PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Entyvio powder for concentrate for solution for infusion 300mg/vial (vedolizumab)
Entyvio solution for injection in pre-filled pen/autoinjector 108mg/0.68ml (vedolizumab)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vedolizumab is a humanised IgG_1 monoclonal antibody that binds to the human $\alpha_4\beta_7$ integrin and is produced in Chinese hamster ovary (CHO) cells.

Vedolizumab Powder for Solution for Infusion

Each vial contains 300 mg of vedolizumab.

After reconstitution, each ml contains 60 mg of vedolizumab.

For the full list of excipients, see section 6.1.

Vedolizumab Solution for Injection

Each prefilled pen/autoinjector delivers 108 mg of vedolizumab in 0.68 mL solution.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Available Pharmaceutical Forms	Strength	Color
Lyophilized cake or Powder for solution for infusion	300 mg	White to off-white
Solution for injection in single-dose prefilled pen/autoinjector	108 mg / 0.68 mL	Colorless to yellow

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ulcerative Colitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's Disease

Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

4.2 Posology and method of administration

Entyvio treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease.

Posology – Intravenous Administration

Ulcerative Colitis

The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Therapy for patients with ulcerative colitis should not be continued if no evidence of therapeutic benefit is observed by Week 14 (see section 5.1).

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to intravenous vedolizumab 300 mg every four weeks.

In patients who have responded to treatment with Entyvio, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Retreatment: If therapy is interrupted and there is a need to restart treatment with intravenous vedolizumab, dosing at every four weeks may be considered (see section 5.1). The treatment interruption period in clinical studies extended up to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with intravenous vedolizumab (see section 4.8).

Crohn's disease

The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Patients with Crohn's disease, who have not shown a response may benefit from a dose of intravenous vedolizumab at Week 10 (see section 4.4). Continue therapy every eight weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14 (see section 5.1).

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to intravenous vedolizumab 300 mg every four weeks.

In patients who have responded to treatment with Entyvio, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

*Retreatment:*If therapy is interrupted and there is a need to restart treatment with intravenous vedolizumab, dosing at every four weeks may be considered (see section 5.1). The treatment interruption period in clinical studies extended up to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with intravenous vedolizumab (see section 4.8).

Posology – Subcutaneous Administration

Ulcerative Colitis and Crohn's Disease

The recommended dose regimen of subcutaneous vedolizumab as a maintenance treatment, following at least two intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks.

The first subcutaneous maintenance dose should be administered in place of the next scheduled intravenous dose and every 2 weeks thereafter. See Intravenous Administration section above for intravenous dosing schedule.

Insufficient data are available to determine if patients who experience a decrease in response on maintenance treatment with subcutaneous vedolizumab would benefit from an increase in dosing frequency.

There are no data on transition of patients from subcutaneous vedolizumab to intravenous vedolizumab during maintenance treatment.

Missed Dose(s)

If treatment with subcutaneous vedolizumab is interrupted or if a patient misses a scheduled dose(s) of subcutaneous vedolizumab, advise the patient to inject the next subcutaneous dose as soon as possible and then every 2 weeks thereafter. The treatment interruption period in clinical studies extended up to 46 weeks with no evident increase in adverse events or injection site reactions during reinitiation of treatment with subcutaneous vedolizumab.

Corticosteroids

In patients who have responded to treatment with subcutaneous vedolizumab, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Paediatric population

The safety and efficacy of vedolizumab in children aged 0 to 17 years old have not been established. No data are available.

Elderly patients

No dose adjustment is required in elderly patients. Population pharmacokinetic analyses showed no effect of age (see section 5.2).

Patients with renal or hepatic impairment
Vedolizumab has not been studied in these patient populations. No dose recommendations can be made.

Method of administration – Intravenous Administration

Intravenous vedolizumab is for intravenous use only. It is to be reconstituted and further diluted prior to intravenous administration, for instructions see section 6.5.

Intravenous vedolizumab is administered as an intravenous infusion over 30 minutes. Do not administer as an intravenous push or bolus. Vedolizumab lyophilized powder must be reconstituted with sterile water for injection and diluted in 250 mL of sterile 0.9% sodium chloride solution or 250mL of sterile Lactated Ringer's solution prior to administration. After the infusion is complete, flush with 30 mL of sterile 0.9% sodium chloride solution or 30mL of sterile Lactated Ringer's solution. Patients should be monitored during and after infusion (see section 4.4).

Method of Administration – Subcutaneous Administration

Vedolizumab in a prefilled pen/autoinjector is for subcutaneous injection only.

After proper training on correct subcutaneous injection technique, a patient or caregiver may inject subcutaneous vedolizumab if their physician determines it is appropriate. Inspect the solution visually for particulate matter and discoloration prior to administration. The solution should be colorless to yellow. Do not use prefilled pen/autoinjector with visible particulate matter or discoloration.

4.3 Contraindications

Hypersensitivity (such as dyspnea, bronchospasm, urticaria, flushing and increased heart rate) to the active substance or to any of the excipients listed in section 6.1.

Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML) (see section 4.4).

4.4 Special warnings and precautions for use

Vedolizumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering vedolizumab. Observe patients during infusion and until the infusion is complete. For the first two infusions, they should also be observed for approximately two hours following completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately one hour following completion of the infusion.

Infusion-related reactions and hypersensitivity reactions

In clinical studies, infusion related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see section 4.8).

If a severe IRR, anaphylactic reaction, or other severe reaction occurs, administration of vedolizumab must be discontinued immediately and appropriate treatment initiated (e.g., epinephrine and antihistamines) (see section 4.3).

If a mild to moderate IRR occurs, the infusion rate can be slowed or interrupted and appropriate treatment initiated (e.g. epinephrine and antihistamines). Once the mild or moderate IRR subsides, continue the infusion. Physicians should consider pre-treatment (e.g., with antihistamine, hydrocortisone and/or paracetamol) prior to the next infusion for patients with a history of mild to moderate IRR to vedolizumab, in order to minimize their risks (see section 4.8).

Infections

Vedolizumab is a gut-selective integrin antagonist with no identified systemic immunosuppressive activity (see section 5.1).

Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier (see section 4.8). Vedolizumab treatment is not to be initiated in patients with active, severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections until the infections are controlled, and physicians should consider withholding treatment in patients who develop a severe infection while on chronic treatment with vedolizumab. Caution should be exercised when considering the use of vedolizumab in patients with a controlled chronic severe infection or a history of recurring severe infections. Patients should be monitored closely for infections before, during and after treatment. Vedolizumab is contraindicated in patients with active tuberculosis (see section 4.3). Before starting treatment with vedolizumab, patients must be

screened for tuberculosis according to the local practice. If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis treatment in accordance with local recommendations, before beginning vedolizumab. In patients diagnosed with TB whilst receiving vedolizumab therapy, then vedolizumab therapy should be discontinued until the TB infection has been resolved.

Some integrin antagonists and some systemic immunosuppressive agents have been associated with progressive multifocal leukoencephalopathy (PML), which is a rare and often fatal opportunistic infection caused by the John Cunningham (JC) virus. By binding to the $\alpha_4\beta_7$ integrin expressed on gut-homing lymphocytes, vedolizumab exerts an immunosuppressive effect specific to the gut. No systemic immunosuppressive effect was noted in healthy subjects.

Healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and other symptoms and consider neurological referral if they occur.

Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months.

If PML is suspected, treatment with vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued.

Malignancies

The risk of malignancy is increased in patients with ulcerative colitis and Crohn's disease. Immunomodulatory medicinal products may increase the risk of malignancy (see section 4.8).

