16 December 2021
EMA/13745/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entyvio

International non-proprietary name: vedolizumab

Procedure No. EMEA/H/C/002782/II/0061

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Term
6-MP	6-mercaptopurine
AE	Adverse event
BID	twice daily
CARP	Chronic antibiotic-refractory pouchitis
CD	Crohn’s disease
CGQL	Cleveland Global Quality of Life
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
D	Day
ECCO	European Crohn’s and Colitis Organisation
FAP	familial adenomatous polyposis
FAS	full analysis set
FC	fecal calprotectin
FMT	fecal microbiome transplantation
GI	Gastrointestinal
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICAM	intracellular adhesion molecule
IFX	infliximab
IPAA	ileal pouch-anal anastomosis
IV	intravenous(ly)
IWRS	Interactive web response system
LOCF	last observation carried forward
MadCAM	mucosal addressin cell adhesion molecule
mPDAI	modified Pouchitis Disease Activity Index
NSAID	Nonsteroidal anti-inflammatory drug
PDAI	Pouchitis Disease Activity Index
PMNL	polymorphonuclear leukocytes

PSC	Primary Sclerosing Cholangitis
pp	percentage points
PPS	per protocol set
PTE	Pretreatment event
RHI	Robarts Histology Index
SAF	Safety analysis set
SES-CD	Simple Endoscopic Score for Crohn's Disease
SOC	Standard of care
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	Upper limit of normal
W	Week

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 23 June 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB and IV

To add a new therapeutic indication "treatment of adult patients with pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with, lost response to, or were intolerant to antibiotic therapy" for Entyvio 300 mg (powder for concentrate for solution for infusion), based on final results from study Vedolizumab-4004 (EARNEST). This was an interventional, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of Entyvio (intravenous) in the treatment of chronic pouchitis. As a consequence, sections 4.1, 4.2, 4.5, 5.1 and 5.2 of the SmPC for Entyvio 300 mg are updated. The Package Leaflet are updated in accordance. Version 7.0 of the RMP is also submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0186/2021 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP 000645-PIP04-20 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one additional year of market protection.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Armando Genazzani Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Start of procedure	17 July 2021
CHMP Rapporteur Assessment Report	17 September 2021
CHMP Co-Rapporteur Assessment Report	n/a
PRAC Rapporteur Assessment Report	16 September 2021
CHMP Co-Rapporteur Critique	22 September 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC endorsed relevant sections of the assessment report[3]	30 September 2021
CHMP members comments	04 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 October 2021
RSI	14 October 2021
Submission	16 November 2021
PRAC Rapporteur Assessment Report	n/a
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
CHMP Rapporteur Assessment Report	03 December 2021
CHMP members comments	06 December 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 December 2021
Opinion	16 December 2021
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Entyvio in comparison with existing therapies	16 December 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Patients with an ileoanal pouch are susceptible to a number of inflammatory complications, of which pouchitis is the most frequent long-term inflammatory complication after ileal pouch-anal anastomosis (IPAA). Pouchitis encompasses a variety of different causes and should be further classified as idiopathic or secondary. Secondary causes of pouchitis are many and include infections, ischemia, Crohn's disease (CD) of the pouch, PSC-associated pouchitis, radiation, and medications, especially nonsteroidal anti-inflammatory drugs (NSAIDs). Secondary causes of pouchitis are important to consider, as up to 20%–30% of patients who present with chronic pouchitis may have an identifiable secondary cause.

Pouchitis as a non-specific inflammation of the ileal reservoir is the most common complication after an IPAA for UC. Its frequency is related to the follow-up duration, occurring in up to 50% of patients 10 years after IPAA. The cumulative incidence of pouchitis in patients with an IPAA following familial adenomatous polyposis is much lower, ranging from 0% to 10% but reasons for the higher frequency of pouchitis in UC patients remain unknown. Acute pouchitis, usually responds to a single or several courses of antibiotic therapy; however, 10% to 15% of patients with acute pouchitis may subsequently develop chronic pouchitis. Pouchitis may be considered treatment-responsive or treatment-refractory based on response to antibiotic monotherapy. Patients with chronic pouchitis not responding to conventional therapy have ongoing symptoms that may lead to pouch failure. The consequences of pouchitis that is inadequately controlled are debilitating such that they affect the work, domestic-life, and social interaction of the affected patients.

State the claimed the therapeutic indication

The proposed indication for vedolizumab IV 300 mg powder for concentrate for solution for infusion is for the treatment of adult patients with pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with, lost response to, or were intolerant to antibiotic therapy.

The MAH claims a new indication i.e. pouchitis, not considering study population already included in the approved indications. The support given in this respect is that pouchitis is considered by clinical experts to be an independent medical entity of IBD and is a distinct target disease separable from UC and CD, the current authorized conditions approved for vedolizumab. Characterization of pouchitis as a distinct disease target has been discussed by the Applicant by elaborating the anatomical characteristics of each disease, the classifications of each disease by International Classification of Diseases and the Medical Dictionary for Regulatory Activities, the difference in diagnostic disease characteristics, and the varying responsiveness to certain treatments.

Epidemiology and risk factors, screening tools/prevention

IPAA is rare in the general population, thus, so too is pouchitis. In the largest epidemiological study, evaluating 62.9 million subjects in a commercial database in the United States (US), 6710 patients were diagnosed with pouchitis based on Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT), the cumulative prevalence of pouchitis between 1999–2018 was estimated to be 1 in 10,000. Another estimate (Orphanet) indicates pouchitis to occur in 1 to 5 per 10,000. This is consistent with an estimation in the European Union (EU) of 2.2 in 10,000 people noted in the Orphan Designations granted in 2009 and 2011 for alicaforsen (EU/3/09/641) and metronidazole (EU/3/11/875). Cumulative pouchitis prevalence includes all patients with pouches who may experience pouchitis at any point in time without considering annual or point prevalence. In addition, cumulative prevalence includes patients with pouches constructed for UC, FAP, and CD, and those who respond to antibiotics, which includes approximately 80% of patients with pouchitis.

For patients with IPAA for UC and active pouchitis inadequately responding to antibiotic therapy, the applicant calculates an estimated prevalence to be approximately 2 to 3 per 100,000 patients. This value was derived utilizing a pouchitis prevalence of 2.2/10,000, and considers that: 1) not all patients had proctocolectomy and an IPAA pouch constructed for treatment of UC, 2) a high proportion of patients respond to antibiotics (approximately 80%), and 3) that some pouch inflammation is related to secondary causes such as infections (*Clostridium difficile* or viral infections).

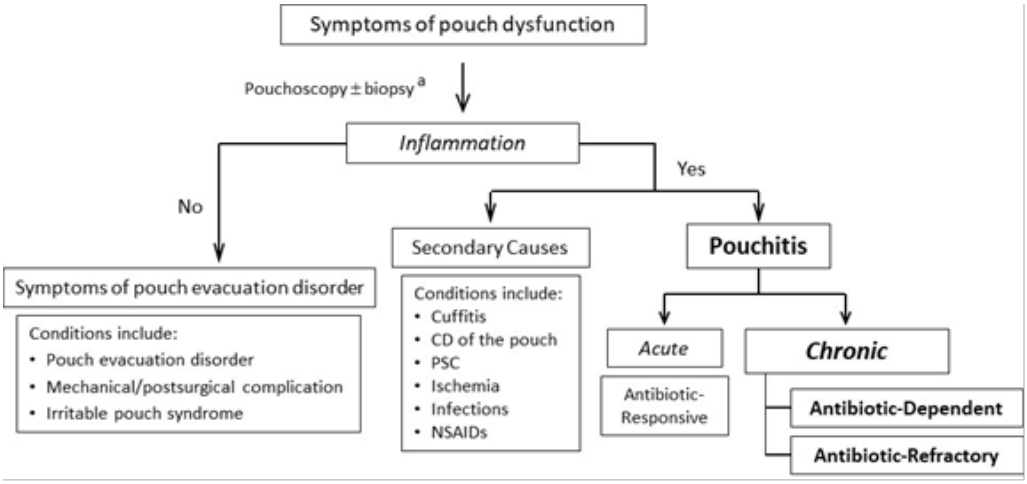
Biologic features, Aetiology and pathogenesis

Inflammatory bowel diseases (IBDs), typically considered as UC and CD, and pouchitis, another inflammatory condition in GI tissue, are complex polygenic disorders, characterized by a dysregulated immune response in the intestinal mucosa. In IBD, there is an inflammatory cascade in which white blood cells migrate from the systemic circulation into the GI tract. Like UC and CD, there is evidence that suggests that aberrant regulation of the mucosal immune system may play a role in the pathogenesis of pouchitis arising from an abnormal mucosal immune response to a dysbiosis of the pouch microbiota. In pouchitis, dysbiosis may contribute to the attraction of leukocytes by altering the integrin-mucosal addressing cell adhesion molecule-1 (MAdCAM-1) interaction in the gut, pointing to integrins as being central to its pathophysiology. An increased proportion of mucosal dendritic cells expressing integrin β7 have been reported in patients with inflammation of the pouch compared with normal pouches, suggesting a possible role for integrin signaling in the pathogenesis of pouchitis.

While pouchitis is the most common complication in patients who undergo IPAA to treat UC, as noted above, it is not completely restricted to patients with UC; however, pouchitis rarely occurs in patients with FAP, indicating that the underlying pathophysiology driving pouchitis shares some common characteristics with the pathophysiology associated with IBD.

Pouchitis (primary idiopathic nonspecific inflammation of the pouch) should not be confused with pouch dysfunction, which although includes pouchitis, also results from secondary causes such as secondary infection, surgery-related mechanical complications, use of nonsteroidal anti-inflammatory drugs, irritable pouch syndrome (IPS), or other autoimmune associations including primary sclerosing cholangitis, celiac disease, or CD of the pouch (Figure 1). Up to 30% of patients who present with chronic pouchitis may actually have an identifiable secondary cause.

Figure 1 Schematic of Pouchitis and Pouch Dysfunction



CD: Crohn's disease; PSC: primary sclerosing cholangitis.
[a] Pouchoscopy allows assessment of inflammation (severity and extent), pre-pouch ileitis, cuffitis, and postsurgical/mechanical complications. Additional biopsy, while providing histologic information, is not used to distinguish acute from chronic inflammation.

Chronic pouchitis is considered to be an independent entity of IBD that shares a similar underlying pathophysiology with UC and CD. As stated in the European Crohn's and Colitis Organisation (ECCO) Guidelines, "although the aetiology of pouchitis remains unknown, it can be inferred from the predilection for patients with UC and the response to antibiotic therapy that the bacterial flora and/or other triggers of inflammation in UC are involved".

Clinical presentation, diagnosis and stage/prognosis

The surgical treatment of choice for patients with ulcerative colitis is removal of the colon followed by construction of an ileal pouch-anal anastomosis (IPAA). Idiopathic inflammation of the "pouch," commonly called pouchitis, is the most common long-term complication in these patients and is characterized by watery, sometimes bloody stool associated with urgency, incontinence, abdominal cramps, malaise, and fever. In addition to these symptoms, biopsy of the pouch shows inflammatory changes with intense infiltration of both acute and chronic inflammatory cells.

Given the nonspecific nature of symptoms, the diagnosis of idiopathic pouchitis cannot be made from symptoms alone. Rather, characteristic endoscopic and histologic findings are required to accurately diagnose idiopathic pouchitis and to rule out secondary causes.

Active pouchitis is characterized by neutrophil infiltration and inflammation of the portion of the small bowel that constitutes the pouch.

Pouchitis may be classified based on duration of pouch-related symptoms as either acute (<4 weeks) or chronic (≥4 weeks). Pouchitis can develop, based on the number of episodes and response to antibiotics, from acute antibiotic-responsive to chronic antibiotic- dependent (≥3 antibiotic-responsive episodes a year; for some authors ≥4 episodes/year); in some patients, the symptoms persist despite a course of more than four weeks of antibiotic therapy (chronic antibiotic-refractory pouchitis or CARP). It is important to emphasize that pouchitis is a spectrum of disease, ranging from acute, antibiotic-responsive to chronic, antibiotic-refractory disease.

In cases where chronic antibiotic-refractory pouchitis is suspected, it is important to rule out other diagnoses, such as a pouch outlet obstruction, strictures, pouch fistula, peripouch inflammation, cuffitis, prepouch ileitis, irritable pouch syndrome or secondary etiologies, such as infections (eg

Clostridium difficile and Cytomegalovirus), non-steroidal anti-inflammatory drug (NSAID) use, concomitant auto-immune disorders (eg coeliac disease) and pouch ischemia. Secondary causes of pouchitis are important to consider, as up to 20%–30% of patients who present with chronic pouchitis may have an identifiable secondary cause.

Management

Currently, there are no approved therapies for pouchitis in the EU, United Kingdom (UK), or US. Because pouchitis represents a disease spectrum ranging from acute antibiotic responsive to chronic antibiotic-refractory, optimal treatment regimens will vary. This condition is largely treated empirically with only small, predominantly retrospective studies having been conducted. Initial treatment of pouchitis focuses on correction of the perceived bacterial dysbiosis, with patients commonly prescribed antibiotics (metronidazole, ciprofloxacin, or rifaximin) as first-line treatment. Patients who develop chronic pouchitis either become dependent on antibiotics for symptom relief or have continuous symptoms despite chronic antibiotic therapy.

A treatment algorithm for chronic pouchitis is summarized in Table 1. This algorithm is based on key clinical guidelines and consensus/review articles that describe widely used unauthorized therapies. The main European evidence-based consensus guidelines are from ECCO and from the British Society of Gastroenterology on the management of IBD. Both guidelines include the ileo-anal pouch disorders.

Table 1 **Treatment Algorithm for Chronic Pouchitis**

Antibiotics	Combination of 2 antibiotics for ≥4 weeks. Ciprofloxacin with metronidazole or rifaximin is the most recommended combination. In the absence of response to antibiotic combination, fecal coliform testing should be considered to identify an appropriate alternative antibiotic and to rule out secondary causes of pouchitis.
Steroids and immunomodulator	Active steroids (oral budesonide, oral beclomethasone) for 8 weeks are alternative to antibiotics. The benefit of the immunomodulator tacrolimus (topical) is also reported.
Biologics	TNF-α antagonist drugs (infliximab as the first choice, and adalimumab as an alternative) are recommended for chronic treatment-refractory pouchitis. Benefit with vedolizumab therapy is reported.

These therapeutic approaches are most often based on small and often observational clinical studies and there is limited evidence of efficacy for the treatment of chronic pouchitis with inadequate response to antibiotics. In addition to the multiple therapeutic agents in Table 1.a, nonpharmacological treatments have also been used in the management of pouchitis that include probiotics, diet, and fecal microbiome transplantation (FMT) agents.

