedolizumab SC group and 54% in the placebo group. The main reason for discontinuation in the maintenance phase was lack of efficacy (73% in the vedolizumab SC group and 71% in the placebo group among those who discontinued) followed by voluntary withdrawal and AEs. This difference in missing data could bias the results. Sensitivity analyses were performed to examine the robustness of the study findings to missing data assumptions, which were generally consistent with the primary results.

Subgroup analyses were performed to examine the consistency of the treatment effect observed for the primary and all secondary outcomes based on age, gender, race, duration of CD, 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. Given the [redacted] of the subgroups, they can be considered underpowered to detect a significant effect from modifiers.

The VISIBLE 2 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 all secondary end points, such as enhanced clinical response and corticosteroid-free clinical remission. In addition, statistical significance was not achieved for the secondary efficacy end point of “enhanced clinical response at week 52,” and statistical significance cannot be formally claimed for any of the end points ranked after this end point, including “corticosteroid-free remission.”

Long-term safety and efficacy of vedolizumab SC in the study population were evaluated in an OLE study of VISIBLE 2, namely SC-3030. This long-term extension study assessed the long-term safety and tolerability of vedolizumab SC in the treatment of CD. Due to the limitation associated with uncontrolled open-label clinical trials, results of this study should be interpreted with caution.

The ITC submitted by the sponsor evaluated the comparative effectiveness and safety of vedolizumab SC relative to other comparators with similar indications. The authors of the review performed an NMA of [redacted]. The key limitations of this NMA included heterogeneity across the included clinical trials in both study design and patient characteristics, and the limited number of trials for certain outcomes.

Interpretation of Results

Efficacy

In VISIBLE 2, more patients in the vedolizumab SC group achieved clinical remission at week 52 (primary efficacy end point) when compared to placebo, with an adjusted risk difference of 13.7% (95% CI, 3.8 to 23.7; P = 0.008). In addition, numerically higher enhanced clinical response at week 52 was observed in the vedolizumab SC group compared with the placebo group; however, the between-group difference did not reach statistical significance (52% versus 44.8%, P = 0.167). Consequently, statistical significance cannot be formally claimed for any of the end points ranked after this end point in the hierarchy; for example, corticosteroid-free remission at week 52. A numerically higher rate of corticosteroid-free remission at week 52 was reported for the vedolizumab group (45.3%) compared with placebo (18.2%). Note that all study participants in the VISIBLE 2 study received 2 induction doses of vedolizumab IV prior to randomization, including those assigned to the placebo arm. Due to several factors, including a possible durable response to IV induction and high corticosteroid use during the maintenance phase ([redacted] in both treatment groups), a relatively high placebo response of 44.8% at week 52 was observed.

For patient-reported outcomes, total scores in the IBDQ (a disease-specific HRQoL assessment tool) suggested improvements for both treatment groups: change from baseline was 63.3 points in the vedolizumab SC group and 55.1 points in the placebo group. It is unclear whether the between-group difference is clinically meaningful. Similar results were observed for the results of EQ-5D VAS and index scores.

Based on the results of the sponsor-submitted NMA, [redacted]. Little should be inferred regarding comparative efficacy or safety based solely on this submitted NMA. The applicability of sponsor's NMA is affected by the limited size of the evidence base (i.e., [redacted]), potential limitations in the submitted analysis, and heterogeneity in trial design and patient populations across trials. Overall, the ability to draw firm conclusions based on these results is limited.

Results of an ongoing, long-term extension study (SC-3030) suggest that [redacted]; however, results of this study should be interpreted with caution, due to the inherent limitations of an uncontrolled, open-label clinical trial.

Harms

Overall, data from the VISIBLE 2 trial, the NMA, and the long-term extension SC-3030 study do not provide important concerns in terms of AEs or SAEs, or harms of special interest established a priori in this review. The incidence of TEAEs was 73.5% in the

vedolizumab SC group and 76.1% in the placebo group. The most common AEs were worsening of CD disease activity, abdominal pain, nasopharyngitis, arthralgia, and upper respiratory tract infections. The incidence of SAEs was comparative between the 2 groups: 8.4% in the vedolizumab SC group and 10.4% in the placebo group. The incidence of withdrawals due to AEs was higher in the placebo group (8.2%) compared to vedolizumab SC (4%).