Prior and concurrent use of biological products

No vedolizumab clinical study data are available for patients previously treated with natalizumab or rituximab.

Patients previously exposed to natalizumab should normally wait a minimum of 12 weeks prior to initiating therapy with vedolizumab, unless otherwise indicated by the patient's clinical condition.

No clinical study data for concomitant use of vedolizumab with biologic immunosuppressants are available. Therefore, the use of vedolizumab in such patients is not recommended.

Live and oral vaccines

In a placebo-controlled study of healthy volunteers, a single 750 mg dose of vedolizumab did not lower rates of protective immunity to hepatitis B virus in subjects who were vaccinated intramuscularly with three doses of recombinant hepatitis B surface antigen. Vedolizumab-exposed subjects had lower seroconversion rates after receiving a killed, oral cholera vaccine. The impact on other oral and nasal vaccines is unknown.

It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating vedolizumab therapy. Patients receiving vedolizumab treatment may continue to receive non-live vaccines (e.g., subunit or inactivated vaccines). There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab. Administration of the influenza vaccine should be by injection in line with routine clinical practice. Other live vaccines may be administered concurrently with vedolizumab only if the benefits clearly outweigh the risks.

Induction of remission in Crohn's disease

Induction of remission in Crohn's disease may take up to 14 weeks in some patients. The reasons for this are not fully known and are possibly related to the mechanism of action. This should be taken into consideration, particularly in patients with severe active disease at baseline not previously treated with TNFα antagonists. (See also section 5.1.)

Exploratory subgroup analyses from the clinical studies in Crohn's disease suggested that vedolizumab administered in patients without concomitant corticosteroid treatment may be less effective for induction of remission in Crohn's disease than in those patients already receiving concomitant corticosteroids (regardless of use of concomitant immunomodulators; see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Vedolizumab has been studied in adult ulcerative colitis and Crohn's disease patients with concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), and aminosalicylates. Population pharmacokinetic analyses suggest that co-administration of such agents did not have a clinically meaningful effect on vedolizumab pharmacokinetics. The effect of vedolizumab on the pharmacokinetics of commonly co-administered medicinal compounds has not been studied.

Vaccinations
Live vaccines, in particular live oral vaccines, should be used with caution concurrently with vedolizumab(see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and to continue its use for at least 18 weeks after the last treatment with vedolizumab.

Pregnancy

There are limited amount of data from the use of vedolizumab in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Vedolizumab is to be used during pregnancy only if the benefits to the mother are considered to outweigh the risk to the unborn child.

Breast-feeding

Vedolizumab has been detected in human milk. The effect of vedolizumab on infants is unknown. In a milk-only lactation study assessing the concentration of vedolizumab in breast milk of lactating women with active ulcerative colitis or Crohn's disease receiving vedolizumab, the concentration of vedolizumab in human breast milk was approximately 0.4% to 2.2% of the maternal serum concentration obtained from historical studies of vedolizumab. The estimated average daily dose of vedolizumab ingested by the infant was 0.02 mg/kg/day, which is approximately 21% of the body weight-adjusted average maternal daily dose.
The use of vedolizumab in lactating women should take into account the benefit of therapy to the mother and potential risks to the infant.

Fertility

There are no data on the effects of vedolizumab on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Vedolizumab may have a minor influence on the ability to drive or operate machines, as dizziness has been reported in a small number of patients.

4.8 Undesirable effects

Summary of safety profile

Clinical trials

Intravenous vedolizumab has been studied in three placebo-controlled clinical studies in patients with ulcerative colitis (GEMINI I) or Crohn's disease (GEMINI II and III). In two controlled studies (GEMINI I and II) involving 1,434 patients receiving intravenous vedolizumab 300 mg at Week 0, Week 2 and then every eight weeks or every four weeks for up to 52 weeks, and 297 patients receiving placebo for up to 52 weeks, adverse events were reported in 84% of vedolizumab-treated patients and 78% of placebo-treated patients. Over 52 weeks, 19% of vedolizumab-treated patients experienced serious adverse events compared to 13% of placebo-treated patients. Similar rates of adverse events were seen in the every eight week and every four week dosing groups in the Phase 3 clinical studies. The proportion of patients who discontinued treatment due to adverse events was 9% for vedolizumab treated patients and 10% for placebo-treated patients. In the combined studies of GEMINI I and II the adverse reactions that occurred in ≥5% were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, cough. Infusion-related reactions were reported in 4% of patients receiving vedolizumab.

In the shorter (10 week) placebo controlled induction studies, GEMINI III, the types of adverse reactions reported were similar but occurred at lower frequency than the longer 52 week studies.

A further 279 patients were treated with intravenous vedolizumab at Week 0 and Week 2 and then with placebo for up to 52 weeks. Of these patients, 84% experienced adverse events and 15% experienced serious adverse events.

Patients (n=1,822) previously enrolled in Phase 2 or 3 intravenous vedolizumab studies were eligible to enroll in an ongoing open-label study and received intravenous vedolizumab 300 mg every four weeks.

Subcutaneous vedolizumab was studied in two double-blind, placebo-controlled clinical studies in adult patients with ulcerative colitis (VISIBLE 1; n=383) or Crohn's disease (VISIBLE 2; n=644) (see section 5.1). The long-term safety and efficacy of subcutaneous vedolizumab treatment are being studied in an ongoing, open-label extension study that includes patients with ulcerative colitis or Crohn's disease. A pooled safety analysis was conducted in patients receiving subcutaneous vedolizumab (N=811) who were randomized in the two placebo-controlled clinical studies (VISIBLE 1 and VISIBLE 2) and in the open-label extension study. The mean duration of exposure in these patients receiving subcutaneous vedolizumab was 591.4 days.

No clinically relevant differences in the overall safety profile and adverse events were observed in patients who received subcutaneous vedolizumab compared to the safety profile observed in clinical studies with intravenous vedolizumab with the exception of injection site reactions (with subcutaneous administration only).

Tabulated list of adverse reactions

The following listing of adverse reactions is based on the clinical studies experience and are displayed by system organ class. Within the system organ classes, adverse reactions are listed under headings of the following frequency categories: very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse Reactions

System Organ Class	**Frequency**	**Adverse Reaction(s)**
Infection and infestation	Very Common	Nasopharyngitis
	Common	Bronchitis, Gastroenteritis, Upper respiratory tract infection, Influenza, Sinusitis, Pharyngitis
	Uncommon	Respiratory tract infection, Vulvovaginal candidiasis, Oral Candidiasis
Nervous system disorders	Very Common	Headache
	Common	Paraesthesia
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain, Nasal congestion, Cough
Gastrointestinal disorders	Common	Anal Abscess, Anal fissure, Nausea, Dyspepsia, Constipation, Abdominal distension, Flatulence, Haemorrhoids
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus, Eczema, Erythema, Night sweats, Acne
	Uncommon	Folliculitis
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia
	Common	Muscle spasms, Back pain, Muscular weakness, Fatigue
General disorders and administration site conditions	Common	Pyrexia, Injection Site reactions*
	Uncommon	Infusion site reaction (including: Infusion site pain and Infusion site irritation), Infusion related reaction Chills, Feeling cold, Pain in extremities

*Subcutaneous administration only

Postmarketing Experience
In the post-marketing setting reports of anaphylaxis have been identified. The frequency of *anaphylaxis in this setting is unknown.*

Description of selected adverse reactions

Infusion-related reactions

In GEMINI I and II controlled studies, 4% of intravenous vedolizumab treated patients and 3% of placebo-treated patients experienced an adverse event defined by the investigator as infusion related reaction (IRR) (see section 4.4). No individual Preferred Term reported as an IRR occurred at a rate above 1%. The majority of IRRs were mild or moderate in intensity and <1% resulted in discontinuation of study treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion. Most infusion related reactions occurred within the first 2 hours. Of those patients who had infusion related reactions, those dosed with intravenous vedolizumab had more infusion related reactions with in the first two hours as compared to placebo patients with infusion

related reactions. Most infusion related reactions were not serious and occurred during the infusion or within the first hour after infusion is completed.