Antibiotics and IBD therapies are currently being used long-term (and off-label) to induce and maintain remission in subjects with chronic pouchitis. However, multiple courses of antibiotics are associated with the development of antibiotic-related side effects and can lead to antibiotic dependence or resistance. Steroids should only be used short-term, and there remains limited evidence to support the use of immunosuppressants long-term. While anti-tumor necrosis factor

(TNFs) have some evidence supporting short-term effectiveness, long-term efficacy appears limited in patients with chronic pouchitis. In addition, anti-TNFs may be hampered by immunogenicity due to prior exposure (pre- and postcolectomy) potentially leading to reduced response or infusion reactions. Overall, the long-term benefit and the effectiveness of various treatment options, including antibiotics, probiotics, and other interventions used for treating pouchitis, are uncertain.

In the largest phase 3 multicenter randomized placebo-controlled study, 138 subjects with chronic antibiotic-refractory pouchitis received 6-week alicaforsen (enema delivery) treatment therapy; however, the co-primary endpoints of endoscopic remission and reduction in stool frequency assessed at 10 weeks were not met. Alicaforsen is an ICAM-1 anti-sense oligonucleotide that targets the mRNA of ICAM-1 and also the toll-like receptor 9 (TLR-9) and was investigated as an agent that modulates immune responses at mucosal surfaces, a recognized target for treatment of IBD.

Patients with pouchitis well-managed on antibiotics generally maintain a good quality of life; however, patients inadequately responding to therapy can experience severe symptoms including increased stool frequency, pain, depression, reduced satisfaction with social role, and fatigue. Furthermore, older age at the time of IPAA may impact the functional outcome and quality of life. Reports from long-term cohort studies demonstrate that inflammatory complications after IPAA create a significant burden for patients after colectomy. The biggest fear for many patients is returning to surgery, having their pouch removed, and being left with a permanent ileostomy. Overall, with no approved or satisfactory treatments available for this condition, a large unmet medical need exists.

2.1.2. About the product

Mode of action

Vedolizumab is a gut selective immunosuppressive biologic. It is a humanized immunoglobulin G1 monoclonal antibody that selectively inhibits the interaction of the α4β7 integrin on memory T and B cells with mucosal addressin cell adhesion molecule-1 expressed on the vascular endothelium in the gut.

Previously approved indications

Entyvio was approved in the EU on 22 May 2014 (procedure EMEA/H/C/002782/0000) as 300 mg powder for concentrate for solution for infusion and is currently approved for the treatment of adult patients with moderately to severely active UC and Crohn's disease who have an inadequate response with, lost response to, or who are intolerant to either conventional therapy or a tumor necrosis factor alpha antagonist.

On 28 April 2020 an extension application was approved to introduce a new pharmaceutical form (solution for injection), associated with a new strength (108 mg) and a new route of administration (subcutaneous use) (procedure EMEA/H/C/002782/0000/X/0040).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The European Medicines Agency (EMA) guideline on the development of new medicinal products for the treatment of UC, CHMP/EWP/18463/2006 Rev.1, includes a subsection for patients with pouchitis. The study is not compliant with the EMA GL with reference to the choice of primary endpoint mPDAI.

The MAH did not seek Scientific advice at the CHMP.

2.1.4. General comments on compliance with GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. The applicant provided justification for not performing an environmental risk assessment. Vedolizumab is a sequence of amino acids and a protein and in accordance with the CHMP guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00) is exempted from testing because of the chemical structure. The justification was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

TABULAR LISTING OF CLINICAL STUDY VEDOLIZUMAB-4004 IN SUBJECTS WITH CHRONIC POUCHITIS

Sponsor/ No. of Sites-Country Study Dates/ Status/ Type of Report/Report Date/ Location	Study Design/ Population	Study Endpoints	Dosing Doses, Route, Regimen	Number of Subjects Planned	Enrolled	Total [a]
Study Vedolizumab-4004: *A randomized, double-blind, placebo-controlled phase 4 study to evaluate the efficacy and safety of Entyvio (Vedolizumab IV) in the treatment of chronic pouchitis*; **Clinical Study Report.**						
Takeda Pharmaceuticals / 31 sites / Europe/North America FPI: 02 Nov 2016/ LPLV: 02 Feb 2021 Completed, Full Report 01 Jun 2021 Mod5.3.5.1\ Vedolizumab-4004	A phase 4, multicenter, randomized, double-blind, placebo-controlled study Subjects: – Aged ≥18 to ≤80 years – History of IPAA for UC completed at least 1 year before D1 (randomization) – Diagnosed with chronic or recurrent pouchitis [b]	**Primary:** Clinically relevant (mPDAI) remission [c] after 14 weeks of treatment. **Secondary:** • Clinically relevant (mPDAI) remission at W34. • PDAI remission [d] at W14 and W34. • Time to PDAI remission. • Partial mPDAI response [e] at W14 and W34. • Change from baseline in PDAI endoscopic subscore at W14 and W34. • Change from baseline in PDAI histologic subscore at W14 and W34. • Change from baseline in total PDAI score at W14 and W34. • Change from baseline in IBDQ and CGQL (Fazio Score) at W14, W22, and W34.	2 treatment arms: Vedolizumab IV (300 mg) on D1, Weeks 2, 6, 14, 22, 30 Placebo IV on D1, Weeks 2, 6, 14, 22, 30 Overall total: Ciprofloxacin (500 mg) twice daily D1 through W4 to all subjects.	55 55 110	51 51 102	51 51 102

CGQL: Cleveland Global Quality of Life; D[#]: Day [n]; FPI: first patient in; IBDQ: Inflammatory Bowel Disease Questionnaire; IPAA: ileal pouch-anal anastomosis; IV: intravenous; LPLV: last patient, last visit; mPDAI: modified Pouchitis Disease Activity Index; PDAI: Pouchitis Disease Activity Index; UC: ulcerative colitis; W: week.

[a] Total number of subjects in the safety population.

[b] Chronic or recurrent pouchitis is defined by an mPDAI score ≥5 assessed as the average from 3 days immediately before baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either (a) ≥3 recurrent episodes within 1 year before the screening period treated with ≥2 weeks of antibiotic or other prescription therapy, or (b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately before baseline endoscopy.

[c] Clinically relevant (mPDAI) remission is defined as mPDAI score <5 and a reduction in overall score by ≥2 points from baseline.

[d] PDAI remission is defined as PDAI score <7 and a reduction of total PDAI score by ≥3 points from baseline.

[e] Partial mPDAI response is defined as a reduction in mPDAI score by ≥2 points from baseline.

2.4. Clinical efficacy

2.4.1. Main study(ies)

Title of Study

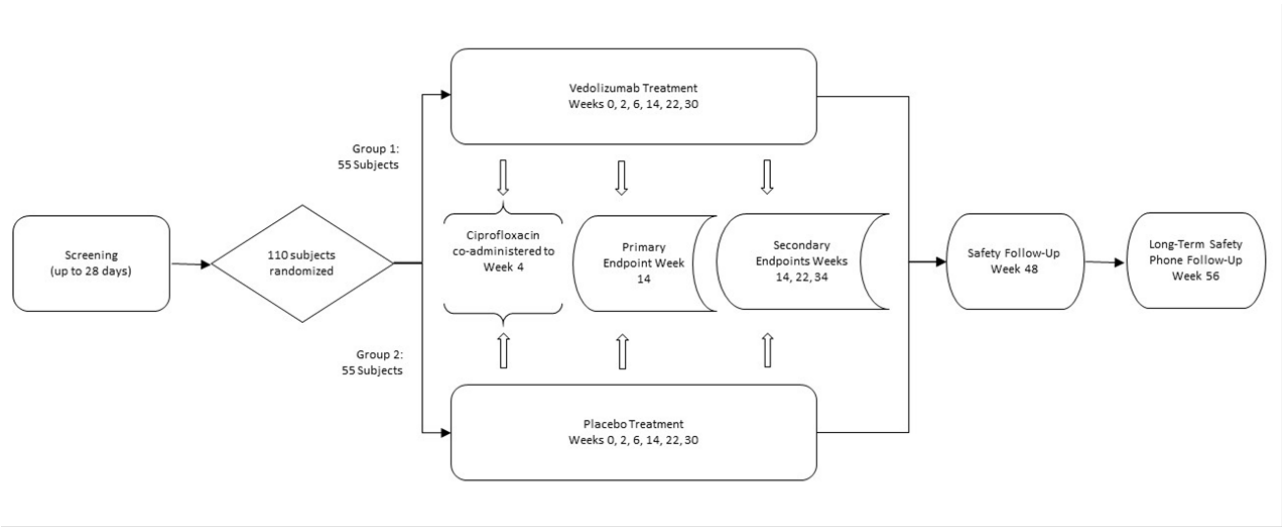
Study Vedolizumab-4004 (EARNEST)

This was a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vedolizumab IV 300 mg in the treatment of adult subjects who had a proctocolectomy and IPAA for treatment of UC and had developed chronic or recurrent pouchitis.

Methods

The design of the pivotal Vedolizumab-4004 Study is presented in the figure below:

Figure 2 ***Study Vedolizumab-4004 Planned Design***



The study comprised a 4-week (28-day) screening period that was followed by a 30 week randomized, double-blind, placebo-controlled treatment period.

The primary efficacy analysis was at 14 weeks and the secondary analysis at W34 (4 weeks after the last dose of study drug), with a final safety follow-up visit at W48. All subjects were expected to complete a long-term follow-up safety survey by telephone at W56, 26 weeks after the last dose of study drug.

The population represented an antibiotic-refractory group of subjects with active disease despite receiving standard therapy, having:

Chronic pouchitis defined as pouchitis requiring maintenance antibiotic therapy taken continuously for ≥ 4 weeks immediately before the baseline endoscopy visit; or

Recurrent pouchitis defined as pouchitis with ≥3 recurrent episodes within 1 year before screening, with each episode being treated with ≥2 weeks of antibiotic or other prescription therapy

Study participants

Key Inclusion criteria:

1. Male or female subject aged 18 to 80 years, inclusive.
2. The subject had a history of IPAA for UC completed at least 1 year before the D1 (Randomization) Visit.
3. The subject had pouchitis that was chronic or recurrent, defined by an mPDAI score ≥5 assessed as the average from 3 days immediately before the baseline endoscopy and a minimum endoscopic subscore of 2 (outside the staple or suture line) with either:

(a) ≥3 recurrent episodes within 1 year before the screening period treated with ≥2 weeks of antibiotic or other prescription therapy, or

(b) requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately before the baseline endoscopy visit.

4. The subject agreed to take ciprofloxacin (500 mg BID) on D1 and through W4, regardless of the previous treatment and to stop any previous antibiotic therapy on D1 of the study. (Additional courses of antibiotics were to be allowed, as needed, for flares after W14.)

Key Exclusion Criteria:

Exclusion criteria were divided into 3 categories: GI, infectious disease, and general exclusion criteria. Subjects meeting any of the following criteria were excluded from the study.

GI Key Exclusion Criteria

1. The subject had CD or CD of the pouch. Subjects were to be excluded if the investigator suspected, on the basis of the screening endoscopy, that the pattern of inflammation was due to CD.

2. The subject had irritable pouch syndrome.

3. The subject had isolated or predominant cuffitis.

4. The subject had mechanical complications of the pouch (eg, pouch stricture or pouch fistula).

5. The subject required or had a planned surgical intervention for UC to occur during the study.

6. The subject had diverting stoma.

Infectious Disease Key Exclusion Criteria

1. The subject had evidence of an active infection (eg, sepsis, cytomegalovirus, or listeriosis)

2. The subject had active or latent tuberculosis (TB), regardless of treatment history, as evidenced by any of the following:

a) A diagnostic TB test performed within 30 days of screening or during the screening period that was positive, as defined by:

i. A positive QuantiFERON test or 2 successive indeterminate QuantiFERON tests OR

ii. A tuberculin skin test reaction ≥10 mm (≥5 mm in subjects receiving the equivalent of >15 mg/day prednisone) OR

b) Chest X-ray within 3 months before D1 that was suspicious for pulmonary TB, and a positive or 2 successive indeterminate QuantiFERON test within 30 days before screening or during the screening period.

3. The subject had chronic hepatitis B virus (HBV) infection or chronic hepatitis C virus (HCV) infection or a known history of HIV infection (or was found to be seropositive at screening) or subject was immunodeficient

4. The subject had evidence of active infection with C difficile during screening (confirmed by laboratory test).

General Key Exclusion Criteria

1. The subject had any prior exposure to vedolizumab, natalizumab, efalizumab, rituximab, etrolizumab, or anti-MAdCAM-1 therapy.

2. The subject had a history of hypersensitivity or allergies to vedolizumab or its components.

3. The subject had allergies to and/or contraindications for ciprofloxacin, a history of tendon disorders related to quinolone administration and/or glucose-6-phosphate dehydrogenase (G6PD) deficiency.

4. The subject was taking, had taken, or was required to take any excluded medications

5. The subject had received any investigational or approved biologic or biosimilar agent within 60 days before randomization

6. The subject had received an investigational nonbiologic therapy within 30 days before randomization.

7. The subject had received an approved nonbiologic therapy (including 5-aminosalicylate [5-ASA], corticosteroid, azathioprine, 6-mercaptopurine [6-MP], etc.) in an investigational protocol within 30 days before randomization.

8. The subject had received any live vaccinations within 30 days before randomization.

9. The subject had a positive PML subjective symptom checklist at screening.

10. The subject had had a kidney, heart, or lung transplant.

11. The subject had a history of malignancy, except for the following: adequately-treated nonmetastatic basal cell skin cancer; squamous cell skin cancer that had been adequately treated and that had not recurred for at least 1 year before the screening visit; and history of cervical carcinoma in situ that had been adequately treated and that had not recurred for at least 3 years before screening. Subjects with a remote history of malignancy were considered.

12. The subject had a history of any major neurological disorders

13. The subject had any unstable or uncontrolled cardiovascular, pulmonary, hepatic, renal, GI, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, neurologic, or other medical disorder

14. The subject had any of the following laboratory abnormalities during the screening period:

i. Hemoglobin level <8 g/dL.

ii. White blood cell count <3 × 109/L.

iii. Lymphocyte count <0.5 × 109/L.

iv. Platelet count <100 × 109/L or >1200 × 109/L.

v. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN).

vi. Alkaline phosphatase >3 × ULN.

vii. Serum creatinine >2 × ULN.

Treatments

Vedolizumab IV (300 mg) or matching placebo IV at W0, W2, W6, W14, W22, and W30 (consistent with the approved dosing for UC).

Prior and Concomitant Treatments

All subjects received concomitant antibiotic treatment with ciprofloxacin (considered a companion antibiotic) 500 mg twice daily through to W4. Additional courses of antibiotics were permitted after W14, as needed for flares.