Based on the results of the sponsor-submitted NMA, [redacted]

In the long-term extension study of the VISIBLE 2 study (SC-3030) to assess the long-term safety and tolerability of vedolizumab SC in the treatment of CD, the interim results suggest that [redacted]

Cost

The average annual drug cost of vedolizumab SC is $21,458 per patient and may be considered cost-neutral when compared to the current list price of vedolizumab IV. Where the price of vedolizumab has been negotiated, in line with the 2016 CADTH recommendation, similar price reductions would be required for vedolizumab SC.

When compared to adalimumab and SEB infliximab (Renflexis), vedolizumab SC is expected to lead to increased annual costs of $967 and $8,596 per patient, respectively, for maintenance treatment. Conversely, vedolizumab SC may be associated with annual cost savings of $4,031 and $8,499 per patient when compared to infliximab (Remicade) and ustekinumab, respectively, for maintenance treatment.

Conclusions

Based on one trial, SC injection of vedolizumab is more effective than placebo in achieving clinical remission in patients with moderately to severely active CD. The benefits related to other outcomes assessed in the trial are uncertain based on failure to detect a statistically significant difference between vedolizumab SC and placebo for the secondary outcome of enhanced clinical response, which was ranked higher than other outcomes in the stepwise analysis procedure. The frequency of AEs was similar between placebo and vedolizumab SC, after 52 weeks of treatment.

Based on one sponsor-submitted review of ITCs, [redacted] due to limitations in its precisions and sources of heterogeneity in the NMA that decrease confidence in the results.

Results from an ongoing, open-label, long-term study suggest that [redacted]. However, these results are of low certainty because of the significant limitations associated with the longer-term study.

At the submitted price based on the recommended dose of 108 mg every 2 weeks, vedolizumab SC has an annual cost of $21,458 per patient in maintenance therapy. This results in cost-neutrality compared to vedolizumab IV on an annual basis; however, information on the comparative efficacy and safety of vedolizumab SC is uncertain and the exclusion of induction therapy costs underestimate total treatment costs versus other comparators.

Appendix 1: Description and Appraisal of Outcome Measures

Aim

To summarize the measurement properties (e.g., reliability, validity, minimally clinically important difference [MCID]) of the following outcome measures used in the VISIBLE 2 study:

- CDAI
- IBDQ
- EQ-5D-3L.

Findings

Table 31: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties total score	MCID
CDAI	Physician-evaluated 8-item CD specific index used to assess CD severity	Validated	NA
IBDQ	Physician-administered 32-item questionnaire used to assess HRQoL in patients with IBD	Validated	16
EQ-5D-3L	Patient-reported generic quality-of-life instrument	Validated	VAS 8.2

CD = Crohn disease; CDAI = Crohn's Disease Activity Index; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; HRQoL = health-related quality of life; IBD = inflammatory bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; NA = not applicable; VAS = Visual Analogue Scale.

CDAI

The National Cooperative Crohn's Disease Study Group developed the CDAI using prospective data from 187 visits of 112 patients suffering from CD.[24] It is a disease-specific index and considered the standard for assessing CD activity. The CDAI consists of 8 domains that are used to evaluate overall disease severity. The overall score is based on the sum of the weighted value of each item and ranges from 0 to 600, where a score of 150 is defined as the threshold between remission and active disease. Scores ranging between 150 and 219 indicate mild to moderate CD and scores ranging between 220 and 450 indicate moderate to severe CD, whereas scores above 450 indicate very severe CD.[25,26] Item scores are derived using patient diaries, which are based on the 7 days preceding each visit. Generally, the CDAI is considered impractical for use in clinical practice, with no clearly defined MCID.[26-28] Originally, changes of 50 points in the CDAI were associated with physician evaluation of "slightly better" and/or "slightly worse" compared to baseline.[24,26,28] However, clinical trials commonly define a change of 50, 60, 70, or 100 points in CDAI as a clinical response.[26] More recently, the FDA and EMA have suggested that a change of 100 points in CDAI is considered to be a more meaningful response (i.e., enhanced clinical response).[26]

Development of the CDAI

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

Multiple regression and backwards stepwise deletions were utilized to assess the correlation between the 18 parameters and the physician global assessment score. Based on the results of the correlations, 8 independently weighted (weighting ranges from 1 to 30) variables were included in the final CDAI formula.