One serious adverse event of IRR was reported in a Crohn's disease patient during the second infusion (symptoms reported were dyspnoea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) and was successfully managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone. In patients who received intravenous vedolizumab at Weeks 0 and 2 followed by placebo, no increase in the rate of IRR was seen upon retreatment with intravenous vedolizumab after loss of response.

Injection-Site Reactions

In pooled safety analysis in patients receiving subcutaneous vedolizumab (N=811) in clinical studies, injection site reactions were reported in 5.1% of patients. Injection-site reactions were mild or moderate in intensity, and none were reported as serious. None resulted in discontinuation of study treatment or changes to the dosing schedule. The majority of injection-site reactions resolved within 1-4 days. Anaphylaxis was not reported following subcutaneous vedolizumab administration in clinical studies.

Infections

In GEMINI I and II controlled studies with intravenous vedolizumab, the rate of infections was 0.85 per patient-year in the vedolizumab-treated patients and 0.70 per patient-year in the placebo-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most patients continued on vedolizumab after the infection resolved.

In GEMINI I and II controlled studies with intravenous vedolizumab, the rate of serious infections was 0.07 per patient year in vedolizumab-treated patients and 0.06 per patient year in placebo--treated- patients. Over time, there was no significant increase in the rate of serious infections.

In controlled and open-label studies in adults with intravenous vedolizumab, serious infections have been reported, which include tuberculosis, sepsis (some fatal), salmonella sepsis, listeria meningitis, and cytomegaloviral colitis.
In clinical studies with intravenous and subcutaneous vedolizumab, the rate of infections in vedolizumab-treated patients with BMI of 30 kg/m^2 and above was higher than for those with BMI of less than 30 kg/m^2.

Immunogenicity
An acid dissociation electrochemiluminescence (ECL) method for detecting antibodies to vedolizumab was developed and validated. The incidence of anti-vedolizumab antibodies to intravenous vedolizumab with the drug-tolerant ECL method for patients in GEMINI 1 and GEMINI 2 studies who had continuous treatment for 52 weeks was 6% (86 out of 1427). Of the 86 patients who tested positive for anti-vedolizumab antibodies, 20 patients were persistently positive and 56 developed neutralizing antibodies to vedolizumab.

The incidence of anti-vedolizumab antibodies to subcutaneous vedolizumab in VISIBLE 1 and VISIBLE 2 with the ECL method in ulcerative colitis or Crohn's disease patients who had continuous treatment for 52 weeks was 3.4% (13 out of 381). Of the 13 patients who tested positive for anti-vedolizumab antibodies, 7 patients were persistently positive and 7 developed neutralizing antibodies to vedolizumab.

Overall, there was no apparent correlation of anti-vedolizumab antibody development to adverse events following intravenous or subcutaneous administration of vedolizumab.

Malignancy

Overall, results from the clinical program to date do not suggest an increased risk for malignancy with vedolizumab treatment; however, the number of malignancies was small and long-term exposure was limited. Long-term safety evaluations are ongoing.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving vedolizumab. In the GEMINI I (UC), GEMINI II (CD) and GEMINI III (CD) studies, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five vedolizumab doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled studies, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with vedolizumab and in patients treated with placebo. In the open-label studies, one additional case of serious hepatitis was observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions.

4.9 Overdose

Doses up to 10 mg/kg (approximately 2.5 times the recommended dose) have been administered intravenously in clinical studies. No dose-limiting toxicity was seen in clinical studies.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: immunosuppressants, selective immunosuppressants, ATC code: L04AA33

5.1 Pharmacodynamic properties

Vedolizumab is a gut-selective immunosuppressive biologic. It is a humanized monoclonal antibody that binds specifically to the $\alpha_4\beta_7$ integrin, which is preferentially expressed on gut homing T helper lymphocytes. By binding to $\alpha_4\beta_7$ on certain lymphocytes, vedolizumab inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not to vascular cell adhesion molecule-1 (VCAM-1). MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to tissues within the gastrointestinal tract. Vedolizumab does not bind to, nor inhibit function of, the $\alpha_4\beta_1$ and $\alpha_E\beta_7$ integrins.

The $\alpha_4\beta_7$ integrin is expressed on a discrete subset of memory T helper lymphocytes which preferentially migrate into the gastrointestinal (GI) tract and cause inflammation that is characteristic of ulcerative colitis and Crohn's disease, both of which are chronic inflammatory immunologically mediated conditions of the GI tract. Vedolizumab reduces gastrointestinal inflammation in UC and CD patients. Inhibiting the interaction of $\alpha_4\beta_7$ with MAdCAM-1 with vedolizumab prevents transmigration of gut-homing memory T helper lymphocytes across the vascular endothelium into parenchymal tissue in nonhuman primates and induced a reversible 3-fold elevation of these cells in peripheral blood. The murine precursor of vedolizumab alleviated gastrointestinal inflammation in colitic cotton-top tamarins, a model of ulcerative colitis.

In healthy subjects, ulcerative colitis patients, or Crohn's disease patients, vedolizumab does not elevate neutrophils, basophils, eosinophils, B-helper and cytotoxic T lymphocytes, total memory T

helper lymphocytes, monocytes or natural killer cells, in the peripheral blood with no leukocytosis observed.

Vedolizumab did not affect immune surveillance and inflammation of the central nervous system in Experimental Autoimmune Encephalomyelitis in non-human primates, a model of multiple sclerosis. Vedolizumab did not affect immune responses to antigenic challenge in the dermis and muscle (see section 4.4). In contrast, vedolizumab inhibited an immune response to a gastrointestinal antigenic challenge in healthy human volunteers (see section 4.4).

Pharmacodynamic effects

In clinical studies with intravenous vedolizumab at doses ranging from 2 to 10 mg/kg, >95% saturation of $\alpha_4\beta_7$ receptors on subsets of circulating lymphocytes involved in gut immune surveillance was observed in patients.

Vedolizumab did not affect $CD4^+$ and $CD8^+$ trafficking into the CNS as evidenced by the lack of change in the ratio of $CD4^+/CD8^+$ in cerebrospinal fluid pre- and post-vedolizumab administration in healthy human volunteers. These data are consistent with investigations in nonhuman primates which did not detect effects on immune surveillance of the CNS.

Clinical efficacy

Ulcerative Colitis – Vedolizumab for Intravenous Administration

The efficacy and safety of intravenous vedolizumab for the treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopic sub score ≥2) was demonstrated in a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 6 and Week 52 (GEMINI I). Enrolled patients had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or the TNFα antagonist infliximab (including primary non-responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

For the evaluation of the Week 6 endpoints, 374 patients were randomised in a double-blind fashion (3:2) to receive intravenous vedolizumab 300 mg or placebo at Week 0 and Week 2. Primary endpoint was the proportion of patients with clinical response (defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) at Week 6. Table 2 shows the results from the primary and secondary endpoints evaluated.

