ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 300 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of vedolizumab.

After reconstitution, each ml contains 60 mg of vedolizumab.

Vedolizumab is a humanised IgG_1 monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised cake or powder.

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

Treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease (see section 4.4). Patients should be given the package leaflet and the Patient Alert Card.

Posology

Ulcerative Colitis

The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter.

Therapy for patients with ulcerative colitis should be discontinued if no evidence of therapeutic benefit is observed by Week 10 (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 4weeks.

In patients who have responded to treatment with vedolizumab, 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 4 weeks may be considered (see section 5.1). The treatment interruption period in clinical trials extended up to 1 year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with vedolizumab (see section 4.8).

Crohn's disease

The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at0, 2and 6weeks and then every 8weeks 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 8weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should be discontinued 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 4weeks.

In patients who have responded to treatment with vedolizumab, 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 4weeks may be considered (see section 5.1). The treatment interruption period in clinical trials extended up to 1year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with vedolizumab (see section 4.8).

Special populations

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.

Paediatric population

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

Method of administration

Entyvio 300 mg powder for concentrate for solution for infusion is for intravenous use only. It is to be reconstituted and further diluted prior to intravenous administration, for instructions see section 6.6.

Entyvio 300 mg powder for concentrate for solution for infusion is administered as an intravenous infusion over 30 minutes. Patients should be monitored during and after infusion (see section 4.4).

4.3 Contraindications

Hypersensitivity 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

Intravenous vedolizumab should be administered in a healthcare setting equipped to allow management of acute hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering intravenous vedolizumab. All patients should be observed continuously during each infusion. 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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 Entyvio 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. 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 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. Although no systemic immunosuppressive effect was noted in healthy subjects the effects on systemic immune system function in patients with Inflammatory Bowel Disease patients is not known.

healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms as outlined in physician education materials and consider neurological referral if they occur. The patient is to be given a Patient Alert Card (see section 4.2). 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 trial data are available for patients previously treated with natalizumab or rituximab. Caution should be exercised when considering the use of vedolizumab in these patients.

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 trial data for concomitant use of vedolizumab with biologic immunosuppressants are available. Therefore, the use of vedolizumab in such patients is not recommended.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving vedolizumab. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Vedolizumab should be discontinued in patients with jaundice or other evidence of significant liver injury

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 3doses 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. 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 trials 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 Entyvio.

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).

As a precautionary measure, it is preferable to avoid the use of vedolizumab during pregnancy unless the benefits clearly outweigh any potential risk to both the mother and foetus.

Breast-feeding

Vedolizumab has been detected in human milk. The effect of vedolizumab on infants is unknown. 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 the safety profile

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection, bronchitis, influenza and sinusitis), headache, nausea, pyrexia, fatigue, cough, arthralgia.

Infusion related reactions (with symptoms such as dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) have also been reported in patients treated with vedolizumab.

Tabulated list of adverse reactions

The following listing of adverse reactions is based on clinical trial and post marketing experience and is 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), uncommon (≥1/1,000 to <1/100) and very rare (< 1/10,000). 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, Herpes zoster
	Very rare	Pneumonia
Immune system disorders	Very rare	Anaphylactic reaction, anaphylactic shock
Nervous system disorders	Very Common	Headache
	Common	Paraesthesia
Eye disorders	Very rare	Blurred vision
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	Very Common	Arthralgia

Table 1. Adverse Reactions

System Organ Class	Frequency	Adverse Reaction(s)
tissue disorders	Common	Muscle spasms, Back pain, Muscular weakness, Fatigue, Pain in the extremity
General disorders and administration site conditions	Common	Pyrexia
	Uncommon	Infusion site reaction (including: Infusion site pain and Infusion site irritation), Infusion related reaction Chills, Feeling cold

Description of selected adverse reactions

Infusion-related reactions

In GEMINI 1 and 2controlled 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.

Infections

In GEMINI 1 and 2controlled 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 1 and 2controlled 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 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 less than 30 kg/m^2.

In clinical studies with intravenous vedolizumab, a slightly higher incidence of serious infections was reported in vedolizumab-treated patients who had prior exposure to TNFα antagonist therapy compared to patients who were naïve to previous TNFα antagonist therapy.

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.

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 asked to report any suspected adverse reactions via
The National Pharmacovigilance and Drug Safety Centre (NPC):

Fax: +966-11-2057662 Call NPC at +966-11-2038222, Ext 2317-2356-2340 Reporting hotline: 19999 E-mail: npc.drug@sfda.gov.sa Website: www.sfda.gov.sa/npc

For other GCC States:

Please contact the relevant competent authority.

4.9 Overdose

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

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 addressing 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).

Immunogenicity
Antibodies to vedolizumab may develop during vedolizumab treatment most of which are neutralising. The formation of anti-Vedolizumab antibodies is associated with increased clearance of vedolizumab and lower rates of clinical remission.
Infusion related reactions after vedolizumab infusion are reported in subjects with anti-Vedolizumab antibodies.