Table 32: Final Items Included in the CDAI and Their Weights

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

Source: Best et al. (1976).[24]

Reliability of the CDAI

Reliability was not originally assessed during the development of the CDAI; however, the index did provide good to very good test-retest reliability based on 2 successive visits involving 32 patients.[24,25] The CDAI was subsequently re-evaluated and re-derived using data collected from 1,058 patients and demonstrated little difference compared to the original formulation; therefore, the original version was recommended.[29]

Validity of the CDAI

Construct validity: The items included in the CDAI were selected by gastroenterologists and are based on accepted features of CD, therefore demonstrating construct validity.[25]

Content validity: The CDAI appears to be responsive as it allows detectible changes in CD severity to be measured (i.e., the CDAI is able to differentiate levels of CD severity). Additionally, the CDAI appears to be widely utilized in clinical trials and is an accepted measure by gastroenterologists as a primary end point to assess CD activity. In contrast,

the CDAI does not appear to be reflective of CD activity for pediatric patients suffering from CD nor does the instrument address all aspects of CD, such as quality of life.[25]

Criterion validity: Selecting a gold-standard measure for comparison is difficult when considering CD due to the heterogeneous nature of its manifestations. Generally, the CDAI does not demonstrate any significant correlation between the overall score and objective measurements such as mucosal healing. However, the lack of correlation may not be indicative of a lack of criterion validity due to the multifaceted nature of CD.[25] Predictability is another component of criterion validity. One study demonstrated that CDAI scores increased 2 months preceding exacerbations of CD and decreased one month following exacerbations of CD, therefore demonstrating criterion validity.[25]

Limitations of the CDAI

The CDAI scores appear to vary depending on the observers' reviews, despite the evaluation of the same case histories.[30] In addition, the overall CDAI scores are based on subjective items such as "general well-being" and "intensity of abdominal pain" based on patient perception.

IBDQ

The IBDQ is a physician-administered questionnaire developed by Guyatt et al.[31,32] to assess HRQoL in patients with IBD (e.g., UC and CD).[33] It is a 32-item Likert-based questionnaire, divided into 4 dimensions (i.e., bowel symptoms [10 items], systemic symptoms [5 items], emotional function [12 items], and social function [5 items]). Patients are asked to recall symptoms and quality of life from the last 2 weeks, with responses graded on a 7-point Likert scale (1 being the worst situation, 7 being the best) with the total IBDQ score ranging between 32 and 224 (i.e., higher scores representing better quality of life). Scores of patients in remission typically range from 170 to 190.

This questionnaire has been validated in a variety of settings, countries, and languages.[33] A review[33] of nine validation studies on the IBDQ in patients with IBD reported that the IBDQ was able to differentiate clinically important differences between patients with disease remission and patients with disease relapse. In a randomized placebo-controlled trial on patients with UC, the IBDQ was able to discriminate changes in the social and emotional state of patients.[32] The IBDQ has demonstrated high test-retest reliability in all 4 dimensional scores. Six studies evaluated the IBDQ for sensitivity to change and all found that changes in HRQoL correlated to changes in clinical activity in patients with CD.[33]

A study conducted by Gregor et al.[34] noted that a clinically meaningful improvement in quality of life would be an increase of at least 16 points in the IBDQ total score or 0.5 points or more per question in patients with CD.

EQ-5D-3L

The EQ-5D is a generic HRQoL instrument that can be applied to a wide range of health conditions and treatments.[35,36] The first of 2 parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has 3 possible levels (1, 2, or 3) for each domain, representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the 5 dimensions, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to

self-reported health states from a set of population-based preference weights.[35,36] The second part is a 20 cm VAS that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and '"best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their health on that day. Hence, the EQ-5D produces 3 types of data for each respondent:

- a profile indicating the extent of problems on each of the 5 dimensions represented by a 5-digit descriptor, such as 11121 or 33211
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the EQ-5D-3L version (corresponding to severe problems on all 5 attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported MCIDs for the 3-level version of the scale range from 0.033 to 0.074.[37]

Studies are emerging supporting the validity of the EQ-5D in patients with IBD, including CD. Both the EQ-VAS and EQ-index scores were found to correlate well with disease activity indices and differed significantly between patients with active disease and remission. Test-retest reliability was high. The EQ-VAS was more responsive to deterioration in health than improvement in health and tended to be more responsive than EQ-index scores.[38]