Table 2. Week 6 Efficacy Results of a 52-Week controlled study (GEMINI I) in Ulcerative Colitis Patients Receiving Intravenous Vedolizumab

Endpoint	Placebo N=149	Vedolizumab N=225
Clinical response	26%	47%*
Clinical remission[§]	5%	17%[†]
Mucosal healing[¶]	25%	41%[‡]

*$p<0.0001$

[†]$p\leq0.001$

[‡]$p<0.05$

[§]Clinical remission: Complete Mayo score of ≤2 points and no individual subscore >1 point

[¶]Mucosal healing: Mayo endoscopic subscore of ≤1 point

The beneficial effect of intravenous vedolizumab on clinical response, remission and mucosal healing was observed both in patients with no prior TNFα antagonist exposure as well as in those who had failed prior TNFα antagonist therapy.

In GEMINI I, two cohorts of patients received intravenous vedolizumab at Week 0 and Week 2: cohort 1 patients were randomised to receive either intravenous vedolizumab 300 mg or placebo in a double-blind fashion, and cohort 2 patients were treated with open--label intravenous vedolizumab 300 mg. To evaluate efficacy at Week 52, 373 patients from cohort 1 and 2 who were treated with intravenous vedolizumab and had achieved clinical response at Week 6 were randomised in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: intravenous -vedolizumab 300 mg every eight weeks, intravenous vedolizumab 300 mg every four weeks, or placebo every four weeks. Beginning at Week 6, patients who had achieved clinical response and were receiving corticosteroids were required to begin a corticosteroid -tapering regimen. Primary endpoint was the proportion of patients in clinical remission at Week 52. Table 3 shows the results from the primary and secondary endpoints evaluated.

Table 3. Week 52 Efficacy Results of a 52-Week Controlled Study (GEMINI I) in Ulcerative Colitis Patients Receiving Intravenous Vedolizumab

Endpoint	Placebo N = 126*	Vedolizumab IV Every 8 Weeks N = 122	Vedolizumab IV Every 4 Weeks N = 125
Clinical remission	16%	42%†	45%†
Durable clinical response¶	24%	57%†	52%†
Mucosal healing	20%	52%†	56%†
Durable clinical remission#	9%	20%§	24%‡
Corticosteroid-free clinical remission♠	14%	31%§	45%†

*The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomised to receive placebo from Week 6 through Week 52.
†p<0.0001
‡p<0.001
§p<0.05
¶Durable clinical response: Clinical response at Weeks 6 and 52
#Durable clinical remission: Clinical remission at Weeks 6 and 52
♠Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids beginning at Week 6 and were in clinical remission at Week 52. Patient numbers were n=72 for placebo, n=70 for intravenous vedolizumab every eight weeks, and n=73 for intravenous vedolizumab every four weeks

Exploratory analyses provide additional data on key subpopulations studied. Approximately one-third of patients had failed prior TNFα antagonist therapy. Among these patients, 37% receiving intravenous vedolizumab every eight weeks, 35% receiving intravenous vedolizumab every four weeks, and 5% receiving placebo achieved clinical remission at Week 52. Improvements in durable clinical response (47%, 43%, 16%), mucosal healing (42%, 48%, 8%), durable clinical remission (21%, 13%, 3%) and corticosteroid free clinical remission (23%, 32%, 4%) were seen in the prior TNFα antagonist failure population treated with intravenous vedolizumab every eight weeks, intravenous vedolizumab every four weeks and placebo, respectively.

Patients who failed to demonstrate response at Week 6 remained in the study and received intravenous vedolizumab every four weeks. Clinical response using partial Mayo scores was achieved at Week 10 and Week 14 by greater proportions of vedolizumab patients (32% and 39%, respectively) compared with placebo patients (15% and 21%, respectively).

Patients who lost response to intravenous vedolizumab when treated every eight weeks were allowed to enter an open-label extension study and receive intravenous vedolizumab every four weeks. In these patients, clinical remission was achieved in 25% of patients at Week 28 and Week 52.

Patients who achieved a clinical response after receiving intravenous vedolizumab at Week 0 and 2 and were then randomised to placebo (for 6 to 52 weeks) and lost response were allowed to enter the open-label extension study and receive intravenous vedolizumab every four weeks. In these patients, clinical remission was achieved in 45% of patients by 28 weeks and 36% of patients by 52 weeks.

In this open-label extension study, the benefits of intravenous vedolizumab treatment as assessed by partial Mayo score, clinical remission, and clinical response were shown for up to 348 weeks.

Health-related quality of life (HRQOL) was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), a disease specific instrument, and SF-36 and EQ-5D, which are generic measures. Exploratory analysis show clinically meaningful improvements were observed for vedolizumab groups, and the improvements were significantly greater as compared with the placebo group at Week 6 and Week 52 on EQ-5D and EQ-5D VAS scores, all subscales of IBDQ (bowel symptoms, systemic function, emotional function and social function), and all subscales of SF-36 including the Physical Component Summary (PCS) and Mental Component Summary (MCS).

Ulcerative Colitis – Vedolizumab for Subcutaneous Administration

The efficacy and safety of subcutaneous vedolizumab for the treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopic sub score ≥2) was demonstrated in a randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 52 (VISIBLE 1).

In VISIBLE 1, enrolled patients (n=383) had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

Patients who achieved clinical response to open-label treatment with intravenous vedolizumab at Week 6 were eligible to be randomized. For the evaluation of the Week 52 endpoints, 216 (56.4%) patients were randomized and treated in a double-blind fashion (2:1:1) to one of the following regimens: subcutaneous vedolizumab 108 mg every 2 weeks, intravenous vedolizumab 300 mg every 8 weeks, or placebo.

The baseline demographics were similar for patients in vedolizumab and placebo groups. Among the randomized patients at baseline, 33% of the patients received prior corticosteroids only, 4% of the patients received prior immunomodulators only (azathioprine or 6-mercaptopurine), and 62% of the patients received prior corticosteroids and immunomodulators. Thirty seven percent of patients had an inadequate response, loss of response, or intolerance to TNFα antagonist therapy. The baseline Mayo score was between 9 to 12 (severe ulcerative colitis) in about 62% and 6 to 8 (moderate ulcerative colitis) in about 38% of the overall study population.

Beginning at Week 6, patients who had achieved clinical response (defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. Primary endpoint was the proportion of patients in clinical remission (complete Mayo score of ≤2 points and no individual subscore >1 point) at Week 52. The secondary endpoints were mucosal healing (Mayo endoscopic subscore of ≤1 point) at Week 52, durable clinical response (clinical response at Weeks 6 and 52), durable clinical remission (clinical remission at Weeks 6 and 52), and corticosteroid-free clinical remission (patients using oral corticosteroids at baseline who had discontinued corticosteroids and

were in clinical remission) at Week 52. Table 4 shows the evaluated results from the primary and secondary endpoints.