Other permitted medicines were:

- if taken at a stabledose ≥2 weeks before the first dose of the study drug and throughout the study until W34: oral 5-ASAs and anti-diarrheals for control of chronic diarrhea,
- if taken at a stabledose ≥8 weeks before randomisation and throughout the study until W34: probiotics and/or immunomodulators (azathioprine, 6-MP),
- if taken at a stable dose for ≥4 weeks before randomization with mandatory tapering after the W4 visit (to be completed by W8: oral corticosteroid therapy for pouchitis (maximum dose of prednisone 20 mg/d, budesonide 9 mg/d, or beclomethasone dipropionate at 5 mg/d, or equivalent),
- Antibiotic therapy for pouchitis, if taken before screening, was to be maintained at a stable dose for 2 weeks before randomization.

Discontinuation Criteria from the Investigational Product:

- pregnancy
- lack of efficacy
- leukopenia or lymphopenia

Objective

To evaluate the efficacy and safety of vedolizumab IV as compared to placebo

Outcomes/endpoints

Primary Endpoint

The primary endpoint is clinically relevant mPDAI remission after 14 weeks of treatment. Clinically relevant remission is defined as an mPDAI score <5 and a reduction of overall score by ≥2 points from baseline at W14.

Secondary Endpoints

Secondary endpoints include:

1. Clinically relevant mPDAI remission at W34.
2. PDAI remission (defined as PDAI score <7 and a decrease in PDAI score by ≥3 points from baseline) at W14 and W34.
3. Time to PDAI remission.
4. Partial mPDAI response (defined as a decrease in mPDAI score by ≥2 points from baseline) at W14 and at W34.
5. Change from baseline in PDAI endoscopic subscore at W14 and W34.

6. Change from baseline in PDAI histologic subscore at W14 and W34.
7. Change from baseline in total PDAI score at W14 and W34.
8. Change from baseline in IBDQ and CGQL at W14, W22, and W34.

Exploratory Endpoints

1. Change from baseline in Robarts Histopathology Index (RHI) at W14 and W34.
2. Change from baseline in biomarkers FC and CRP at W14 and W34.
3. Time to relapse of pouchitis symptoms and number of relapses.
4. Changes in number of ulcers in the pouch, proportion of surface area in the pouch that is ulcerated, and SES-CD score in the pouch at W14 and W34 compared to baseline.
5. SES-CD response, defined as 50% reduction from baseline in SES-CD score.
6. Change in stool frequency recorded in the diary at W14 and W34 compared to baseline.
7. Normalization of stool frequency at W14 and W34.
8. Sustained mPDAI remission (ie, mPDAI remission at both W14 and W34).
9. Sustained PDAI remission (ie, PDAI remission at both W14 and W34).
10. Corticosteroid-free mPDAI remission at W14 and W34.
11. Corticosteroid-free PDAI remission at W14 and W34.
12. Change in PDAI components at W14 and W34 compared to baseline.

The PDAI (18-point overall score), developed to standardize diagnostic criteria and assess the severity of pouchitis, is an objective and quantitative tool used for assessing pouch inflammation after IPAA and is shown in Table 9.c. It contains 3 separate 6-point scales based on clinical symptoms, endoscopic findings, and histologic change. Patients with a total PDAI score >7 points are classified as having pouchitis.

The mPDAI consists of 2 separate 6-point scales from the clinical symptoms and endoscopic findings domains of the PDAI without inclusion of the histological findings domain (Table 2). The mPDAI uses a cut off of 5 for pouchitis. In addition, the total mPDAI score was used to assess disease severity whereby a total mPDAI score <5 was considered quiescent disease; 5 to 8 was moderately active; and a score 9 to 12 was severely active.

Table 2 The Pouchitis disease activity index (PDAI)

Table 9.c The Pouchitis Disease Activity Index (PDAI)

Criteria		Score	Subtotal
Clinical	**Stool frequency**		
	Usual postoperative stool frequency	0	
	1-2 stools/day >postoperative usual	1	
	3 or more stools/day >postoperative usual	2	
	Rectal bleeding		
	None or rare	0	
	Present daily	1	
	Fecal urgency or abdominal cramps		
	None	0	
	Occasional	1	
	Usual	2	
	Fever (temperature >37.8 ◦C)		
	Absent	0	
	Present	1	
Endoscopic inflammation	Edema	1	
	Granularity	1	
	Friability	1	
	Loss of vascular pattern	1	
	Mucus exudates	1	
	Ulceration	1	
Acute histologic inflammation	**Polymorphic nuclear leukocyte infiltration**		
	None	0	
	Mild	1	
	Moderate + crypt abscess	2	
	Severe + crypt abscess	3	
	Ulceration per low power field (mean)		
	0%	0	
	<25%	1	
	25%-50%	2	
	>50%	3	
			Total PDAI

Table 3 **Summary and Description of All Efficacy Measures assembled by the assessor**

Assessment Endpoint	Description	Measurement Timepoint(s)
Primary efficacy endpoint		
Clinically relevant mPDAI remission	Defined as mPDAI score <5 and a reduction of overall score by ≥2 points from baseline. The mPDAI (modified Pouchitis Disease Activity Index) consists of 2 separate 6-point scales from the clinical symptoms and endoscopic findings domains of the PDAI without inclusion of the histological findings domain.	At Weeks 0, 14*, 34** *At Week 14 was the Primary endpoint **At Week 34 was the Secondary endpoint
Secondary efficacy endpoints		
PDAI remission	Defined as PDAI score <7 and a decrease in PDAI score by ≥3 points from baseline. The PDAI (Pouchitis Disease Activity Index 18-point overall score) is shown in Table 9.c. It contains 3 separate 6-point scales based on clinical symptoms, endoscopic findings, and histologic change. Patients with a total PDAI score >7 points are classified as having pouchitis.	At Weeks 0, 14, 34
Time to PDAI remission	Defined as the first visit on which the PDAI score is < 7 and a decrease in the PDAI score of ≥ 3 points from baseline occurred	At Weeks 0, 14, 34
Partial mPDAI response	Defined as a decrease in mPDAI score by ≥2 points from baseline	At Weeks 0, 14, 34
Change from baseline in PDAI endoscopic subscore	Endoscopic PDAI subscore consists of 6-point scale for the following features: edema, granularity, friability, loss of vascular pattern, mucus exudates, ulceration	At Weeks 0, 14, 34
Change from baseline in PDAI histologic subscore	Endoscopic PDAI subscore consists of 6-point scale for the following features: Polymorphic nuclear leukocyte infiltration (none, mild, moderate + crypt abscess, severe + crypt abscess) and mean ulceration per low power field (0%, <25%, 25%-50%, >50%)	At Weeks 0, 14, 34
Change from baseline in PDAI total score	PDAI (Pouchitis Disease Activity Index 18-point overall score) – see above	At Weeks 0, 14, 34

Table 3 **Summary and Description of All Efficacy Measures assembled by the assessor**

Assessment Endpoint	Description	Measurement Timepoint(s)
Change from baseline in IBDQ	The IBDQ (Inflammatory Bowel Disease Questionnaire) includes 32 questions on 4 domains: bowel systems (10 items), emotional function (12 items), social function (5 items), and systemic function (5 items). Subjects were asked to recall symptoms and QOL over the 2-week period before the study visits and rate each question on a 7-point Likert scale. A total IBDQ score, ranging from 32 to 224, was calculated by summing the scores in each domain, with higher total scores indicating a higher QOL. IBDQ remission (IBDQ score ≥170), IBDQ improvement (change from baseline in IBDQ score by ≥16 points	At Weeks 0, 14, 22, 34
Change from baseline in CGQL	The CGQL (Cleveland Global Quality of Life) was developed for subjects with IPAA and includes: current QOL, current quality of health, and current energy level, with each component scored on a 0 (worst) to 10 (best) scale. The CGQL utility score, ranging from 0 to 10, is calculated by summing the component scores and dividing by 30. Subjects were asked to rate the 3 individual components for each of 3 days before endoscopy. The CGQL utility scores were then averaged to derive the Fazio score. An increase in the Fazio score from baseline over time indicates improved QOL.	At Weeks 0, 14, 22, 34
Exploratory endpoints		
Change from baseline in RHI	The Robarts Histopathology Index (RHI) is a histopathological index that was developed and validated for UC. The index includes 4 histologic components: presence of chronic inflammatory infiltrates; the presence of neutrophils in the lamina propria neutrophils, the presence of neutrophils in the epithelium and the presence of erosion or ulceration. The total score ranges from 0 (no disease activity) to 33 (severe disease activity) Histological remission, defined as a RHI <3 Minimal histological activity, defined as a RHI <5	At Weeks 0, 14, 34
Change from baseline in FC	Fecal calprotectin (FC), a biomarker of intestinal inflammatory activity.	At Weeks 0, 14, 22, 30, 34

Table 3 **Summary and Description of All Efficacy Measures assembled by the assessor**

Assessment Endpoint	**Description**	**Measurement Timepoint(s)**
Change from baseline in CRP	CRP (C-reactive protein)	At Weeks 0, 14, 30, 34
Time to relapse of pouchitis symptoms and number of relapses	A relapse was defined as a worsening in pouchitis symptoms after previous (documented) clinical remission (W14), identified by any of the following events: an AE with Preferred Term "pouchitis"; an AE noted as related to flare; worsening of pouchitis symptoms reported on the flare CRF; start or change of concomitant medication identified as used for treatment of flare. The time to relapse of pouchitis (in days) was derived as the time between the day clinical remission was achieved (ie, the day the W14 mPDAI assessment was done) and the first day of relapse.	
Changes in number of ulcers in the pouch, proportion of surface area in the pouch that is ulcerated, and SES-CD score in the pouch	The SES-CD (Simple Endoscopic Score for Crohn's Disease) scores 4 endoscopic variables, each on a scale from 0 to 3: presence and size of ulcers; extent of ulcerated surface, including aphthous and non-aphthous ulcers; extent of affected surface; and presence and type of narrowing. An adaptation of the SES-CD for pouchitis (one segment only, the pouch) was utilized as an additional endoscopic tool to evaluate macroscopic inflammation. The presence and numbers of ulcers (for endpoints all ulcers, aphthous ulcers, and non-aphthous ulcers) and the proportion of surface area ulcerated (total area [from SES-CD] and area excluding aphthous ulcers) SES-CD response defined as ≥50% reduction from baseline in SES-CD score SES-CD remission defined as SES-CD score ≤2	At Weeks 0, 14, 34

Table 3 **Summary and Description of All Efficacy Measures assembled by the assessor**

Assessment Endpoint	Description	Measurement Timepoint(s)
Change in stool frequency	Stool frequency was evaluated based on the mean stool frequency over 3 days (before a visit) as reported in the patient's diary. Excess frequency was defined as the difference between the mean stool frequency at a visit and the normal postoperational stool frequency (recorded at baseline). Normalization of stool frequency was defined as mean stool frequency ≤ normal postoperational stool frequency + 0.5. Relevant stool frequency reduction was defined as ≥ 30% reduction in stool frequency or normalization.	At Weeks 0, 14, 34
Sustained mPDAI remission	mPDAI remission at both W14 and W34	At Weeks 14, 34
Sustained PDAI remission	PDAI remission at both W14 and W34	At Weeks 14, 34
Corticosteroid-free mPDAI remission	mPDAI remission without use of concomitant corticosteroid for pouchitis at the assessment time point W14 or W34	At Weeks 0, 14, 34
Corticosteroid-free PDAI remission	PDAI remission without use of concomitant corticosteroid for pouchitis at the assessment time point W14 or W34	At Weeks 0, 14, 34
Change in PDAI components compared to baseline	The clinical, endoscopic and histologic PDAI components (see above)	At Weeks 0, 14, 34

Sample size

The study initially aimed to recruit 200 subjects. This sample size was based on remission rates observed in patients with moderate to severe UC. However, given the rarity of the disease, recruitment of such large numbers became challenging. Furthermore, the sample size was later re-estimated based on published data on efficacy of infliximab (IFX) in patients with pouchitis based on the mPDAI. A total of 98 evaluable subjects (49 per treatment group) were required to provide 80% power to detect a 25% difference in clinical remission rates between vedolizumab and placebo at the 2-sided significance level of 0.05, assuming a placebo remission rate of 15%. The revised planned sample size was 110 subjects to account for attrition. The 25% treatment difference was based on the average of the postinduction remission (complete response) rates observed in 2 studies with IFX (32% and 21%).

No statistical adjustments were made for multiple comparisons of other efficacy endpoints, and the p-values provided for all other endpoints are therefore considered 'nominal' rather than confirmatory.

Randomisation

An IWRS was accessed at screening to obtain a subject study-specific identification number (subject number) that was used to assigned subjects in a 1:1 ratio to receive infusions of vedolizumab IV or placebo IV.

Randomization was stratified to achieve equal distribution across vedolizumab IV or placebo IV treatment groups by subject disease type: subjects with chronic pouchitis using antibiotic therapy at a stable dose for at least 4 weeks before randomization, and subjects with recurrent pouchitis who had experienced at least 3 episodes of pouchitis despite treatment (with pulse antibiotics or other prescription therapy) during the 1 year before baseline endoscopy (introduced with implementation of protocol amendment 03). The randomization schedule was generated by the IWRS before the start of the study.

Blinding (masking)

To maintain the blind, all study site personnel other than the investigational pharmacist were blinded to the treatment assignments for the duration of the study. The unblinded pharmacist obtained treatment assignments through the IWRS.

The study drug blind was maintained using the IWRS. The IWRS assigned a Med ID to subjects randomized to the vedolizumab IV treatment group and provided that Med ID to the unblended site pharmacist/nurse by email notification. To maintain the blind, prepared study drug was covered in a blinding bag before dispensing.

Statistical methods

Analysis Sets

Safety Analysis Set (SAF) includes all randomized subjects who received at least 1 dose of the study drug medication, analyzed according to the treatment they actually received.

Full Analysis Set (FAS) includes all randomized subjects who received at least 1 dose of the study drug medication, analyzed according to the treatment they were randomized to. The FAS was used for the efficacy analysis. For this study, the FAS and SAF are identical.

Per Protocol Set (PPS) includes all subjects in the FAS who did not have any major protocol violations.

Methods for Handling Missing Data

Missing Efficacy Data

In general, continuous efficacy endpoints were analyzed once "as observed" and once with missing data imputed using last observation carried forward (LOCF) imputation. For analysis of response-type (binary) efficacy endpoints, all subjects with missing data for determination of the efficacy endpoint status were considered nonremitters/nonresponders in the analysis.

Key features on handling of missing (m)PDAI data include:

- For "as observed" summaries, missing (m)PDAI data were not imputed.