A study by Coteur et al.[39] explored MCID estimates within the CD patient population using data from multinational, multi-centre, double-blind, placebo-controlled, parallel-group clinical trials in which clinical remission of CD was assessed using the CDAI measure as the primary outcome. Secondary outcomes included the IDBQ and EQ-5D VAS score. All end points were measured at weeks 0, 6, 16, and 26 using standardized procedures. Six estimates of MCID were evaluated for the EQ-5D VAS score to determine the most appropriate measure to use as the anchor: 2 analyses utilizing anchor-based methods and 4 analyses utilizing distribution-based methods. For the anchor-based estimates, a linear regression was performed using the 2 anchors and the CDAI and IBDQ. The MCID estimates for the EQ-5D VAS score were then extracted from the regression equations, with a change of 16 points for the IBDQ total score or a score change of 50 points for the CDAI score considered meaningful. For distribution-based estimates, measures rely on the statistical distributions of HRQoL data, and include effect size measures (0.2 and 0.5 were used and suggested as small to moderate effect sizes), the standard error of measurement, and the standard error of the difference. Overall, the MCID for the EQ-5D VAS score ranged from 4.2 to 14.8, depending on the approach. Because changes in the EQ-5D VAS score showed greater correlations with score changes in the IBDQ than with CDAI, the IBDQ was selected as the best anchor, with a corresponding MCID of 8.2. The values derived by the IBDQ anchor-based method were similar to the values obtained by the distribution-based methods and were representative of small to moderate effect sizes.

Appendix 2: Additional Outcome Measures

Table 33: [redacted]

Efficacy outcome	Anti–TNF alpha–naive patients		Anti–TNF alpha–exposed patients		Anti–TNF alpha–failure patients	
Total # of patients	**ENTYVIO SC N = 275**	**Placebo N = 134**	**ENTYVIO SC N = 275**	**Placebo N = 134**	**ENTYVIO SC N = 275**	**Placebo N = 134**
Clinical remission at 52 weeks	**N = 107**	**N = 63**	**N = 17**	**N = 12**	**N = 151**	**N = 59**
n (%) (95% CI)	52 (48.6) [redacted]	27 (42.9) [redacted]	[redacted]	[redacted]	70 (46.4) [redacted]	17 (28.8) [redacted]
Difference, % (95% CI)	4.3 (−11.6 to 20.3)	NA	[redacted]	NA	17.6 (3.8 to 31.4)	NA
P value	0.591	NA	[redacted]	NA	0.019	NA
Enhanced clinical response at 52 weeks	**N = 107**	**N = 63**	**N = 17**	**N = 12**	**N = 151**	**N = 59**
n (%) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference, % (95% CI)	[redacted]	NA	[redacted]	NA	[redacted]	NA
Corticosteroid-free clinical remission at 52 weeks	**N = 39**	**N = 22**	NA	NA	**N = 52**	**N = 20**
n (%) (95% CI)	16 (41.0) [redacted]	4 (18.2) [redacted]	NA	NA	24 (46.2) [redacted]	3 (15.0) [redacted]
Difference, % (95% CI)	22.8 (−3.2 to 46.8)	NA	NA	NA	31.2 (5.2 to 54.5)	NA

CI = confidence interval; NA = not applicable; SC = subcutaneous; TNF = tumour necrosis factor.

Source: Clinical Summary in Entyvio SC submission.[16]

Appendix 3: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - Vedolizumab SC was assumed to capture market share from [redacted]; however, given the potential convenience of administration and reduced health care resource utilization, market share uptake from [redacted] may be underestimated.
  - Ustekinumab's market share was likely overestimated based on historical claims data and ongoing negotiation with pCPA.
  - The cost comparison with vedolizumab IV was uncertain given the potential negotiated drug price according to the pricing condition recommended by CADTH.
  - The sponsor did not include comparator induction costs, which are anticipated to be higher for vedolizumab SC.
- CADTH reanalyses included removing the market shares for ustekinumab.
- CADTH's base case did not change based on reanalyses: vedolizumab SC remained cost-neutral over the 3-year time horizon. However, it is probable that the costs for vedolizumab SC will be higher in the induction year; therefore, the budget impact is likely underestimated and would result in increased expenditures if market share uptake includes [redacted]. Where market share uptake was assumed to include [redacted], the 3-year budget impact was $1,929,135. In a scenario analysis in which a price reduction of 40% was assumed for vedolizumab IV, the 3-year budget impact was $31,986,913.