Table 4. Week 52 Efficacy Results from a 52-Week Controlled Study (VISIBLE 1) in Ulcerative Colitis Patients receiving Subcutaneous Vedolizumab

Endpoint[*]	Placebo[†] N= 56	Vedolizumab SC 108 mg Every 2 Weeks N=106	Vedolizumab IV 300 mg Every 8 Weeks N=54	Estimate[‡] of Treatment Difference (95% CI) Vedolizumab SC vs. Placebo	P-value[‡]
Clinical remission[§]	14.3%	46.2%	42.6%	32.3 (19.7, 45.0)	p<0.001
Mucosal healing[#]	21.4%	56.6%	53.7%	35.7 (22.1, 49.3)	p<0.001
Durable clinical response[**]	28.6%	64.2%	72.2%	36.1 (21.2, 50.9)	p<0.001
Durable clinical remission[††]	5.4%	15.1%	16.7%	9.7 (-6.6, 25.7)	p = 0.076
Corticosteroid-free remission[‡‡]	8.3%	28.9%	28.6%	20.6 (-4.5, 43.7)	p = 0.067

[*]Endpoints are presented in the order that fixed-sequence testing was performed for control of Type 1 error at 5%
[†]The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.
‡Estimate of treatment difference and the p-value for all endpoints is based on the Cochran-Mantel-Haenszel method
[§]Clinical remission: Complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52
[#]Mucosal healing: Mayo endoscopic subscore of ≤1 point
[**]Durable clinical response: Clinical response at Weeks 6 and 52
[††]Durable clinical remission: Clinical remission at Weeks 6 and 52
[‡‡]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52. Patient numbers using oral corticosteroids at baseline were n=24 for placebo, n=45 for subcutaneous vedolizumab and n=21 for intravenous vedolizumab
NS = non significant (2-tailed p-value > 0.05)

The primary and secondary endpoints were analyzed in subgroups of patients who had failed prior TNFα antagonist therapy (37%; n=80) and patients who were naïve to previous TNFα antagonist therapy (63%; n=136). Results of study patients treated with placebo and subcutaneous vedolizumab in these subgroups are presented in Table 5.

Table 5. Results From a 52-Week Controlled Study (VISIBLE 1) in Ulcerative Colitis Patients Receiving Subcutaneous Vedolizumab Analysed by Response to Prior Previous TNFα Antagonist Therapy

	Treatment once every 2 weeks	
	Placebo N (%)	**Vedolizumab SC 108 mg N (%)**
Failure prior TNFα antagonist therapy	N = 19	N = 39
Clinical remission	1 5.3%)	13 (33.3%)
Mucosal healing	1 (5.3%)	18 (46.2%)
Durable clinical response	3 (15.8%)	26 (66.7%)
Durable clinical remission	0 (0%)	1(2.6%)
Corticosteroid free clinical remission[a]	1(8.3%)	6 (27.3%)
Naive TNFα antagonist therapy	N = 37	N = 67
Clinical remission	7 (18.9%)	36 (53.7%)
Mucosal healing	11(29.7%)	42 (62.7%)
Durable clinical response	13 (35.1%)	42 (62.7%)
Durable clinical remission	3 (8.1%)	15 (22.4%)
Corticosteroid free clinical remission[b]	1 (8.3%)	7 (30.4%)

[a] Patients who had failed prior TNFα antagonist therapy and using oral corticosteroids at baseline were n = 12 for placebo and n = 22 for subcutaneous vedolizumab

[b] Patients who were naïve to prior TNFα antagonist therapy and using oral corticosteroids at baseline were n = 12 for placebo and n = 23 for subcutaneous vedolizumab

Health-related quality of life (HRQOL) was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), a disease specific instrument, and EQ-5D, which is a generic measure. Work productivity was assessed by work productivity and activity impairment questionnaire (WPAI-UC). Patients treated with subcutaneous vedolizumab maintained improvements in IBDQ, EQ-5D and WPAI-UC scores at week 52 to a greater extent than patients who received placebo.

Patients who completed VISIBLE 1 were eligible to enroll in an ongoing, open-label extension study to evaluate long-term safety and efficacy of subcutaneous vedolizumab treatment in patients with ulcerative colitis or Crohn's disease.

Patients in VISIBLE 1 who did not achieve clinical response at Week 6 received a third dose of vedolizumab 300 mg by intravenous infusion at Week 6. Of patients who received a third dose of vedolizumab 300 mg by intravenous infusion at Week 6, 79.7% (114/143) achieved a clinical response at Week 14. Patients who achieved a clinical response at Week 14 were eligible to enter the open-label extension study and receive subcutaneous vedolizumab 108 mg every 2 weeks. Clinical remission as assessed by the partial Mayo score (a standardized measure that includes 3 of the 4 scored subscales of the complete Mayo score: stool frequency, rectal bleeding, and physician global assessment) was achieved by 39.2% (40/102) of these patients at Week 40 after transitioning to subcutaneous vedolizumab in the open-label extension study. Patients randomized to intravenous vedolizumab

treatment group in VISIBLE 1 received vedolizumab 300 mg intravenously at weeks 0, 2, and 6 and every 8 weeks thereafter until Week 52. At Week 52, these patients entered the open-label extension study and received subcutaneous vedolizumab 108 mg every 2 weeks. Clinical remission as assessed by the partial Mayo score was maintained in 77% of patients at 24 weeks after transitioning to subcutaneous vedolizumab in the open-label extension study.

Crohn's Disease – Vedolizumab for Intravenous Administration

The efficacy and safety of intravenous vedolizumab for the treatment of adult patients with moderately to severely active Crohn's Disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450) were evaluated in two studies (GEMINI II and III). Enrolled patients have failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral corticosteroids, immunomodulators, and antibiotics were permitted.

The GEMINI II Study was a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 6 and Week 52. Patients (n=368) were randomised in a double-blind fashion (3:2) to receive two doses of intravenous vedolizumab 300 mg or placebo at Week 0 and Week 2. The two primary endpoints were the proportion of patients in clinical remission (defined as CDAI score ≤150 points) at Week 6 and the proportion of patients with enhanced clinical response (defined as a ≥100point decrease in CDAI score from baseline) at Week 6 (see Table 4).

GEMINI II contained two cohorts of patients that received intravenous vedolizumab at Weeks 0 and 2: Cohort 1 patients were randomised to receive either intravenous vedolizumab 300 mg or placebo in a double-blind fashion, and Cohort 2 patients were treated with open-label intravenous vedolizumab 300 mg. To evaluate efficacy at Week 52, 461 patients from Cohorts 1 and 2, who were treated with intravenous vedolizumab and had achieved clinical response (defined as a ≥70point decrease in CDAI score from baseline) at Week 6,were randomised in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: intravenous vedolizumab 300 mg every eight weeks, intravenous vedolizumab 300 mg every four weeks, or placebo every four weeks. Patients showing clinical response at Week 6 were required to begin corticosteroid tapering. Primary endpoint was the proportion of patients in clinical remission at Week 52 (see Table 5).

The GEMINI III Study was a second randomised, double-blind, placebo-controlled study that evaluated efficacy at Week 6 and Week 10 in the subgroup of patients defined as having failed at least one conventional therapy and failed TNFα antagonist therapy (including primary non-responders) as well as the overall population, which also included patients who failed at least one conventional therapy and were naïve to TNFα antagonist therapy. Patients (n=416), which included approximately 75% TNFα antagonist failures patients, were randomised in a double-blind fashion (1:1) to receive either intravenous vedolizumab 300 mg or placebo at Weeks 0, 2, and 6. The primary endpoint was the proportion of patients in clinical remission at Week 6 in the TNFα antagonist failure subpopulation. As noted in Table 4, although the primary endpoint was not met, exploratory analyses show that clinically meaningful results were observed.