- For all other summaries and analyses, if mPDAI and PDAI post-baseline assessments were partially missing, then the missing mPDAI/PDAI components were imputed with LOCF, thereby considering baseline data and unscheduled data (eg, reported at early discontinuation). Consequently, the respective PDAI domain subscore(s) and total PDAI score (and total mPDAI score, if applicable) were derived using the imputed individual components. Individual (m)PDAI components at baseline were not imputed.
- For summaries based on LOCF, completely missing mPDAI and PDAI assessments were imputed using LOCF.
- For primary analysis of PDAI-related response-type (binary) efficacy endpoints (such as mPDAI remission, PDAI remission, and partial PDAI response, etc), subjects with completely missing mPDAI and PDAI assessments at the respective analysis time point were considered as nonremitters/nonresponders. Sensitivity analysis to assess the impact of dropouts for different missing mechanisms was performed using a full LOCF approach and using a hybrid approach based on reason for dropout.

Missing Safety Data

In general, safety data were not imputed and reported data were summarized.

Efficacy Analysis

The primary efficacy analyses were based on the FAS. The primary statistical comparison for these efficacy endpoints between vedolizumab and placebo is based on the difference in response rates (vedolizumab minus placebo) expressed in percentage points (pp) and presented with corresponding 95% CI, and the chi-squared test (2-sided) or, if the number of responders or non-responders in either of the 2 treatment groups was ≤5, the exact method test (ie, Fisher' s exact test).

Formal statistical inference was performed only for the primary endpoint; however, further statistical tests for comparisons between the 2 treatment groups (vedolizumab IV and placebo) were performed for multiple secondary and exploratory efficacy endpoints. Because no multiplicity adjustment for inferential testing for secondary and exploratory endpoints was preplanned, p-values from these tests are presented as nominal p-values. All statistical testing was performed at 2-sided 0.05 level of significance.

Primary Efficacy Endpoint

Clinical remission at W14 was undertaken on the FAS and a sensitivity analysis undertaken based on the PPS. Central readers used the endoscopy images/videos performed at screening (baseline), W14, and W34/ET. To account for the stratified randomization, response rates were also analyzed stratified by type of pouchitis using the Cochran-Mantel-Haenszel (CMH) test, showing the risks of response, relative to placebo with 95% CI overall, and for the 2 types of pouchitis. The p-value for association between treatment and response was obtained from the CMH statistics. These additional analyses were conducted for clinical remission at W14 and W34 for the FAS and PPS, only if the number of responders and nonresponders in both treatment groups was >5. For these analyses, all subjects with missing data for determination of response at a time point were considered non-responders (nonresponse imputation).

Secondary Efficacy Endpoints

No multiplicity adjustment for inferential testing of the secondary and exploratory endpoints was considered; therefore, p-values were presented as nominal p-values only.

Time to PDAI remission was analyzed using KM product limit methods and Cox proportional hazard regression (for FAS only). Subjects who did not achieve PDAI remission were censored at the time of their last PDAI assessment.

Total PDAI and PDAI subscores (mPDAI score, clinical symptoms, endoscopic inflammation, and histologic inflammation) and their changes were summarized using descriptive statistics for the FAS and the PPS based on observed data. FAS analyses were repeated with missing data imputed using the LOCF approach.

Subgroup analyses for the primary and secondary (clinical remission at W34, PDAI remission at W14 and W34, and clinical response at W14 and W34) efficacy endpoints were performed by pouchitis classification, prior anti-TNF failure for pouchitis (started postcolectomy), prior anti-TNF exposure (pre- or postcolectomy), baseline severity based on mPDAI, baseline PMNL, time from IPAA to start of treatment, baseline FC, and baseline CRP. Analyses for PDAI remission at W14 and W34 were repeated for subgroups by baseline severity based on PDAI.

Sensitivity analyses were based on the FAS for the following endpoints:

- Clinical remission at W14 and W34.
- PDAI remission at W14 and W34.
- Clinical response at W14 and W34.
- Sustained mPDAI remission.
- Sustained PDAI remission.

The following sensitivity analyses were performed:

1. Imputation of all missing data using LOCF.

2. Hybrid approach whereby interim missing data were imputed using LOCF and missing data after study drug discontinuation were imputed based on the primary reason for study drug discontinuation: missing data after study drug discontinuations due to AE or lack of efficacy were imputed using the nonresponse imputation (as done in the initial approach); missing data after study discontinuations for other reasons was imputed using LOCF.

3. Non-response imputation for use of concomitant antibiotics relevant for UC/pouchitis (other than companion antibiotic given per protocol) before W14.

<u>Exploratory</u> Efficacy Endpoints

Sustained mPDAI remission and sustained PDAI remission were analyzed in the same manner as the primary endpoint for the FAS and PPS.

The time to relapse of pouchitis (in days) was derived as the time between the day clinical remission was achieved (ie, the day the W14 mPDAI assessment was done) and the first day of relapse. Subjects without relapse after clinical remission until study completion or early study discontinuation, were censored at the time of their assessment, including the safety follow-up assessment.

The total SES-CD score was summarized by descriptive statistics (including Wilcoxon rank-sum tests), once for observed data and once with LOCF applied. SES-CD response were summarized using response-type frequency tables with non-response imputation applied for the subset of subjects having at least 1 SES-CD assessment.

Response concerning the PDAI-assessed clinical symptoms stool frequency and rectal bleeding were summarized by frequency tables for the FAS and PPS based on observed data; additionally,

normalization of symptoms was summarized for the FAS and PPS applying nonresponse imputation for missing data.

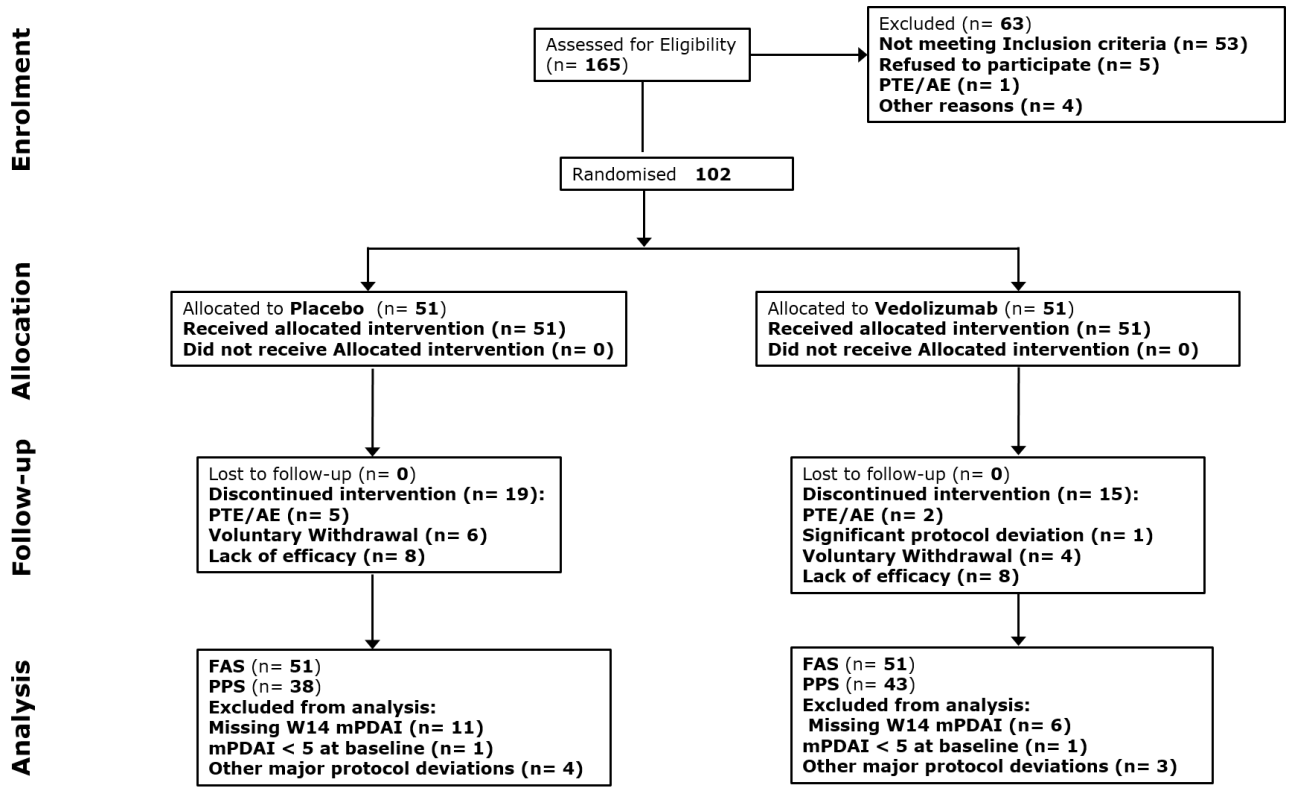
The single PDAI components (clinical, endoscopic and histologic) were summarized by frequency tables for the FAS and PPS based on observed data. Corticosteroid-free clinical remission and corticosteroid-free PDAI remission at W14 and W34 were summarized using response-type frequency tables for the FAS, once for all subjects in the analysis population and once for the subset of subjects with concomitant corticosteroid use at baseline.

Safety Analysis

All safety analyses were performed using the SAF. The number and percentage of subjects with TEAEs (defined as an AE with onset or worsening after first administration of study drug, regardless of relationship to study drug), AESIs, and SAEs that occurred on or after the first dose date, and up to 18 weeks (126 days) after the last dose date of the study drug, were summarized

Results

Participant flow



Recruitment

The study enrolled subjects at 31 sites worldwide (13 sites in North America and 18 sites in Europe [EU]).

Date first subject signed informed consent form: 12 October 2016

Date of last subject's last visit/contact: 02 February 2021

Date of last subject's last procedure (Week 14) for collection of data for primary endpoint: 11 June 2020

Date of last dose of study drug: 01 October 2020

Conduct of the study

Amendments

Five amendments to the original protocol (11 February 2016) were issued. The amendments generally cluster in 2 groups: amendments 01 through 03 were completed within 14 months of the original protocol (01 June 2016 through 21 April 2017) and early in the conduct of the study (first subject enrolled November 2016); and amendments 04 and 05 near the end of the study conduct (14 September 2020 and 20 October 2020, respectively).

- The principal changes in each amendment are summarized below.

Protocol Amendment 01 (Global, Dated 01 June 2016)

- Clarification to the main exclusion criterion that an investigator should exclude a subject whose screening endoscopy showed a pattern of inflammation possibly due to CD.
- Clarification that the primary efficacy analysis includes all randomized subjects.

Protocol Amendment 02 (Global, Dated 20 October 2016)

- Clarifications as related to ciprofloxacin:

- Exclusion of subjects with tendon disorders related to quinolone administration.

- Exclusion of subjects with G6PD deficiency per the ciprofloxacin summary of product characteristics.

- Addition of 3 therapies to the excluded medications list known to interact with ciprofloxacin.

- Extension of the exclusion period for prior exposure to nonbiological agents to 5 half-lives of that agent.
- Clarification that poststudy, vedolizumab use would be by prescription only at the discretion of the treating physician.

Protocol Amendment 03 (Global, Dated 21 April 2017) - Principal changes:

- Changed the assessment of the primary endpoint to be conducted using mPDAI score (including definition of clinically relevant remission using this scoring tool) rather than the PDAI score, which became a secondary endpoint.
- Added the specification that for subjects to be enrolled in the study they had to have a minimum endoscopic subscore of 2 and meet the definitions for recurrent or chronic pouchitis

- Reduced the number of biopsy samples collected at each endoscopy and specified that biopsies were to be assessed by trained central histopathologists.
- Revised the sample size calculation to be consistent with published remission rates and clinically significant effects observed in subjects with pouchitis rather than the prior estimates based on subjects with UC.
- Added a futility analysis after 25 subjects per treatment group complete W14 assessments.

Protocol Amendment 04 (Global, Dated 14 September 2020)

- Addition of exploratory objectives and corresponding exploratory endpoints to assess ulceration in the pouch, including the number of ulcers and the ulcerated surface area.
- Addition of a description of the SES-CD procedure and scoring instrument as adapted for evaluation in only the pouch.

Protocol Amendment 05 (Local/Germany, Dated 20 October 2020)

Protocol deviations

Of the 102 subjects, 39 subjects (38.2 %) had at least 1 study-specific significant protocol deviation (20 and 19 subjects in the placebo and vedolizumab IV groups, respectively). Significant protocol deviations included failure to satisfy entry criteria, receipt of concomitant medications (including antibiotics given after the first dose of study drug and before W14, excluding the companion antibiotic administered per protocol from D1 to W4), study procedures not performed per protocol (including missing W14 endoscopies or endoscopy recordings of poor quality), and study medication errors.

Table 10.c Significant Protocol Deviations (All Randomized Subjects)

	Number of Subjects (%)		
	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)
Subjects with at least 1 significant protocol deviation	20 (39.2)	19 (37.3)	39 (38.2)
Significant protocol deviation category			
Entry criteria	1 (2.0)	2 (3.9)	3 (2.9)
Concomitant medication	11 (21.6)	11 (21.6)	22 (21.6)
Procedure not performed per protocol	10 (19.6)	4 (7.8)	14 (13.7)
Study medication	1 (2.0)	2 (3.9)	3 (2.9)

Baseline data

The vedolizumab and placebo groups were generally well balanced with respect to demographics at baseline and baseline disease characteristics.