Summary of Sponsor's Budget Impact Analysis

The submitted budget impact analysis (BIA) assessed the introduction of vedolizumab SC as treatment for adult patients with moderately to severely active CD. The analysis was undertaken from a drug plan perspective using a claims-based approach. A 3-year time horizon was used, from 2021 to 2023, with 2020 as a base year. Claims were forecasted over the time horizon based on 4 years of historical public claims data. The relevant comparators for this analysis included intravenous (IV) vedolizumab, adalimumab, infliximab, and ustekinumab. The base case included drug acquisition costs, dispensing fees, and mark-up, with a scenario analysis performed from the health care payer perspective that also included administration costs.

In the reference scenario, the sponsor only considered vedolizumab available as an IV formulation and included the comparators adalimumab and infliximab, with a proportion of market shares for ustekinumab projected in jurisdictions where funding has yet to be received. Vedolizumab SC was introduced in the new drug scenario and was only assumed to capture market share from [redacted]: [redacted]% of the total vedolizumab share in year 1, [redacted]% in year 2, and [redacted]% by year 3. The market shares of [redacted] remained unchanged. Key inputs to the BIA are documented in Table .

Table 34: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1/2/3)
Target population (number of claims for CD drugs in base year)	
British Columbia	61,734
Alberta	43,830
Saskatchewan	25,164
Manitoba	11,020
Ontario	86,546
New Brunswick	4,826
Nova Scotia	5,528
Prince Edward Island	893
Newfoundland	1,717
NIHB	1,720
Market uptake for Ontario (3 years)	
Uptake (reference scenario)	
Vedolizumab IV	[redacted]
Adalimumab	[redacted]
Infliximab (Inflectra)	[redacted]
Infliximab (Remicade)	[redacted]
Infliximab (Renflexis)	[redacted]
Ustekinumab (projected)	[redacted]
Uptake (new drug scenario)	
Vedolizumab SC	[redacted]
Vedolizumab IV	[redacted]
Adalimumab	[redacted]
Infliximab (Inflectra)	[redacted]
Infliximab (Remicade)	[redacted]
Infliximab (Renflexis)	[redacted]
Ustekinumab (projected)	[redacted]
Cost of treatment in Ontario per patient (includes dispensing fees and mark-up)	
Cost of treatment annually (maintenance therapy)	
Vedolizumab SC	$22,845
Vedolizumab IV	$22,845
Adalimumab	$21,394
Infliximab (Inflectra)	$13,550
Infliximab (Remicade)	$25,387
Infliximab (Renflexis)	$12,731
Ustekinumab	$31,849
Mark-up	6.0%
Dispensing fee	$8.83

CD = Crohn disease; NIHB = non-insured health benefits; SC = subcutaneous.

Note: Results may not be representative of overall Canadian clinical practice because market shares and dispensing fees differ by province.

Summary of the Sponsor's Budget Impact Analysis Results

Results of the sponsor's base case suggested the introduction of vedolizumab SC would be cost-neutral (i.e., annual budget impact of $0) over the total 3-year time horizon. This was based on [redacted] according to the recommended dosing and market share uptake [redacted]. As part of scenario analyses when adopting a health care payer perspective, vedolizumab SC was associated with a cost savings of $5,224,410 over the 3-year time horizon.

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified the following key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Inappropriate uptake of ustekinumab:** Ustekinumab for the treatment of CD is currently only reimbursed by the province of Saskatchewan; however, the sponsor's assumed uptake of ustekinumab in other jurisdictions over the 3-year time horizon was not supported by historical claims data. Specifically, in jurisdictions other than Saskatchewan the sponsor assumed market shares of [redacted]%, [redacted]%, and [redacted]% in years 1, 2, and 3, respectively. Based on the lack of historical data suggesting use of ustekinumab for CD in Canada, CADTH considered the assumptions regarding market share uptake for ustekinumab to be inappropriate. In addition, pCPA negotiations for ustekinumab for CD were concluded without agreement in March 2019, indicating there may be limited uptake of this treatment in CD by the public drug plans.[22]
  - CADTH removed all market uptake by ustekinumab in the new and reference scenarios (except for Saskatchewan) as part of the CADTH base case. As CADTH retained the sponsor's estimates for market share uptake, [redacted]
- **Vedolizumab SC only captures market share from [redacted]:** The sponsor assumed that vedolizumab SC would [redacted] capture market share from [redacted] as part of the base case. In some cases, however, it may be reasonable to assume vedolizumab SC would capture market share from [redacted] due to the convenience of self-administering an SC treatment rather than travelling to a clinic for IV infusion.