Table 5. Efficacy Results for a 52-Week Controlled Study (GEMINI II) and a 10-Week Controlled Study (GEMINI III) at Week 6 and Week 10 in Patients with Crohn's Disease Receiving Intravenous Vedolizumab

Study Endpoint	Placebo	Vedolizumab IV
GEMINI II Study		
Clinical remission, Week 6		
Overall	7% (n = 148)	15%* (n = 220)
TNFα Antagonist(s) Failure	4% (n = 70)	11% (n = 105)
TNFα Antagonist(s) Naïve	9% (n = 76)	17% (n = 109)
Enhanced clinical response, Week 6		
Overall	26% (n = 148)	31%[†] (n = 220)
TNFα Antagonist(s) Failure	23% (n = 70)	24% (n = 105)
TNFα Antagonist(s) Naïve	30% (n = 76)	42% (n = 109)
Serum CRP change from baseline to Week 6, median (mcg/mL)		
Overall[‡]	-0.5 (n = 147)	-0.9 (n = 220)
GEMINI III Study		
Clinical remission, Week 6		
Overall[‡]	12% (n = 207)	19% (n = 209)
TNFα Antagonist(s) Failure[¶]	12% (n = 157)	15%[§] (n = 158)
TNFα Antagonist(s) Naïve	12% (n = 50)	31% (n = 51)
Clinical remission, Week 10		
Overall	13% (n = 207)	29% (n = 209)
TNFα Antagonist(s) Failure[¶,‡]	12% (n = 157)	27% (n = 158)
TNFα Antagonist(s) Naïve	16% (n = 50)	35% (n = 51)
Sustained clinical remission[#,¶]		
Overall	8% (n = 207)	15% (n = 209)
TNFα Antagonist(s) Failure[¶,‡]	8% (n = 157)	12% (n = 158)
TNFα Antagonist(s) Naïve	8% (n = 50)	26% (n = 51)
Enhanced clinical response, Week 6		
Overall^	23% (n = 207)	39% (n = 209)
TNFα Antagonist(s) Failure[‡]	22% (n = 157)	39% (n = 158)
TNFα Antagonist(s) Naïve^	24% (n = 50)	39% (n = 51)

*$p<0.05$
[†]not statistically significant
[‡]secondary endpoint to be viewed as exploratory by pre-specified statistical testing procedure
[§]not statistically significant, the other endpoints were therefore not tested statistically
[¶]n=157 for placebo and n=158 for vedolizumab
[#]Sustained clinical remission: clinical remission at Weeks 6 and 10
^Exploratory Endpoint

Table 6. Efficacy Results for a 52-Week Controlled Study at Week 52 (GEMINI II) in Patients with Crohn's Disease Receiving Intravenous Vedolizumab

	Placebo N=153*	Vedolizumab IV Every 8 Weeks N=154	Vedolizumab IV Every 4 Weeks N=154
Clinical remission	22%	39%[†]	36%[‡]
Enhanced clinical response	30%	44%[‡]	45%[‡]
Corticosteroid-free clinical remission[§]	16%	32%[‡]	29%[‡]
Durable clinical remission[¶]	14%	21%	16%

*The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomised to receive placebo from Week 6 through Week 52.

[†]$p<0.001$

[‡]$p<0.05$

[§]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids beginning at Week 6 and were in clinical remission at Week 52. Patient numbers were n=82 for placebo, n=82 for intravenous vedolizumab every eight weeks, and n=80 for intravenous vedolizumab every four weeks

[¶]Durable clinical remission: Clinical remission at ≥80% of study visits including final visit (Week 52)

Exploratory analyses examined the effects of concomitant corticosteroids and immunomodulators on induction of remission with intravenous vedolizumab. Combination treatment, most notably with concomitant corticosteroids, appeared to be more effective in inducing remission in Crohn's disease than vedolizumab alone or with concomitant immunomodulators, which showed a smaller difference from placebo in the rate of remission. Clinical remission rate in GEMINI II at Week 6 was 10% (difference from placebo 2%, 95% CI: -6, 10) when administered without corticosteroids compared to 20% (difference from placebo 14%, 95% CI: -1, 29) when administered with concomitant corticosteroids. In GEMINI III at Week 6 and 10 the respective clinical remission rates were 18% (difference from placebo 3%, 95% CI: -7, 13) and 22% (difference from placebo 8%, 95% CI: -3, 19) when administered without corticosteroids compared to 20% (difference from placebo 11%, 95% CI: 2, 20) and 35% (difference from placebo 23%, 95% CI: 12, 33) respectively when administered with concomitant corticosteroids. These effects were seen whether or not immunomodulators were also concomitantly administered.

Exploratory analyses provide additional data on key subpopulations studied. In GEMINI II, approximately half of patients had previously failed TNFα antagonist therapy. Among these patients, 28% receiving intravenous vedolizumab every eight weeks, 27% receiving intravenous vedolizumab every four weeks, and 13% receiving placebo achieved clinical remission at Week 52. Enhanced clinical response was achieved in 29%, 38%, 21%, respectively, and corticosteroid free clinical remission was achieved in 24%, 16%, 0%, respectively.

Patients who failed to demonstrate response at Week 6 in GEMINI II were retained in the study and received intravenous vedolizumab every four weeks. Enhanced clinical response was observed at Week 10 and Week 14 for greater proportions of intravenous vedolizumab patients 16% and 22%, respectively, compared with placebo patients 7% and 12%, respectively. There was no clinically meaningful difference in clinical remission between treatment groups at these time points. Analyses of Week 52 clinical remission in patients who were non-responders at Week 6 but achieved response at Week 10 or Week 14 indicate that non-responder CD patients may benefit from a dose of intravenous vedolizumab at Week 10.

Patients who lost response to intravenous vedolizumab when treated every eight weeks in GEMINI II were allowed to enter an open-label extension study and received intravenous vedolizumab every four weeks. In these patients, clinical remission was achieved in 23% of patients at Week 28 and 32% of patients at Week 52.

Patients who achieved a clinical response after receiving intravenous vedolizumab at Week 0 and 2 and were then randomised to placebo (for 6 to 52 weeks) and lost response were allowed to enter the open-label extension study and receive intravenous vedolizumab every four weeks. In these patients, clinical remission was achieved in 46% of patients by 28 weeks and 41% of patients by 52 weeks.

In this open-label extension study, clinical remission and clinical response were observed in patients for up to 124 weeks.

Exploratory analysis showed clinically meaningful improvements were observed for the intravenous vedolizumab every four weeks and every eight weeks groups in GEMINI II and the improvements were significantly greater as compared with the placebo group from baseline to Week 52 on EQ5D and EQ5D VAS scores, total IBDQ score, and IBDQ subscales of bowel symptoms and systemic function.

Crohn's Disease – Vedolizumab for Subcutaneous Administration

The efficacy and safety of subcutaneous vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease (CDAI score of 220 to 450) was demonstrated in a randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 52 (VISIBLE 2).

In VISIBLE 2, enrolled patients (n=644) had inadequate response to, loss of response to, or intolerance to one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

Patients who achieved clinical response to open-label treatment with intravenous vedolizumab at Week 6 were eligible to be randomized. For the evaluation of the Week 52 endpoints, 409 (64%) patients were randomized and treated in a double-blind fashion (2:1) to receive subcutaneous vedolizumab 108 mg (n=275) or subcutaneous placebo (n=134) every 2 weeks.

The baseline demographics were similar for patients in vedolizumab and placebo groups. Among the randomized patients at baseline, 22% of the patients received prior corticosteroids only, 5% of the patients received prior immunomodulators only (azathioprine or 6-mercaptopurine), and 71% of the patients received prior corticosteroids and immunomodulators. Forty-two percent of patients (39% vedolizumab arm; 47% placebo arm) did not have any prior experience with TNFα antagonist therapy. The baseline CDAI was >330 (severe Crohn's disease) in about 41% and ≤330 (moderate Crohn's disease) in about 59% of the overall study population.

Beginning at Week 6, patients who had achieved clinical response (defined as a ≥70-point decrease in the CDAI score from baseline) and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. The primary endpoint was the proportion of patients with clinical remission (CDAI score ≤150) at Week 52. The secondary endpoints were the proportion of patients with enhanced clinical response (≥100 point decrease in CDAI score from baseline) at Week 52, the proportion of patients with corticosteroid-free remission (patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission) at Week 52, and the proportion of TNFα antagonist naïve patients who achieved clinical remission (CDAI score ≤150) at Week 52. Table 7 shows the evaluated results from the primary and secondary endpoints.