Table 11.c Demographic and Baseline Characteristics (FAS)

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)
Age (years) [a]			
Mean (SD)	42.9 (13.48)	40.8 (11.32)	41.9 (12.44)
Median	45.0	42.0	43.0
Minimum, maximum	19, 68	19, 67	19, 68
Age categories, n (%)			
<35 years	19 (37.3)	15 (29.4)	34 (33.3)
35 to <65 years	28 (54.9)	35 (68.6)	63 (61.8)
≥65 years	4 (7.8)	1 (2.0)	5 (4.9)
Gender, n (%)			
Male	38 (74.5)	32 (62.7)	70 (68.6)
Female	13 (25.5)	19 (37.3)	32 (31.4)
Ethnicity, n (%) [b]			
Hispanic or Latino	0	0	0
Non-hispanic and Latino	11 (100.0)	12 (100.0)	23 (100.0)
Not collected	40	39	79
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	6 (12.2)	3 (6.1)	9 (9.2)
Black or African American	1 (2.0)	1 (2.0)	2 (2.0)
Native Hawaiian or other Pacific Islander	0	0	0
White	42 (85.7)	44 (89.8)	86 (87.8)
Multiracial [c]	0	1 (2.0)	1 (1.0)
Missing	2	2	4
Weight (kg) [d]			
Mean (SD)	79.60 (19.115)	72.13 (17.588)	75.87 (18.658)
Median	76.60	69.00	74.85
Minimum, maximum	47.0, 143.3	42.2, 125.0	42.2, 143.3
BMI (kg/m^2) [e]			
Mean (SD)	25.74 (5.125)	24.13 (4.891)	24.93 (5.049)
Median	24.98	23.37	24.22
Minimum, maximum	18.4, 45.2	17.1, 43.8	17.1, 45.2
BMI categories, n (%) [f]			
Underweight (BMI <18.5)	1 (2.0)	4 (7.8)	5 (4.9)
Normal (BMI 18.5 to <25.0)	25 (49.0)	30 (58.8)	55 (53.9)
Overweight (BMI 25.0 to <30.0)	18 (35.3)	11 (21.6)	29 (28.4)
Obesity (BMI ≥30.0)	7 (13.7)	6 (11.8)	13 (12.7)
Smoking classification, n (%)			
Never smoked	29 (56.9)	35 (68.6)	64 (62.7)
Current smoker	7 (13.7)	4 (7.8)	11 (10.8)
Ex-smoker	15 (29.4)	12 (23.5)	27 (26.5)
Female reproductive status, n (%)			
Postmenopausal	5 (38.5)	5 (26.3)	10 (31.3)
Surgically sterile	2 (15.4)	2 (10.5)	4 (12.5)
Female of childbearing potential	6 (46.2)	12 (63.2)	18 (56.3)
N/A (subject is male)	38	32	70
Geographical region, n (%)			
Europe	33 (64.7)	30 (58.8)	63 (61.8)
Central Europe [t]	20 (39.2)	15 (29.4)	35 (34.3)
Southern Europe [g]	13 (25.5)	15 (29.4)	28 (27.5)
North America	18 (35.3)	21 (41.2)	39 (38.2)
Canada	7 (13.7)	9 (17.6)	16 (15.7)
US	11 (21.6)	12 (23.5)	23 (22.5)

Table 2.a Pouchitis-Related Baseline Characteristics (FAS) –integrated by Assessor

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)
Type of pouchitis, n (%) [a]			
Chronic pouchitis	25 (49.0)	29 (56.9)	54 (52.9)
Recurrent pouchitis	26 (51.0)	22 (43.1)	48 (47.1)
Type of pouchitis as randomized, n (%) [b]			
Chronic pouchitis	25 (49.0)	26 (51.0)	51 (50.0)
Recurrent pouchitis	26 (51.0)	25 (49.0)	51 (50.0)
Time since ileal pouch-anal anastomosis (years)			
Mean (SD)	10.60 (7.442)	12.31 (7.684)	11.45 (7.576)
Median	8.40	12.43	9.18
Minimum, maximum	1.5, 29.9	1.8, 32.3	1.5, 32.3
Time since IPAA subgroups, n (%)			
1 to <3 years	6 (11.8)	4 (7.8)	10 (9.8)
3 to <7 years	15 (29.4)	12 (23.5)	27 (26.5)
≥7 years	30 (58.8)	35 (68.6)	65 (63.7)
Baseline mPDAI [c]			
Mean (SD)	8.0 (1.75)	8.1 (1.62)	8.0 (1.68)
Median	8.0	8.0	8.0
Minimum, maximum	4, 11	4, 11	4, 11
Baseline mPDAI categories, n (%) [c]			
<5 (quiescent)	1 (2.0)	1 (2.0)	2 (2.0)
5 to 8 (moderately active)	31 (60.8)	32 (62.7)	63 (61.8)
9 to 12 (severely active)	19 (37.3)	18 (35.3)	37 (36.3)
Baseline PDAI			
n	51	50	101
Mean (SD)	10.5 (2.48)	10.5 (2.20)	10.5 (2.33)
Median	10.0	10.5	10.0
Minimum, maximum	7, 16	6, 14	6, 16
Baseline PDAI categories, n (%)			
<7 (quiescent)	0	3 (6.0)	3 (3.0)

Table 2.a Pouchitis-Related Baseline Characteristics (FAS) –integrated by Assessor

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)
7 to 12 (moderately active)	41 (80.4)	39 (78.0)	80 (79.2)
13 to 18 (severely active)	10 (19.6)	8 (16.0)	18 (17.8)
Missing	0	1	1
Baseline PDAI stool frequency, n (%)			
0 = usual postoperative stool frequency	2 (3.9)	3 (5.9)	5 (4.9)
1 = 1-2 stools/day > postoperative usual	6 (11.8)	6 (11.8)	12 (11.8)
2 = 3 or more stools/day > postoperative usual	43 (84.3)	42 (82.4)	85 (83.3)
Baseline PMNL infiltration, n (%)			
0 (none)	0	3 (6.0)	3 (3.0)
1 (mild)	11 (21.6)	8 (16.0)	19 (18.8)
2 (moderate + crypt abscess)	29 (56.9)	28 (56.0)	57 (56.4)
3 (severe + crypt abscess)	11 (21.6)	11 (22.0)	22 (21.8)
Missing	0	1	1
Prior anti-TNF exposure for UC or pouchitis, n (%)			
Anti-TNF naïve	20 (39.2)	18 (35.3)	38 (37.3)
Anti-TNF experienced	31 (60.8)	33 (64.7)	64 (62.7)
Prior anti-TNF started postcolectomy, n (%)			
Anti-TNF failure (with reason) [d]			
Any failure	12 (23.5)	15 (29.4)	27 (26.5)
Inadequate response	8 (15.7)	10 (19.6)	18 (17.6)
Loss of response	5 (9.8)	5 (9.8)	10 (9.8)
Intolerance	2 (3.9)	3 (5.9)	5 (4.9)
Anti-TNF used/no failure	1 (2.0)	0	1 (1.0)
Anti-TNF not used	38 (74.5)	36 (70.6)	74 (72.5)
Concomitant use of corticosteroids at baseline, n (%) [e]			
Yes	8 (15.7)	5 (9.8)	13 (12.7)
No	43 (84.3)	46 (90.2)	89 (87.3)
Baseline CRP (mg/L)			
Mean (SD)	5.39 (7.676)	5.34 (6.577)	5.36 (7.112)

Table 2.a Pouchitis-Related Baseline Characteristics (FAS) –integrated by Assessor

	Placebo IV (N = 51)	**Vedolizumab IV 300 mg (N = 51)**	**Total (N = 102)**
Median	2.90	3.30	2.95
Minimum, maximum	0.3, 41.7	0.4, 39.2	0.3, 41.7
Baseline CRP categories, n (%)			
≤2.87 mg/L	25 (49.0)	25 (49.0)	50 (49.0)
>2.87 mg/L to ≤5 mg/L	11 (21.6)	10 (19.6)	21 (20.6)
>5 mg/L to ≤10 mg/L	8 (15.7)	8 (15.7)	16 (15.7)
>10 mg/L	7 (13.7)	8 (15.7)	15 (14.7)
Baseline fecal calprotectin (µg/g)			
Mean (SD)	834.5 (1162.36)	951.4 (1025.49)	892.9 (1092.21)
Median	358.0	648.0	477.0
Minimum, maximum	60, 6368	22, 4082	22, 6368
Baseline fecal calprotectin categories, n (%)			
≤250 µg/g	17 (33.3)	15 (29.4)	32 (31.4)
>250 µg/g to ≤500 µg/g	12 (23.5)	8 (15.7)	20 (19.6)
>500 µg/g	22 (43.1)	28 (54.9)	50 (49.0)
Baseline SES-CD score in pouch			
n	49	48	97
Mean (SD)	5.5 (2.44)	5.8 (2.30)	5.7 (2.37)
Median	6.0	5.5	6.0
Minimum, maximum	0, 10	0, 10	0, 10
Baseline SES-CD score in pouch categories, n (%)			
≤2	4 (8.2)	1 (2.1)	5 (5.2)
3 to 6	29 (59.2)	28 (58.3)	57 (58.8)
>6	16 (32.7)	19 (39.6)	35 (36.1)
Missing	2	3	5
Baseline PDAI rectal bleeding, n (%)			
None or Rare	43 (84.3)	39 (76.5)	82 (80.4)
Present Daily	8 (15.7)	12 (23.5)	20 (19.6)
Baseline PDAI Fecal Urgency/Abdominal Cramps, n (%)			

Table 2.a Pouchitis-Related Baseline Characteristics (FAS) –integrated by Assessor

	Placebo IV (N = 51)	**Vedolizumab IV 300 mg (N = 51)**	**Total (N = 102)**
None	4 (7.8)	4 (7.8)	8 (7.8)
Occasional	17 (33.3)	20 (39.2)	37 (36.3)
Usual	30 (58.8)	27 (52.9)	57 (55.9)
Baseline PDAI Fever, n (%)			
Absent	49 (96.1)	51 (100.0)	100 (98.0)
Present	2 (3.9)	0	2 (2.0)
Baseline PDAI Endoscopic Ulceration, n (%)			
Absent	15 (29.4)	11 (21.6)	26 (25.5)
Present	36 (70.6)	40 (78.4)	76 (74.5)
Baseline PDAI Edema, n (%)			
Absent	3 (5.9)	2 (3.9)	5 (4.9)
Present	48 (94.1)	49 (96.1)	97 (95.1)
Baseline PDAI Friability, n (%)			
Absent	10 (19.6)	11 (21.6)	21 (20.6)
Present	41 (80.4)	40 (78.4)	81 (79.4)
Baseline PDAI Loss of Vascular Pattern, n (%)			
Absent	5 (9.8)	1 (2.0)	6 (5.9)
Present	46 (90.2)	50 (98.0)	96 (94.1)
Baseline PDAI Ulceration per Low Power Field, n (%)	N=51	N=50	N=101
0%	33 (64.7)	34 (68.0)	67 (66.3)
<25%	8 (15.7)	9 (18.0)	17 (16.8)
25-50%	8 (15.7)	4 (8.0)	12 (11.9)
>50%	2 (3.9)	3 (6.0)	5 (5.0)

[a] Type of pouchitis was derived from case report form–reported data on prior episodes and prior use of antibiotics. If a subject met both criteria for chronic and recurrent, the subject was categorized as chronic.

[b] Type of pouchitis was reported in the interactive web response system as follows:
"Antibiotic use = YES AND 3 current episodes of pouchitis = NO or YES" corresponds to chronic pouchitis.
"Antibiotic use = NO AND 3 current episodes of pouchitis = YES" corresponds to recurrent pouchitis.

[c] Subjects with mPDAI score <5 after adjudication of endoscopy were enrolled with mPDAI score ≥5 based on initial endoscopy reading.

[d] Multiple reasons for failure of prior anti-TNF treatment were possible

[e] Concomitant corticosteroids included corticosteroids for UC or pouchitis starting before and ongoing on Day 1

Prior treatments

The most frequently reported prior medications for pouchitis (ie, started postcolectomy) were: ciprofloxacin (88.2%), metronidazole (68.6%), loperamide (25.5%), budesonide (22.5%), infliximab (21.6%), mesalazine (18.6%) and adalimumab (13.7%).

Sixty-four subjects (62.7%) studied (33 subjects [64.7%] in the vedolizumab group and 31 subjects [60.8%] in the placebo group) had received an anti–tumor necrosis factor (TNF) therapy either pre- or postcolectomy. However, the majority of patients in the placebo group (74.5%) as well as in the vedolizumab group (70.6%) wasn't treated with anti-TNF therapy for the pouchitis (see the table above). Fifteen subjects (29.4%) in the vedolizumab group and 12 subjects (23.5%) in the placebo group had used and experienced failure of anti-TNF therapy postcolectomy.

Ten subjects (19.6%) in the vedolizumab group and 12 subjects (23.5%) in the placebo group had received infliximab, while 9 subjects (17.6%) in the vedolizumab group and only 5 subjects (9.8%) in the placebo group had received adalimumab for pouchitis.

Only 22.5% of patients received probiotics (21.6% in the vedolizumab vs 23.5% in the placebo group).

At baseline, corticosteroid use was recorded for 5 subjects (9.8%) in the vedolizumab group and 8 subjects (15.7%) in the placebo group, each of whom had who had been taking stable doses of these agents for at least 4 weeks before randomization (as permitted by the protocol).

Table 11.f Prior Medications for Pouchitis Started Postcolectomy by Preferred Medication Name Reported in ≥10% of Subjects in Any Treatment Group (FAS)

	Number of Subjects (%)		
Preferred Medication Name	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)
Patients with any prior medications for the treatment of pouchitis started postcolectomy	51 (100.0)	51 (100.0)	102 (100.0)
Ciprofloxacin	42 (82.4)	48 (94.1)	90 (88.2)
Metronidazole	33 (64.7)	37 (72.5)	70 (68.6)
Loperamide	13 (25.5)	13 (25.5)	26 (25.5)
Budesonide	12 (23.5)	11 (21.6)	23 (22.5)
Infliximab	12 (23.5)	10 (19.6)	22 (21.6)
Mesalazine	8 (15.7)	11 (21.6)	19 (18.6)
VSL#3	8 (15.7)	7 (13.7)	15 (14.7)
Adalimumab	5 (9.8)	9 (17.6)	14 (13.7)
Rifaximin	8 (15.7)	5 (9.8)	13 (12.7)
Beclometasone	5 (9.8)	4 (7.8)	9 (8.8)
Levofloxacin	5 (9.8)	4 (7.8)	9 (8.8)
Azathioprine	6 (11.8)	3 (5.9)	9 (8.8)
Alicaforsen	3 (5.9)	5 (9.8)	8 (7.8)
Prednisolone	1 (2.0)	6 (11.8)	7 (6.9)

Source: Table 15.1.12.2.1.

FAS: full analysis set; IV: intravenous.

WHODRUG Version 01MAR2016 was used to code medication history. Subjects with >1 medication within a preferred medication name are counted only once for each name. Percentages are based on the total number of subjects in the treatment group.

Prior medication refers to any medication for treatment of prior pouchitis that was started postcolectomy and before Day 1 in this study.

Preferred medication names are sorted using decreasing frequency based on the total number of subjects.

The following reasons for the discontinuation of two principal antibiotic classes used are reported:

Table 15.1.12.3.1
Reasons for Discontinuation of Prior Medications for Pouchitis Started Post-Colectomy
Full Analysis Set

	Number of Subjects (%)		
Therapeutic Classification Subclassification Reason for Discontinuation	Placebo IV (N=51)	Vedolizumab IV 300 mg (N=51)	Total (N=102)
ANTIINFECTIVES FOR SYSTEMIC USE (continued)			
QUINOLONE ANTIBACTERIALS			
Any Failure	7 (13.7)	11 (21.6)	18 (17.6)
Inadequate response	6 (11.8)	9 (17.6)	15 (14.7)
Loss of response	1 (2.0)	2 (3.9)	3 (2.9)
Intolerance	0	0	0
Other	38 (74.5)	35 (68.6)	73 (71.6)
Reason Not Recorded	2 (3.9)	1 (2.0)	3 (2.9)
OTHER ANTIBACTERIALS			
Any Failure	6 (11.8)	11 (21.6)	17 (16.7)
Inadequate response	6 (11.8)	9 (17.6)	15 (14.7)
Loss of response	1 (2.0)	2 (3.9)	3 (2.9)
Intolerance	0	0	0
Other	29 (56.9)	26 (51.0)	55 (53.9)
Reason Not Recorded	2 (3.9)	2 (3.9)	4 (3.9)

It could be noted that around 15% of patients reported inadequate response for each type of antibiotics while only 3% each reported loss of response; the intolerance was not reported and majority of patients reported "other" as a reason for discontinuation of antibiotic therapy.