  As a scenario analysis, the sponsor assumed that vedolizumab SC would capture market share from [redacted]. CADTH assessed the effect of this market share assumption without consideration of ustekinumab as a comparator given the limitation above.
  - CADTH assumed that vedolizumab SC would capture market share from [redacted], as part of a scenario analysis.
- **Consideration of induction costs:** The sponsor did not include costs associated with the induction phase of both SC and IV therapies in their analysis. As noted in the Issues for Consideration section, first-year induction therapy costs were more than those of subsequent maintenance years. Therefore, the sponsor's consideration of only maintenance treatment likely underestimates the budget impact for vedolizumab SC if market share is expected to be captured from [redacted]. As the sponsor's BIA does not separate incident versus prevalent patients and implicitly assumes all patients are initiated and continued according to the maintenance dosing

regimen, CADTH was unable to explore the impact of including induction treatment costs on the budget impact.

  - Due to structural limitations, CADTH was unable to assess the inclusion of induction treatment costs.

- **Price reduction of vedolizumab SC:** In 2016, CADTH previously reviewed vedolizumab IV and recommended a price reduction (of approximately 40%) to that of the least-costly alternative biologic treatment option, infliximab (Renflexis).[23] Where participating drug plans were able to negotiate this price reduction for vedolizumab IV, a similar price reduction would need to be included for vedolizumab SC to be considered cost-neutral.

  - CADTH assumed a price reduction of 40% of vedolizumab IV as part of a scenario analysis.

CADTH Reanalyses of the Budget Impact Analysis

Based on the limitations identified by CADTH, the market share uptake of ustekinumab was adjusted as part of CADTH's base-case analysis (Table). However, as vedolizumab SC captured market share only from [redacted] in the sponsor's model and there were limited data to inform the potential uptake from [redacted], the CADTH results do not change: vedolizumab SC remains cost-neutral (Table).

Table 35: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to derive the CADTH base case		
None		
Changes to derive the CADTH base case		
1. Inappropriate uptake of ustekinumab (**CADTH base case**)	Ustekinumab market shares (Y1/Y2/Y3) [redacted]%/[redacted]%/[redacted]%	Ustekinumab market shares (Y1/Y2/Y3) 0%/0%/0%

Y1 = year 1; Y2 = year 2; Y3 = year 3.

CADTH explored the potential uptake of market share from [redacted] in a scenario analysis using the estimates provided by the sponsor, with an overview of the included market shares presented in Table . When including market share uptake from [redacted], the 3-year budget impact was $1,929,135 (Table).

CADTH explored a scenario in which participating drug plans were assumed to have successfully negotiated a 40% price reduction for vedolizumab IV (based on the expected price reduction to match the costs of SEB infliximab [Renflexis]). The 3-year budget impact was $31,986,913 and participating drug plans would be required to negotiate a similar price reduction for vedolizumab SC to remain cost-neutral.

Table 36: CADTH Scenario Analyses on the Submitted Budget Impact Analysis

Stepped analysis	CADTH base case	CADTH scenario
Scenario analyses		
1. Assume market uptake from [redacted]	Capture rate from comparators (Y1/Y2/Y3) Vedolizumab IV: [redacted]%/ [redacted]%/[redacted]% Adalimumab: [redacted]%/[redacted]%/[redacted]% Infliximab (Inflectra): [redacted]%/[redacted]%/[redacted]% Infliximab (Remicade): [redacted]%/[redacted]%/[redacted]% Infliximab (Renflexis): [redacted]%/[redacted]%/[redacted]% Ustekinumab: [redacted]%/[redacted]%/[redacted]%	Capture rate from comparators (Y1/Y2/Y3) Vedolizumab IV: [redacted]%/[redacted]%/[redacted]% Adalimumab: [redacted]%/[redacted]%/[redacted]% Infliximab (Inflectra): [redacted]%/[redacted]%/[redacted]% Infliximab (Remicade): [redacted]%/[redacted]%/[redacted]% Infliximab (Renflexis): [redacted]%/[redacted]%/[redacted]% Ustekinumab: 0%/0%/0%
2. Vedolizumab IV price reduction	0%	40%

Y1 = year 1; Y2 = year 2; Y3 = year 3.

Note: CADTH comparator market shares were based on the Ontario market and were assumed to be representative of the pan-Canadian perspective.

Table 37: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	3-year total
Submitted base case	$0
CADTH base case	$0
CADTH scenario analysis 1 – market share from [redacted]	$1,929,135
CADTH scenario analysis 2 – 40% price reduction vedolizumab IV	$31,986,913

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

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