Table 7. Week 52 Efficacy Results from a 52-Week Controlled Study (VISIBLE 2) in Crohn's Disease Patients receiving Subcutaneous Vedolizumab

Endpoint[*]	Placebo[†] N= 134	Vedolizumab SC 108 mg Every 2 Weeks N=275	Estimate[‡] of Treatment Difference (95% CI) Vedolizumab SC vs. Placebo	P-value[‡]
Clinical remission[§]	34.3%	48.0%	13.7 (3.8, 23.7)	p = 0.008
Enhanced clinical response[#]	44.8%	52.0%	7.3 (-3.0, 17.5)	p = 0.167 (NS)
Corticosteroid-free remission [**]	18.2%	45.3%	27.1 (11.9, 42.3)	p = 0.002[‡‡]
Clinical Remission in TNFα antagonist naïve patients[††]	42.9%	48.6%	4.3 (-11.6, 20.3)	p = 0.591[‡‡]

[*]Endpoints are presented in the order that fixed-sequence testing was performed for control of Type 1 error at 5%

[†]The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.

[‡]Estimate of treatment difference and the p-value for all endpoints is based on the Cochran-Mantel-Haenszel method

[§]Clinical remission: CDAI score ≤150, at Week 52

[#]Enhanced clinical response: ≥100-point decrease in CDAI score from baseline (Week 0), at Week 52

[**]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline (Week 0) who had discontinued corticosteroids and were in clinical remission at Week 52. Patient numbers using oral corticosteroids at baseline were n=44 for placebo and n=95 for subcutaneous vedolizumab.

[††] Clinical remission (CDAI score ≤150, at Week 52) in TNFα antagonist naïve patients (n=63 placebo; n=107 subcutaneous vedolizumab

[‡‡] nominal p-value

NS = non significant (2-tailed p-value > 0.05)

The primary and secondary endpoints were analyzed in subgroups of patients who were naïve to prior TNFα antagonist therapy (42%; n= 170), patients who had failed prior TNFα antagonist therapy (51%; n= 210), and patients who had exposure to prior TNFα antagonist therapy but did not experience treatment failure (7%; n= 29).

In patients who were naïve to previous TNFα antagonist therapy or who had failed prior TNFα antagonist therapy, a greater proportion of vedolizumab-treated patients achieved clinical remission, enhanced clinical response and corticosteroid-free remission at Week 52 compared with patients who received placebo. See Table 8 and Table 9 below. Similar results for clinical remission and enhanced clinical response were observed in patients who had prior exposure to TNFα antagonist therapy but did not experience treatment failure.

Table 8. Week 52 Efficacy Results in TNFα antagonist naïve patients from a 52-Week Controlled Study (VISIBLE 2) in Crohn's Disease Patients receiving Subcutaneous Vedolizumab

Endpoint	Placebo N= 63	Vedolizumab SC 108 mg Every 2 Weeks N = 107	Treatment Difference (95% CI) Vedolizumab SC vs. Placebo
Clinical remission	42.9%	48.6%	4.3 (-11.6, 20.3)

Enhanced clinical response	47.6%	54.2%	4.4 (-11.6, 20.3)
Corticosteroid-free remission **	18.2%	41.0%	22.8 (-3.2, 46.8)

** Patients who were naïve to prior TNFα antagonist therapy and using oral corticosteroids at baseline were n=22 for placebo and n=39 for subcutaneous vedolizumab

Table 9. Week 52 Efficacy Results in Patients who failed TNFα antagonist therapy from a 52-Week Controlled Study (VISIBLE 2) in Crohn's Disease Patients receiving Subcutaneous Vedolizumab

Endpoint	Placebo N= 59	Vedolizumab SC 108 mg Every 2 Weeks N = 151	Treatment Difference (95% CI) Vedolizumab SC vs. Placebo
Clinical remission	28.8%	46.4%	17.6 (3.8, 31.4)
Enhanced clinical response	45.8 %	49.0%	3.2 (-11.8, 18.2)
Corticosteroid-free remission **	15.0%	46.2%	31.2 (5.2, 54.5)

** Patients who had failed prior TNFα antagonist therapy and using oral corticosteroids at baseline were n=20 for placebo and n=52 for subcutaneous vedolizumab

HRQOL was assessed by IBDQ, a disease specific instrument, and EQ-5D (including EQ-5D VAS scores), which is a generic measure. Patients treated with subcutaneous vedolizumab maintained improvements in IBDQ and EQ-5D scores at Week 52 to a greater extent than patients who received placebo. Work productivity was assessed by WPAI-CD. Patients treated with subcutaneous vedolizumab maintained improvements in WPAI-CD scores at Week 52 to a greater extent than patients who received placebo.

Patients who completed VISIBLE 2 were eligible to enroll in an ongoing, open-label extension study to evaluate long-term safety and efficacy of subcutaneous vedolizumab treatment in patients with ulcerative colitis or Crohn's disease.

Paediatric population

The safety and efficacy of vedolizumab in children aged 0 to 17 years old have not been established. No data are available. (see section 4.2).

5.2 Pharmacokinetic properties

Absorption

The single and multiple dose pharmacokinetics of vedolizumab have been studied in healthy subjects and in patients with moderate to severely active ulcerative colitis or Crohn's disease.

In patients administered 300 mg intravenous vedolizumab as a 30 minute intravenous infusion on Weeks 0 and 2, mean serum trough concentrations at Week 6 were 27.9 mcg/ml (SD ± 15.51) in ulcerative colitis and 26.8 mcg/ml (SD ± 17.45) in Crohn's disease. In studies with intravenous vedolizumab starting at Week 6, patients received 300 mg intravenous vedolizumab every eight or four weeks. In patients with ulcerative colitis, mean steady-state serum trough concentrations were 11.2 mcg/ml (SD ± 7.24) and 38.3 mcg/ml (SD ± 24.43), respectively. In patients with Crohn's disease mean steady-state serum trough concentrations were 13.0 mcg/ml (SD ± 9.08) and 34.8 mcg/ml (SD ± 22.55), respectively.

In clinical studies in patients with ulcerative colitis or Crohn's disease receiving subcutaneous vedolizumab, starting at Week 6, patients received 108 mg subcutaneous vedolizumab every 2 weeks. The mean steady state serum trough concentrations were 35.8 mcg/mL (SD ± 15.2) in patients with ulcerative colitis and 31.4 mcg/mL (SD ± 14.7) in patients with Crohn's disease.

The bioavailability of vedolizumab following single-dose subcutaneous administration of 108 mg relative to single-dose intravenous administration was approximately 75%. The median time to reach maximum serum concentration (t_{max}) was 7 days (range 3 to 14 days), and the mean maximum serum concentration (C_{max}) was 15.4 mcg/mL (SD ± 3.2).

Distribution

Population pharmacokinetic analyses indicate that the distribution volume of vedolizumab is approximately 5 litres. The plasma protein binding of vedolizumab has not been evaluated. Vedolizumab is a therapeutic monoclonal antibody and is not expected to bind to plasma proteins.

Vedolizumab does not pass the blood brain barrier after intravenous administration. Vedolizumab 450 mg administered intravenously was not detected in the cerebrospinal fluid of healthy subjects.