Pharmacodynamic effects

In clinical trials 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 and safety

Ulcerative Colitis

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 1). 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 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 GEMINI 1

Endpoint	Placebo N=149	Vedolizumab IV 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 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 1, 2cohorts of patients received vedolizumab at Week 0 and Week 2: cohort 1 patients were randomised to receive either vedolizumab 300 mg or placebo in a double-blind fashion, and cohort 2 patients were treated with open-label vedolizumab 300 mg. To evaluate efficacy at Week 52, 373 patients from cohort 1 and 2 who were treated with 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: vedolizumab 300 mg every 8weeks, vedolizumab 300 mg every 4weeks, or placebo every 4weeks. 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 GEMINI 1

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 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 vedolizumab every 8weeks, and n=73 for vedolizumab every 4weeks

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 vedolizumab every 8weeks, 35% receiving vedolizumab every 4weeks, 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 Vedolizumab every 8weeks, vedolizumab every 4weeks and placebo, respectively.

Patients who failed to demonstrate response at Week 6 remained in the study and received vedolizumab every 4weeks. 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 vedolizumab when treated every 8weeks were allowed to enter an open-label extension study and receive vedolizumab every 4weeks. 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 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 vedolizumab every 4weeks. 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 vedolizumab treatment as assessed by partial Mayo score, clinical remission, and clinical response were shown for up to 196 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).

Crohn's Disease

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 2studies (GEMINI 2 and3). 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 2 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 2doses of vedolizumab 300 mg or placebo at Week 0 and Week 2. The 2primary 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 ≥100-point decrease in CDAI score from baseline) at Week 6 (see Table 4).

GEMINI 2 contained 2cohorts of patients that received vedolizumab at Weeks 0 and 2: Cohort 1 patients were randomised to receive either vedolizumab 300 mg or placebo in a double-blind fashion, and Cohort 2 patients were treated with open-label vedolizumab 300 mg. To evaluate efficacy at Week 52, 461 patients from Cohorts 1 and 2, who were treated with vedolizumab and had achieved clinical response (defined as a ≥70-point 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: vedolizumab 300 mg every 8weeks, vedolizumab 300 mg every 4weeks, or placebo every 4weeks. 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 3 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 1conventional therapy and failed TNFα antagonist therapy (including primary non-responders) as well as the overall population, which also included patients who failed at least 1conventional 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 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 4. Efficacy Results for GEMINI 2 and 3Studies at Week 6 and Week 10

Study Endpoint	**Placebo**	**Vedolizumab IV**
GEMINI 2 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 3 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 5. Efficacy Results for GEMINI 2 at Week 52

	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 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 vedolizumab every 8weeks, and n=80 for vedolizumab every 4weeks

¶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 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 2 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 3 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 2, approximately half of patients had previously failed TNFα antagonist therapy. Among these patients, 28% receiving vedolizumab every 8weeks, 27% receiving vedolizumab every 4weeks, and 13% receiving placebo achieved clinical remission at Week 52. Enhanced clinical response was achieved in 29%, 38%, 21%, respectively, and corticosteriod-free clinical remission was achieved in 24%, 16%, 0%, respectively.

Patients who failed to demonstrate response at Week 6 in GEMINI 2 were retained in the study and received vedolizumab every 4weeks. Enhanced clinical response was observed at Week 10 and Week 14 for greater proportions of 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 vedolizumab at Week 10.

Patients who lost response to vedolizumab when treated every 8weeks in GEMINI 2 were allowed to enter an open-label extension study and received vedolizumab every 4weeks. 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 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 vedolizumab every 4weeks. 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 196 weeks.

Exploratory analysis showed clinically meaningful improvements were observed for the vedolizumab every 4weeks and every 8weeks groups in GEMINI 2 and the improvements were significantly greater as compared with the placebo group from baseline to Week 52 on EQ-5D and EQ-5D VAS scores, total IBDQ score, and IBDQ subscales of bowel symptoms and systemic function.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with vedolizumab in one or more subsets of the paediatric population in ulcerative colitis and Crohn's disease (see section 4.2).

5.2 Pharmacokinetic properties

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 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 8or 4weeks. 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.

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.

Elimination

Population pharmacokinetic analyses indicate that vedolizumab has a total body clearance of approximately 0.169 L/day and a serum half-life of 24days. The exact elimination route of vedolizumab is not known. Population pharmacokinetic analyses suggest that while low albumin, higher body weight and prior treatment with anti-TNF drugs 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 Preclinical 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

L-histidine
L-histidine monohydrochloride
L-arginine hydrochloride
Sucrose
Polysorbate 80

6.2 Incompatibilities

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

6.3 Shelf life

3 years

In-use stability of the reconstituted solution in the vial has been demonstrated for 8 hours at 2°C-8°C.
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. A 24 hour period may include up to 8 hours at 2°C-8°C for reconstituted solution in the vial and up to 12 hours at 20°C-25°C for diluted solution in the infusion bag but the infusion bag must be stored in the refrigerator (2°C-8°C) for the rest of the 24 hour period.
Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

	Storage Condition	
	Refrigerator (2°C- 8°C)	20°C-25°C
Reconstituted solution in the vial	8 hours	Do not hold[1]

Diluted solution in 0.9% sodium chloride solution	24 hours[2,3]	12 hours[2]

[1] Up to 30 minutes are allowed for reconstitution
[2] This time assumes the reconstituted solution is immediately diluted in the 0.9% sodium chloride 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.
[3] This period may include up to 12 hours at 20°C-25°C.

6.4 Special precautions for storage

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 6.3.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

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 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 liquid 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, and gently mix the infusion bag (5 ml of 0.9% sodium chloride 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).

Once reconstituted, the infusion solution should be used as soon as possible.

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.

7. MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Dybendal Alle 10
2630 Taastrup
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

2-647-16

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Date of first authorisation: 30 Jan 2017

10. DATE OF REVISION OF THE TEXT

July 2020