Concomitant treatment

Concomitant antibiotic therapy for pouchitis (other than the protocol defined use of ciprofloxacin for the first 4 weeks) was prohibited from Day 1 through W14, but was allowed after W14 as needed. Despite concomitant antibiotic therapy being prohibited before W14, a similar proportion of subjects in both treatment groups (10 of 45 subjects [22.2%] in the vedolizumab group and 8 of 40 subjects [20.0%] in the placebo group) were receiving concomitant antibiotic therapy at W14. At W34, 7 of 33 subjects (21.2%) in the vedolizumab group and 4 of 32 subjects (12.5%) in the placebo group were taking a concomitant antibiotic.

Table 11.j Concomitant Antibiotics for Pouchitis Taken by Visit (FAS)

	Number of Subjects (%)		
Visit	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)
Overall [a]			
n	51	51	102
Subjects with antibiotic use	19 (37.3)	30 (58.8)	49 (48.0)
Subjects without antibiotic use	32 (62.7)	21 (41.2)	53 (52.0)
Day 1 [b]			
n	51	51	102
Subjects with antibiotic use	1 (2.0)	3 (5.9)	4 (3.9)
Subjects without antibiotic use	50 (98.0)	48 (94.1)	98 (96.1)
Week 14 [c]			
n	40	45	85
Subjects with antibiotic use	8 (20.0)	10 (22.2)	18 (21.2)
Subjects without antibiotic use	32 (80.0)	35 (77.8)	67 (78.8)
Week 34 [c]			
n	32	33	65
Subjects with antibiotic use	4 (12.5)	7 (21.2)	11 (16.9)
Subjects without antibiotic use	28 (87.5)	26 (78.8)	54 (83.1)

Source: Table 15.1.12.6.1.

FAS: full analysis set; IV: intravenous.

All subjects received companion antibiotic treatment through Week 4 (not considered in this table). Additional courses of antibiotics were allowed, as needed, for flares after Week 14.

Percentages are based on the number of subjects with data at each visit.

[a] Overall includes all antibiotics taken during the study on/after Day 1, excluding antibiotics stopped on Day 1.

[b] Day 1 includes antibiotic use ongoing at Day 1 or started on Day 1, excluding antibiotics stopped at Day 1.

[c] Week 14/Week 34 includes antibiotic use on Week 14/Week 34 analysis visit where mPDAI was assessed.

Corticosteroid use at any time during the study (on/after D1) was reported in 7 subjects (13.7%) in the vedolizumab group and 11 subjects (21.6%) in the placebo group, being highest at D1 (4 subjects (7.8%) in the vedolizumab and 7 subjects (13.7%) in the placebo arm) and with gradual overall reduction of the number of patients throughout the study period (at W14 and W34 only 2 subjects and 1 subject per group, respectively, received the corticosteroids).

While is noted that 17.6 % of subjects in the placebo arm and 19.6% in the vedolizumab arm received vedolizumab as concomitant medication (Table 11h in the 4004 CSR), in the CSR is also stated that "in

Table 2.a Pouchitis-Related Baseline Characteristics (FAS) –integrated by Assessor

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Total (N = 102)

all cases vedolizumab was given after the end of study drug treatment (or after W34) so that it did not impact the efficacy assessments" that could be confirmed by the raw data tables.

Numbers analysed

Full Analysis Set: subjects 51 in the vedolizumab and 51 in the placebo arm.

Per Protocol Analysis Set: which excluded 8 subjects in the vedolizumab group and 13 subjects in the placebo group from the FAS.

Outcomes and estimation

Primary Endpoint Result –Clinical Remission (mPDAI) at Week 14

The primary analysis of clinical remission, based on the full analysis set (FAS), showed that the remission rate observed among subjects receiving vedolizumab (16 subjects; 31.4%) was statistically significantly higher than among placebo-treated subjects (5; 9.8%). The treatment difference was 21.6 percentage points (pp) (p = 0.013).

Table 15.2.2.1.1.1
mPDAI Remission by Visit
Full Analysis Set

Visit	Placebo IV (N=51)	Vedolizumab IV 300 mg (N=51)
Week 14		
n	51	51
Responders (%) (95% CI)*	5 (9.8) (3.3, 21.4)	16 (31.4) (19.1, 45.9)
Non-Responders (%) (95% CI)*	46 (90.2) (78.6, 96.7)	35 (68.6) (54.1, 80.9)
Observed	38	30
Imputed	8	5
Difference, Vedolizumab - Placebo (p.p.) (95% CI)*		21.6 (4.9, 37.5)
p-value, Vedolizumab vs Placebo‡		0.013
Adjusted Difference, Vedolizumab - Placebo†		
Common Adjusted Difference (p.p.) (95% CI)		21.7 (6.5, 37.0)
Stratum Chronic Pouchitis (p.p.) (95% CI)		15.6 (-5.1, 36.2)
Stratum Recurrent Pouchitis (p.p.) (95% CI)		28.7 (6.1, 51.2)
p-value, Vedolizumab vs Placebo		0.007

mPDAI=Modified Pouchitis Disease Activity Index; p.p.=percentage points; LOCF=Last Observation Carried Forward.
* The 95% CI of the percentages were calculated using the exact method.
‡ p-value for the treatment difference in responder rates from chi-squared test; if the number of responders or non-responders in either of the two treatment arms is <=5, the corresponding p-value from Fisher's Exact test is shown.
† The risk difference, 95% CI and p-value were obtained using a Cochran-Mantel-Haenszel test stratified by type of pouchitis.
Note 1: mPDAI remission is defined as a mPDAI score <5 points and a reduction from baseline of mPDAI score of >=2 points. Responders are defined as subjects achieving mPDAI remission.
Note 2: 'Observed' includes subjects with partially reported mPDAI (missing components imputed using LOCF). Subjects with completely missing mPDAI at the visit are considered non-responders and are shown under 'Imputed'.
Note 3: Baseline is defined as the last observation prior to the first dose of study medication.

Table 2.c Additional Analyses of Clinical Remission at Week 14

Clinical Remission	Placebo IV	Vedolizumab IV 300 mg
PPS	**N = 38**	**N = 43**
Number (%) of subjects achieving clinical mPDAI remission	5 (13.2)	14 (32.6)
95% CI [a]	4.4, 28.1	19.1, 48.5
Difference, vedolizumab - placebo (pp)		19.4
95% CI [a]		0.4, 37.4
Nominal p-value, vedolizumab vs placebo [b]		0.064
Sensitivity Analyses [c]		
LOCF [c]	**N = 51**	**N = 51**
Number (%) of subjects achieving clinical mPDAI remission	6 (11.8)	16 (31.4)
95% CI [a]	4.4, 23.9	19.1, 45.9
Difference, vedolizumab - placebo (pp)		19.6
95% CI [a]		3.2, 35.5
Nominal p-value, vedolizumab vs placebo [b]		0.016
Hybrid Analysis [c]	**N = 51**	**N = 51**
Number (%) of subjects achieving mPDAI clinical remission	6 (11.8)	16 (31.4)
95% CI [a]	4.4, 23.9	19.1, 45.9
Difference, vedolizumab - placebo (pp)		19.6
95% CI [a]		3.2, 35.5
Nominal p-value, vedolizumab vs placebo [b]		0.016
Concomitant Antibiotic Use Prior to W14 [c]	**N = 51**	**N = 51**
Number (%) of subjects achieving mPDAI clinical remission	5 (9.8)	13 (25.5)
95% CI [a]	3.3, 21.4	14.3, 39.6
Difference, vedolizumab - placebo (pp)		15.7
95% CI [a]		0.7, 31.4
Nominal p-value, vedolizumab vs placebo [b]		0.067

Clinical remission refers to clinically relevant mPDAI remission.

In the PPS, subjects with missing data at a time point were imputed as not achieving remission.

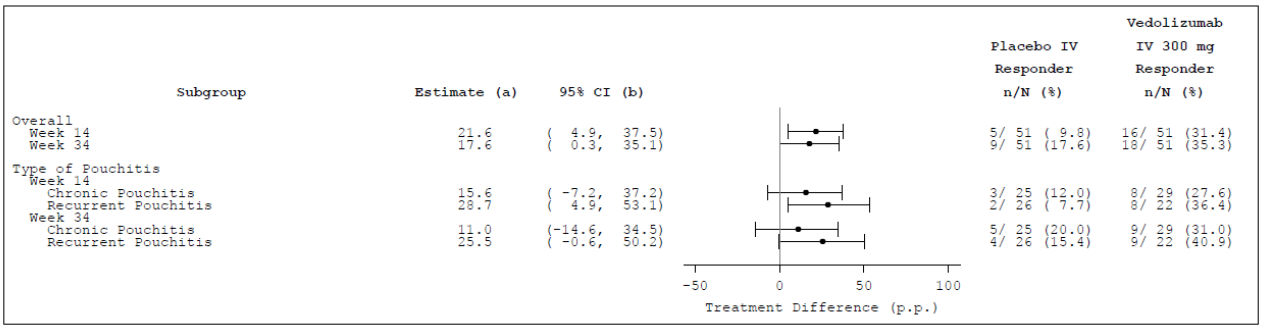
[a] The 95% CI of the percentages were calculated using the exact method.

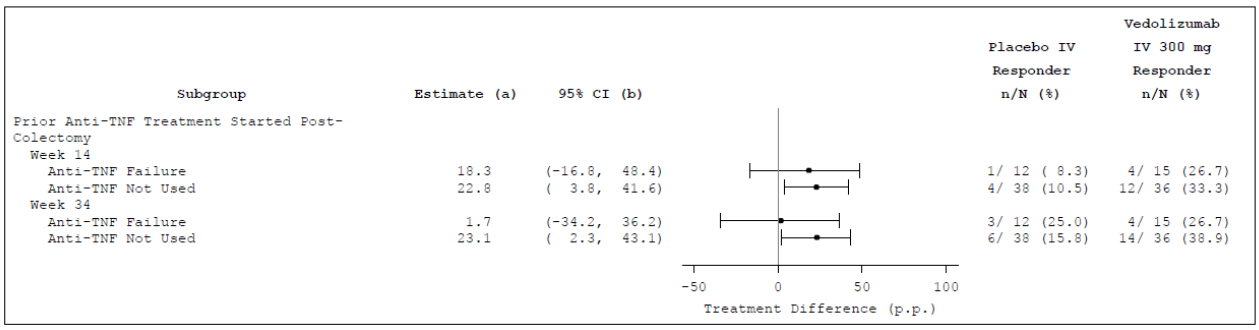
[b] The p-value for the treatment difference in remission rates was obtained from the chi-squared test; if the number of responders or nonresponders in either of the 2 treatment groups was ≤5, the corresponding p-value from Fisher's Exact test is shown. All p-values are nominal as no adjustment was made for multiplicity

[c] In the analysis of data with LOCF imputation applied, completely missing mPDAI data at W14 was imputed using LOCF. In the hybrid approach, completely missing mPDAI at W14 was imputed based on the reason for drop-out (adverse event or lack of efficacy were imputed as nonremission). In the analysis accounting for concomitant antibiotic use before W14, subjects with missing data at a time point, and those receiving concomitant antibiotics before W14 were imputed as not achieving remission.

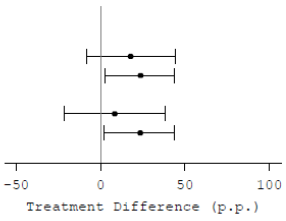
Subgroup analyses were done by type of pouchitis, prior anti-TNF failure for pouchitis (started postcolectomy), prior anti-TNF exposure, baseline severity based on mPDAI, baseline PMNL, time from IPAA to start of treatment, baseline FC, and baseline CRP. Results from subgroup analyses were illustrated in forest plots for the treatment difference in response rates with corresponding 95% CI by subgroup.

Figure 15.2.2.11
Forest Plot of mPDAI Remission by Subgroup and Visit
Full Analysis Set

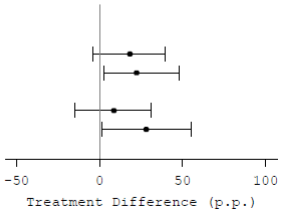




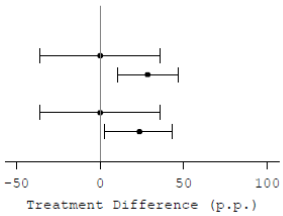
Subgroup	Estimate (a)	95% CI (b)	Placebo IV Responder n/N (%)	Vedolizumab IV 300 mg Responder n/N (%)
Prior Anti-TNF Exposure (for UC or Pouchitis)				
Week 14				
Anti-TNF Naïve	17.8	(-8.5, 44.4)	2/ 20 (10.0)	5/ 18 (27.8)
Anti-TNF Experienced	23.7	(2.7, 43.4)	3/ 31 (9.7)	11/ 33 (33.3)
Week 34				
Anti-TNF Naïve	8.3	(-21.5, 38.4)	5/ 20 (25.0)	6/ 18 (33.3)
Anti-TNF Experienced	23.5	(1.8, 43.9)	4/ 31 (12.9)	12/ 33 (36.4)



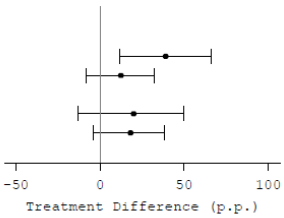
Subgroup	Estimate (a)	95% CI (b)	Placebo IV Responder n/N (%)	Vedolizumab IV 300 mg Responder n/N (%)
Baseline Severity Based on mPDAI				
Week 14				
5 to 8 (Moderately Active)	18.2	(-3.9, 39.3)	5/ 31 (16.1)	11/ 32 (34.4)
9 to 12 (Severely Active)	22.2	(2.3, 47.6)	0/ 19 (0.0)	4/ 18 (22.2)
Week 34				
5 to 8 (Moderately Active)	8.6	(-15.1, 31.2)	8/ 31 (25.8)	11/ 32 (34.4)
9 to 12 (Severely Active)	28.1	(1.1, 55.2)	1/ 19 (5.3)	6/ 18 (33.3)



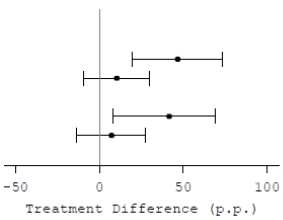
Subgroup	Estimate (a)	95% CI (b)	Placebo IV Responder n/N (%)	Vedolizumab IV 300 mg Responder n/N (%)
Baseline PMNL				
Week 14				
0 - 1 = None/Mild	0.0	(-36.0, 36.0)	2/ 11 (18.2)	2/ 11 (18.2)
>= 2 = Moderate/Severe + Crypt Abscess	28.4	(10.1, 46.5)	3/ 40 (7.5)	14/ 39 (35.9)
Week 34				
0 - 1 = None/Mild	0.0	(-36.0, 36.0)	2/ 11 (18.2)	2/ 11 (18.2)
>= 2 = Moderate/Severe + Crypt Abscess	23.5	(2.6, 43.2)	7/ 40 (17.5)	16/ 39 (41.0)