Excretion and Elimination

Population pharmacokinetic analyses based on intravenous and subcutaneous data indicate that the clearance of vedolizumab is approximately 0.162 L/day (through linear elimination pathway) and a serum half-life of 26 days. The exact elimination route of vedolizumab is not known. Population pharmacokinetic analyses suggest that while low albumin, higher body weight, prior treatment with anti-TNF drugs and presence of anti-vedolizumab antibody may increase vedolizumab clearance, the magnitude of their effects is not considered to be clinically relevant.

Linearity

Vedolizumab exhibited linear pharmacokinetics at serum concentrations greater than 1 mcg/ml.

Special populations

Age does not impact the vedolizumab clearance in ulcerative colitis and Crohn's disease patients based on the population pharmacokinetic analyses. No formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of vedolizumab.

5.3 Nonclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, as well as reproductive and development toxicology studies.

Long-term animal studies with vedolizumab to assess its carcinogenic potential have not been conducted because pharmacologically responsive models to monoclonal antibodies do not exist. In a pharmacologically responsive species (cynomolgus monkeys), there was no evidence of cellular hyperplasia or systemic immunomodulation that could potentially be associated with oncogenesis in 13- and 26-week toxicology studies. Furthermore, no effects were found of vedolizumab on the proliferative rate or cytotoxicity of a human tumour cell line expressing the $\alpha_4\beta_7$ integrin in vitro.

No specific fertility studies in animals have been performed with vedolizumab. No definitive conclusion can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity study, but given the lack of binding of vedolizumab to male reproductive tissue in monkey

and human, and the intact male fertility observed in β7 integrin-knockout mice, it is not expected that vedolizumab will affect male fertility.

Administration of vedolizumab to pregnant cynomolgus monkeys during most of gestation resulted in no evidence of effects on teratogenicity, prenatal or postnatal development in infants up to 6 months of age. Low levels (<300 mcg/L) of vedolizumab were detected on post-partum Day 28 in the milk of 3 of 11 cynomolgus monkeys treated 100 mg/kg of vedolizumab dosed every 2 weeks and not in any animals that received 10 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vedolizumab Powder for Solution for Infusion
L-histidine
L-histidine monohydrochloride
L-arginine hydrochloride
sucrose
polysorbate 80

Vedolizumab Solution for Subcutaneous Injection
Citric acid monohydrate
Sodium citrate dihydrate
L-histidine
L-histidine monohydrochloride
L-arginine hydrochloride
Polysorbate 80
Sterile water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Special precautions for storage

Vedolizumab Powder for Solution for Infusion
Store in a refrigerator (2°C-8°C). Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.5.

Vedolizumab Solution for Injection

Store in a refrigerator (2ºC-8ºC) in its original carton in order to protect from light. If needed, the prefilled pen/autoinjector can be left out of the refrigerator in its original carton at room temperature (up to 25°C) for up to 7 days. Do not use the prefilled pen/autoinjector if left out of the refrigerator for more than 7 days.

Keep the prefilled pen/autoinjector in its original carton until time of use in order to protect from light.

Do not freeze.

6.4 Nature and contents of container

Vedolizumab Powder for Solution for Infusion
Entyvio 300 mg powder for concentrate for solution for infusion in Type 1 glass vial (20 ml) fitted with rubber stopper and aluminium crimp protected by a plastic cap.

Each pack contains 1 vial.

Vedolizumab Solution for Injection
Type I 1 mL long glass syringe with a fixed 27-gauge thin wall, ½ inch needle. The syringe is prefilled and assembled into an autoinjector (prefilled pen/autoinjector). The syringe has a rubber needle cover encased in a plastic shell and rubber stopper.

The subcutaneous vedolizumab prefilled pen/autoinjector is a single-dose, disposable drug delivery system with mechanical injection operation. Each prefilled pen is equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.

6.5 Special precautions for disposal and other handling

Vedolizumab Powder for Solution for Infusion

Instructions for reconstitution and infusion

1. Use aseptic technique when preparing Entyvio solution for intravenous infusion.
2. Remove flip-off cap from the vial and wipe with alcohol swab. Reconstitute intravenous vedolizumab with 4.8 ml of sterile water for injection at room temperature (20°C - 25°C), using a syringe with a 21-25 gauge needle.
3. Insert the needle into the vial through the centre of the stopper and direct the stream of sterile water for injection to the wall of the vial to avoid excessive foaming.
4. Gently swirl the vial for at least 15 seconds. Do not vigorously shake or invert.
5. Let the vial sit for up to 20 minutes at room temperature (20°C -25°C) to allow for reconstitution and for any foam to settle; the vial can be swirled and inspected for dissolution during this time. If not fully dissolved after 20 minutes, allow another 10 minutes for dissolution.
6. Inspect the reconstituted solution visually for particulate matter and discoloration prior to dilution. Solution should be clear or opalescent, colourless to light yellow and free of visible particulates. Reconstituted solution with uncharacteristic colour or containing particulates must not be administered.
7. Once dissolved, gently invert vial 3 times.
8. Immediately withdraw 5 ml (300 mg) of reconstituted Entyvio using a syringe with a 21-25 gauge needle.
9. Add the 5 ml (300 mg) of reconstituted Entyvio to 250 ml of sterile 0.9% sodium chloride solution or 250mL of Lactated Ringer's solution, and gently mix the infusion bag (5 ml of solution does not have to be withdrawn from the infusion bag prior to adding Entyvio). Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Administer the infusion solution over 30 minutes (see section 4.2).

Entyvio does not contain preservatives. Once reconstituted, the infusion solution should be used as soon as possible.

Stability of reconstituted vedolizumab solution in vial:
In-use stability of the reconstituted solution in the vial has been demonstrated for 8 hours at 2°C-8°C.

Stability of diluted vedolizumab solution in 0.9% sodium chloride solution:
In-use stability of the diluted solution in 0.9% sodium chloride solution in infusion bag has been demonstrated for 12 hours at 20°C-25°C or 24 hours at 2°C-8°C.

The combined in-use stability of vedolizumab in the vial and infusion bag with 0.9% sodium chloride is a total of 12 hours at 20°C-25°C or 24 hours at 2°C-8°C. This hold time may include up to 8 hours at 2°C-8°C in the vial. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

Stability of the diluted vedolizumab solution in Lactated Ringer's solution:
In-use stability of the diluted solution in Lactated Ringer's solution in the infusion bag has been demonstrated for 8 hours at 2°C-8°C.
The combined in-use stability of vedolizumab in the vial and infusion bag diluted with Lactated Ringer's solution is a total of 8 hours at 2°C-8°C. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

	Storage Condition	
	2°C – 8°C	20°C – 25°C
Reconstituted Solution in the Vial	8 hours	Do not hold
Diluted Solution in 0.9% sodium chloride solution	24 hours*, †	12 hours*
Diluted Solution in Lactated Ringer's solution	8 hours*	Do not hold

* This time assumes the reconstituted solution is immediately diluted in the 0.9% sodium chloride solution or Lactated Ringer's solution and held in the infusion bag only. Any time that the reconstituted solution was held in the vial should be subtracted from the time the solution may be held in the infusion bag.
† This period may include up to 12 hours at 20°C – 25°C.

Do not store any unused portion of the reconstituted solution or infusion solution for reuse.

Each vial is for single-use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Vedolizumab Solution for Injection

After removing the prefilled pen/autoinjector from the refrigerator, wait 30 minutes before injecting to allow the solution to reach room temperature. Do not leave the prefilled pen/autoinjector in direct sunlight.

Each prefilled pen/autoinjector is for single-use only.

Do not freeze. Do not use subcutaneous vedolizumab if it has been frozen.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT REGISTRANT

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8. DATE OF REVISION

December 2022