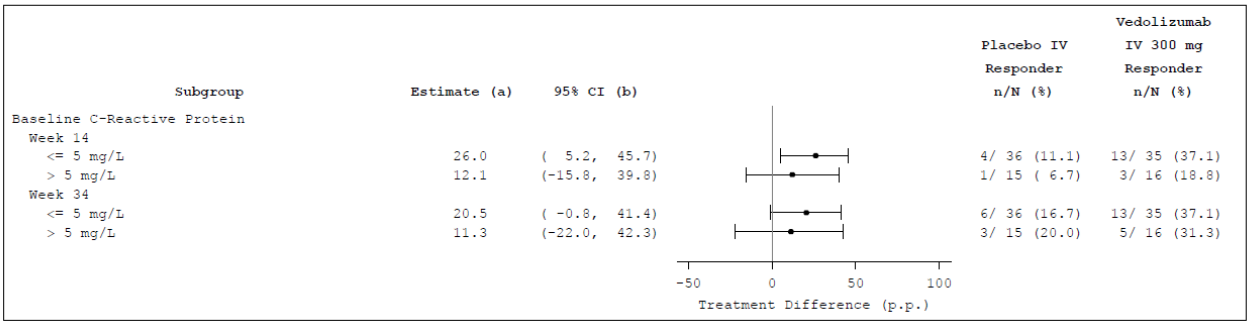


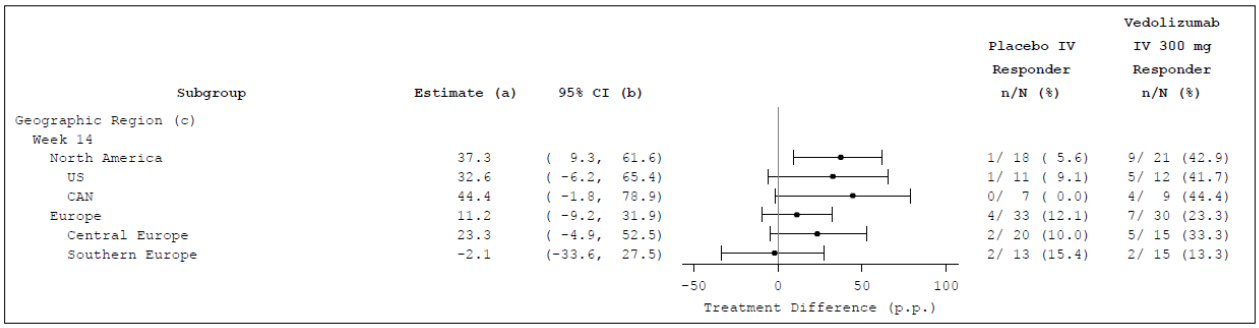
Subgroup	Estimate (a)	95% CI (b)	Placebo IV Responder n/N (%)	Vedolizumab IV 300 mg Responder n/N (%)
Time from IPAA to Start of Treatment				
Week 14				
< 7 years	39.0	(11.8, 66.0)	1/ 21 (4.8)	7/ 16 (43.8)
>= 7 years	12.4	(-8.2, 32.1)	4/ 30 (13.3)	9/ 35 (25.7)
Week 34				
< 7 years	19.9	(-13.1, 50.0)	5/ 21 (23.8)	7/ 16 (43.8)
>= 7 years	18.1	(-3.9, 38.2)	4/ 30 (13.3)	11/ 35 (31.4)

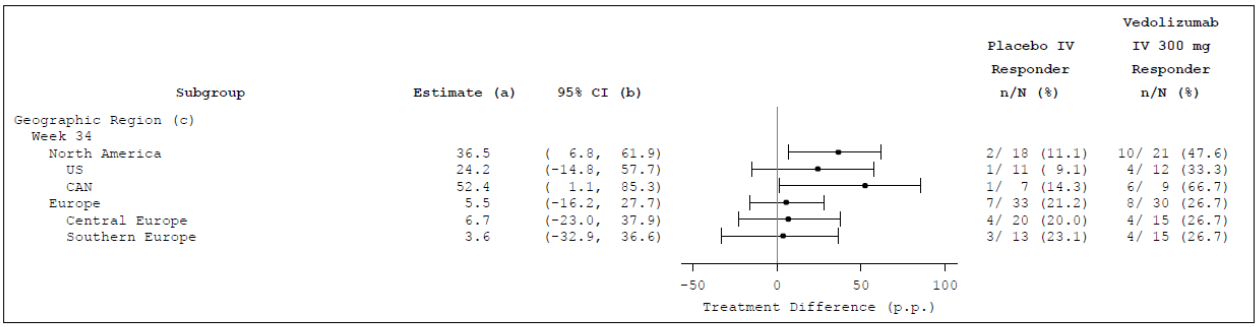


Subgroup	Estimate (a)	95% CI (b)	Placebo IV Responder n/N (%)	Vedolizumab IV 300 mg Responder n/N (%)
Baseline Fecal Calprotectin				
Week 14				
<= 250 µg/g	46.7	(19.5, 73.4)	0/ 17 (0.0)	7/ 15 (46.7)
> 250 µg/g	10.3	(-9.4, 30.0)	5/ 34 (14.7)	9/ 36 (25.0)
Week 34				
<= 250 µg/g	41.6	(7.8, 69.2)	2/ 17 (11.8)	8/ 15 (53.3)
> 250 µg/g	7.2	(-13.6, 27.5)	7/ 34 (20.6)	10/ 36 (27.8)









mPDAI=Modified Pouchitis Disease Activity Index; p.p.=percentage points; LOCF=Last Observation Carried Forward; Anti-TNF=Tumor Necrosis Factor-alpha Antagonist; UC=ulcerative colitis; PMNL=Polymorphic Nuclear Leukocyte Infiltration; IPAA=Ileal Pouch Anal Anastomosis.
(a) Estimate is the treatment difference Vedolizumab-Placebo (p.p.).
(b) The 95% CI of the percentages were calculated using the exact method.
(c) Central Europe includes GBR, BEL, DEU, NLD; Southern Europe includes ESP, FRA, ITA.
Note 1: Source tables: 15.2.2.1.1.1, 15.2.2.2.1, 15.2.2.3.1, 15.2.2.4.1, 15.2.2.5.1, 15.2.2.6.1, 15.2.2.7.1, 15.2.2.8.1, 15.2.2.9.1, 15.2.2.10.1.
Note 2: mPDAI remission is defined as a mPDAI score <5 points and a reduction from baseline of mPDAI score of >=2 points. Responders are defined as subjects achieving mPDAI remission.
Note 3: 'Observed' includes subjects with partially reported mPDAI (missing components imputed by LOCF). Subjects with completely missing mPDAI at the visit are considered non-responders and are shown under 'Imputed'.
Note 4: Baseline is defined as the last observation prior to the first dose of study medication.

At week 14, the mPDAI remission rates in the vedolizumab group were generally higher compared with placebo except in subgroups based on baseline non/mild PMNL histology and Southern Europe geographic region (France, Spain, Italy). Subgroup analyses based on baseline disease characteristics suggested a greater treatment response among patients with recurrent pouchitis, moderate/severe+crypt abscess histology, < 7years from IPAA to start of treatment, FC ≤250 mcg/g, CRP≤5 mg/L, North America geographic region.

At week 34, the mPDAI remission rates in the vedolizumab group were generally higher compared with placebo except in subgroups based on anti-TNF postcolectomy failure, baseline non/mild PMNL histology and Southern Europe geographic region (France, Spain, Italy). Subgroup analyses based on baseline disease characteristics suggested a greater treatment response among patients with recurrent pouchitis, anti-TNF not used post-colectomy, anti-TNF experienced (UC or pouchitis), severely active

disease (mPDAI), moderate/severe+crypt abscess histology, FC ≤250 mcg/g, CRP≤5 mg/L, North America geographic region.

The analogue analysis results of PDAI remission at W14 and W34 are generally overlapping with mPDAI remission results except that at W34 anti-TNF naïve performs slightly better with vedolizumab than anti-TNF experienced postcolectomy.

Secondary efficacy endpoints:

- **Clinically relevant mPDAI remission at W34**

Table 2.d Clinical (mPDAI) Remission at Week 34 (FAS)

Clinical Remission	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)
Week 34		
Number (%) of subjects achieving clinical remission (mPDAI)	9 (17.6)	18 (35.3)
95% CI [a]	8.4, 30.9	22.4, 49.9
Difference, vedolizumab - placebo (pp)		17.6
95% CI [a]		0.3, 35.1
Nominal p-value, vedolizumab vs placebo [b]		0.043

Clinical remission refers to clinically relevant mPDAI remission.

Subjects with missing data at a time point were considered as not being in remission.

[a] The 95% CI of the percentages were calculated using the exact method.

[b] Nominal p-value for the treatment difference in remission rates was obtained from the chi-squared test (no adjustment done for multiplicity).

Table 15.2.2.1.1.1
mPDAI Remission by Visit
Full Analysis Set

Visit	Placebo IV (N=51)	Vedolizumab IV 300 mg (N=51)
Week 34		
n	51	51
Responders (%) (95% CI)*	9 (17.6) (8.4, 30.9)	18 (35.3) (22.4, 49.9)
Non-Responders (%) (95% CI)*	42 (82.4) (69.1, 91.6)	33 (64.7) (50.1, 77.6)
Observed	23	19
Imputed	19	14
Difference, Vedolizumab - Placebo (p.p.) (95% CI)*		17.6 (0.3, 35.1)
p-value, Vedolizumab vs Placebo‡		0.043
Adjusted Difference, Vedolizumab - Placebo†		
Common Adjusted Difference (p.p.) (95% CI)		17.8 (0.9, 34.8)
Stratum Chronic Pouchitis (p.p.) (95% CI)		11.0 (-12.0, 34.0)
Stratum Recurrent Pouchitis (p.p.) (95% CI)		25.5 (0.7, 50.3)
p-value, Vedolizumab vs Placebo		0.044

mPDAI=Modified Pouchitis Disease Activity Index; p.p.=percentage points; LOCF=Last Observation Carried Forward.
* The 95% CI of the percentages were calculated using the exact method.
‡ p-value for the treatment difference in responder rates from chi-squared test; if the number of responders or non-responders in either of the two treatment arms is <=5, the corresponding p-value from Fisher's Exact test is shown.
† The risk difference, 95% CI and p-value were obtained using a Cochran-Mantel-Haenszel test stratified by type of pouchitis.
Note 1: mPDAI remission is defined as a mPDAI score <5 points and a reduction from baseline of mPDAI score of >=2 points. Responders are defined as subjects achieving mPDAI remission.
Note 2: 'Observed' includes subjects with partially reported mPDAI (missing components imputed using LOCF). Subjects with completely missing mPDAI at the visit are considered non-responders and are shown under 'Imputed'.
Note 3: Baseline is defined as the last observation prior to the first dose of study medication.

The treatment difference of mPDAI remission rates at W34 was 17.6 pp (nominal p = 0.043). Results for the PPS showed that the remission rate in this population was 16.2 pp higher in the vedolizumab group than in the placebo group (nominal p value = 0.112). In the LOCF and hybrid analyses the remission rates were 17.6 pp higher with vedolizumab than with placebo (nominal p = 0.048). A further analysis, undertaken to assess the impact of concomitant antibiotic use, showed the treatment difference of 15.7 pp (nominal p = 0.054).

- **PDAI remission at W14 and at W34**

Table 2.g PDAI Remission at Week 14 and Week 34: (FAS)

	Week 14		**Week 34**	
Visit	**Placebo IV (N = 51)**	**Vedolizumab IV 300 mg (N = 51)**	**Placebo IV (N = 51)**	**Vedolizumab IV 300 mg (N = 51)**
FAS	**N = 51**	**N = 51**	**N = 51**	**N = 51**
Number (%) of subjects achieving PDAI remission	5 (9.8)	18 (35.3)	9 (17.6)	19 (37.3)
95% CI [a]	3.3, 21.4	22.4, 49.9	8.4, 30.9	24.1, 51.9
Difference, vedolizumab - placebo (pp)		25.5		19.6
95% CI [a]		8.0, 41.4		1.9, 37.0
Nominal p-value, vedolizumab vs placebo [b]		0.004		0.027
PPS	**N = 38**	**N = 43**	**N = 38**	**N = 43**
Number (%) of subjects achieving PDAI remission	5 (13.2)	16 (37.2)	8 (21.1)	17 (39.5)

Table 2.g PDAI Remission at Week 14 and Week 34: (FAS)

	Week 14		Week 34	
Visit	**Placebo IV (N = 51)**	**Vedolizumab IV 300 mg (N = 51)**	**Placebo IV (N = 51)**	**Vedolizumab IV 300 mg (N = 51)**
95% CI [a]	4.4, 28.1	23.0, 53.3	9.6, 37.3	25.0, 55.6
Difference, vedolizumab - placebo (pp)		24.1		18.5
95% CI [a]		4.6, 42.2		-2.8, 38.0
Nominal p-value, vedolizumab vs placebo [c]		0.021		0.072
LOCF [c]	**N = 51**	**N = 51**	**N = 51**	**N = 51**
Number (%) of subjects achieving PDAI remission	6 (11.8)	18 (35.3)	10 (19.6)	19 (37.3)
95% CI [a]	4.4, 23.9	22.4, 49.9	9.8, 33.1	24.1, 51.9
Difference, vedolizumab - placebo (pp)		23.5		17.6
95% CI [a]		6.5, 39.6		-0.6, 35.1
Nominal p-value, vedolizumab vs placebo [c]		0.005		0.048
Hybrid [c]	**N = 51**	**N = 51**	**N = 51**	**N = 51**
Number (%) of subjects achieving PDAI remission	6 (11.8)	18 (35.3)	10 (19.6)	19 (37.3)
95% CI [a]	4.4, 23.9	22.4, 49.4	9.8, 33.1	24.1, 51.9
Difference, vedolizumab - placebo (pp)		23.5		17.6
95% CI [a]		6.5, 39.6		-0.6, 35.1
Nominal p-value, vedolizumab vs placebo [c]		0.005		0.048
Concomitant Antibiotic Use Prior to Week 14 [c]	**N = 51**	**N = 51**	**N = 51**	**N = 51**
Number (%) of subjects achieving PDAI remission	4 (7.8)	14 (27.5)	7 (13.7)	16 (31.4)
95% CI [a]	2.2, 18.9	15.9, 41.7	5.7, 26.3	19.1, 45.9
Difference, vedolizumab - placebo (pp)		19.6		17.6
95% CI [a]		4.8, 35.1		1.1, 33.8
Nominal p-value, vedolizumab vs placebo [c]		0.018		0.033

PDAI remission was defined as a PDAI score of <7 points and a reduction from the baseline PDAI score of ≥3 points

Subjects with missing data at a time point were considered as not being in remission.

Table 2.g PDAI Remission at Week 14 and Week 34: (FAS)

Visit	Week 14		Week 34	
	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)

[a] The 95% CI of the percentages were calculated using the exact method.

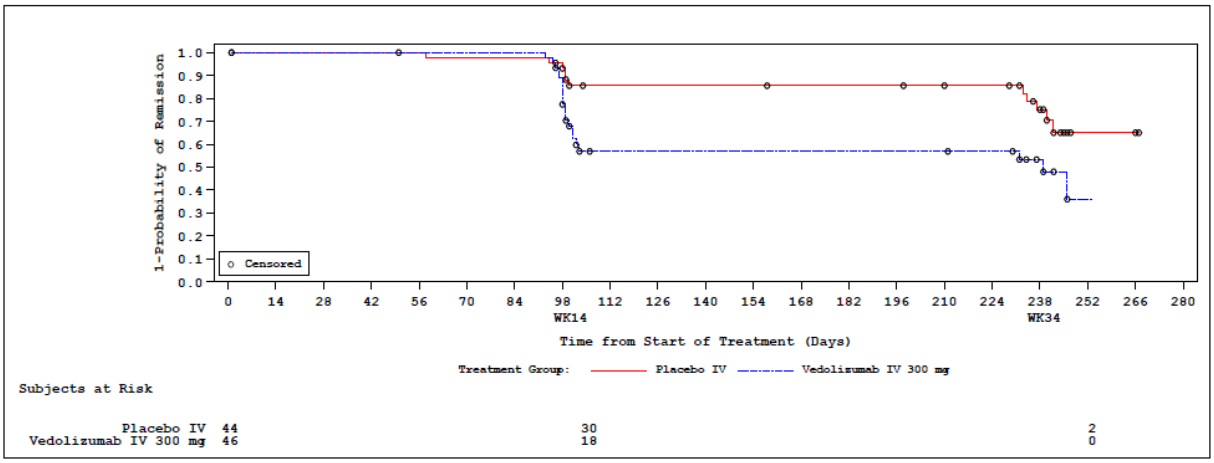
[b] The p-value for the treatment difference in remission rates was obtained from the chi-squared test; if the number of responders or non-responders in either of the 2 treatment groups was ≤5, the corresponding p-value from Fisher's Exact test is shown. All p-values are nominal as no adjustment for multiplicity was done.

[c] In the analysis of data with LOCF imputation applied, completely missing PDAI data at W14 was imputed using LOCF. In the hybrid approach, completely missing PDAI at W14 was imputed based on the reason for drop-out (adverse event or lack of efficacy were imputed as non-remission). In the analysis accounting for concomitant antibiotic use before W14, subjects receiving concomitant antibiotics before W14 were imputed as not achieving remission

The sensitivity analysis using the LOCF and hybrid approach and analysis accounting for concomitant antibiotic before Week 14 all supported the superiority of vedolizumab over placebo in inducing PDAI remission at W14 and W34. The PPS analysis was supportive only for W14 results.

- **Time to PDAI remission**

Figure 15.2.8.2
Kaplan Meier Plot of Time to PDAI Remission - Subjects with non-missing PDAI score at Baseline
Full Analysis Set



PDAI=Pouchitis Disease Activity Index.
Note 1: PDAI remission is defined as a PDAI score <7 points and a reduction from baseline PDAI score of >=3 points.
Note 2: Subjects that did not achieve PDAI remission during the study were censored at the time of their last PDAI assessment. Subjects whose last PDAI assessment was their baseline assessment were censored at Day 1.
Note 3: Subjects at Risk shown for Day 1, Week 14 (Day 106 = Day 99 + 7 days) and Week 34 (Day 253 = Day 239 + 14 days).

In the vedolizumab group 18 subjects had achieved PDAI remission by Day 106 (W14 +7 days), and 21 had achieved remission by Day 253 (W34 + 14 days). In the placebo group 6 subjects had achieved PDAI remission by Day 106, and 11 by Day 253. The median time to PDAI remission in the vedolizumab group was estimated as 239 days (and was not estimable for placebo).

Hazard Ratio, Vedolizumab vs Placebo 3.95 (95% CI 1.7, 9.4)

- **Partial mPDAI response at W14 and at W34**

Table 2.f Clinical (mPDAI) Response at Week 14 and Week 34 (FAS)

Visit	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)
Week 14		
Number (%) of subjects achieving clinical response	17 (33.3)	32 (62.7)
95% CI [a]	20.8, 47.9	48.1, 75.9
Difference, vedolizumab - placebo (pp)		29.4
95% CI [a]		8.0, 47.6
Nominal p-value, vedolizumab vs placebo [b]		0.003
Week 34		
Number (%) of subjects achieving clinical response	15 (29.4)	26 (51.0)
95% CI [a]	17.5, 43.8	36.6, 65.2
Difference, vedolizumab - placebo (pp)		21.6
95% CI [a]		1.9, 39.8
Nominal p-value, vedolizumab vs placebo [b]		0.026

mPDAI clinical response refers to partial mPDAI response.

Subjects with missing data at a time point were considered nonresponders.

[a] The 95% CI of the percentages were calculated using the exact method.

[b] Nominal p-value for the treatment difference in responder rates was obtained from the chi-squared test (no adjustment was done for multiplicity).

Partial mPDAI response at W14 FAS is supported by PPS and sensitivity analyses other than non-response imputation for use of Concomitant antibiotic, where p=0.061. Partial mPDAI response at W34 was supported by sensitivity analyses but for PPS p=0.088.

- **Change from baseline in PDAI endoscopic subscore at W14 and at W34**

Table 15.2.13.1.1.1
PDAI Endoscopic Inflammation Subscore and Change from Baseline by Visit (Observed Data)
Full Analysis Set

	Placebo IV (N=51)		Vedolizumab IV 300 mg (N=51)	
Visit	Value At Visit	Change From Baseline	Value At Visit	Change From Baseline
Baseline				
n	51		51	
Mean (SD)	4.5 (1.36)		4.6 (1.15)	
Median	5.0		5.0	
Min, Max	1, 6		2, 6	
Week 14				
n	40	40	45	45
Mean (SD)	4.3 (1.68)	-0.1 (1.22)	3.4 (1.84)	-1.2 (1.64)
Median	5.0	0.0	4.0	-1.0
Min, Max	0, 6	-3, 2	0, 6	-5, 2
p-value *				0.002
WMW Odds Estimator * (95% CI)				2.29 (1.12, 3.46)
HL Estimate for Difference * (95% CI)				-1.00 (-2.00, 0.00)
Week 34				
n	32	32	33	33
Mean (SD)	3.5 (2.11)	-0.9 (1.93)	2.7 (1.84)	-1.7 (2.10)
Median	3.0	0.0	2.0	-2.0
Min, Max	0, 6	-5, 2	0, 6	-5, 3
p-value *				0.063
WMW Odds Estimator * (95% CI)				1.73 (0.71, 2.75)
HL Estimate for Difference * (95% CI)				-1.00 (-2.00, 0.00)

PDAI=Pouchitis Disease Activity Index.
*p-value from Wilcoxon rank-sum test, Wilcoxon-Mann-Whitney (WMW) odds estimator and Hodges-Lehmann (HL) estimate.
Note 1: Endoscopic inflammation subscore is the sum of: Edema, Granularity, Friability, Loss of vascular pattern, Mucus exudates and Ulceration.
Note 2: Baseline is defined as the last observation prior to the first dose of study medication.

Mean changes from baseline in the PDAI endoscopic inflammation domain score at W14 were greater in the vedolizumab group (-1.2; N = 45) than in the placebo group (-0.1; N = 41). At W34, the change from baseline in the endoscopic inflammation domain score was -1.7 in the vedolizumab group (N = 33) and -0.9 in the placebo group (N = 32)

- **Change from baseline in PDAI histologic subscore at W14 and at W34**

Table 15.2.14.1.1
PDAI Histologic Subscore and Change from Baseline by Visit (Observed Data)
Full Analysis Set

	Placebo IV (N=51)		Vedolizumab IV 300 mg (N=51)	
Visit	Value At Visit	Change From Baseline	Value At Visit	Change From Baseline
Baseline				
n	51		50	
Mean (SD)	2.6 (1.39)		2.5 (1.42)	
Median	2.0		2.0	
Min, Max	1, 6		0, 6	
Week 14				
n	41	41	45	44
Mean (SD)	2.4 (1.50)	-0.1 (1.48)	2.0 (1.89)	-0.5 (2.11)
Median	2.0	0.0	1.0	-1.0
Min, Max	0, 6	-2, 4	0, 6	-5, 5
p-value *				0.173
WMW Odds Estimator * (95% CI)				1.40 (0.71, 2.10)
HL Estimate for Difference * (95% CI)				0.00 (-1.00, 0.00)

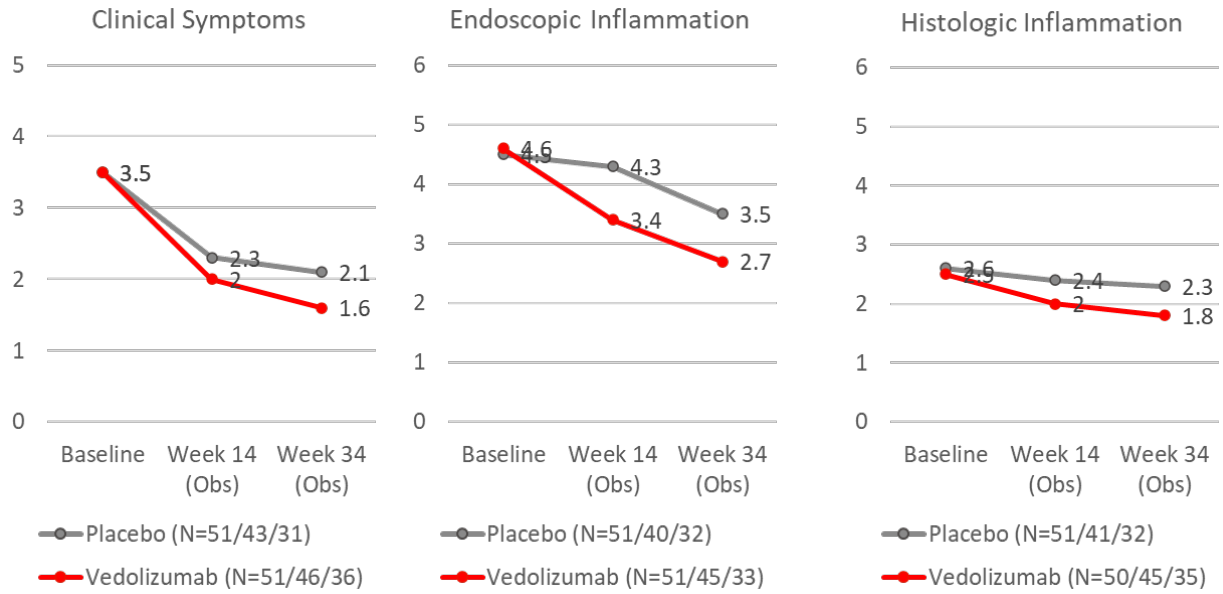
Week 34				
n	32	32	35	34
Mean (SD)	2.3 (1.51)	-0.1 (1.56)	1.8 (1.59)	-0.4 (1.94)
Median	2.0	0.0	1.0	-1.0
Min, Max	0, 6	-3, 4	0, 6	-4, 6
p-value *				0.247
WMW Odds Estimator * (95% CI)				1.39 (0.61, 2.17)
HL Estimate for Difference * (95% CI)				0.00 (-1.00, 0.00)

PDAI=Pouchitis Disease Activity Index.
*p-value from Wilcoxon rank-sum test, Wilcoxon-Mann-Whitney (WMW) odds estimator and Hodges-Lehmann (HL) estimate.
Note 1: PDAI Acute Histologic Inflammation Subscore is the sum of two components: Polymorphic Nuclear Leukocyte Infiltration and Ulceration per Low Power Field (mean).
Note 2: Baseline is defined as the last observation prior to the first dose of study medication.

Mean changes from baseline in the histological domain score, suggested slightly greater improvement in the vedolizumab group than in the placebo group. At W14, the mean change was -0.5 in the vedolizumab group and -0.1 in the vedolizumab group. At W34 the mean changes were -0.4 and -0.1, respectively.

Overall, only endoscopic subscore (Figure 2.c) showed important differences between placebo and vedolizumab group, that were also statistically significant at W14. The results of clinical and histologic subscores revealed only tendency of numerically better results with vedolizumab than with placebo.

Figure 2.c Mean Changes in PDAI Domain Scores: Observed Data (FAS)



- **Change from baseline in Total PDAI score at Weeks 14 and 34**

Table 15.2.6.1.1.1
PDAI Score and Change from Baseline by Visit (Observed Data)
Full Analysis Set

Visit	Placebo IV (N=51) Value At Visit	Placebo IV (N=51) Change From Baseline	Vedolizumab IV 300 mg (N=51) Value At Visit	Vedolizumab IV 300 mg (N=51) Change From Baseline
Baseline				
n	51		50	
Mean (SD)	10.5 (2.48)		10.5 (2.20)	
Median	10.0		10.5	
Min, Max	7, 16		6, 14	
Week 14				
n	40	40	45	44
Mean (SD)	9.0 (2.76)	-1.4 (2.70)	7.5 (3.89)	-3.1 (3.95)
Median	9.0	-2.0	8.0	-3.5
Min, Max	3, 16	-6, 6	1, 16	-12, 5
p-value *				0.025
WMW Odds Estimator * (95% CI)				1.79 (0.86, 2.72)
HL Estimate for Difference * (95% CI)				-2.00 (-3.00, 0.00)
Week 34				
n	31	31	32	31
Mean (SD)	8.0 (3.40)	-2.1 (3.48)	6.1 (3.42)	-3.9 (4.24)
Median	8.0	-2.0	6.0	-4.0
Min, Max	1, 15	-12, 4	1, 14	-12, 5
p-value *				0.062
WMW Odds Estimator * (95% CI)				1.76 (0.69, 2.83)
HL Estimate for Difference * (95% CI)				-2.00 (-4.00, 0.00)

PDAI=Pouchitis Disease Activity Index.
*p-value from Wilcoxon rank-sum test, Wilcoxon-Mann-Whitney (WMW) odds estimator and Hodges-Lehmann (HL) estimate.
Note: Baseline is defined as the last observation prior to the first dose of study medication.

At W14, the mean change from baseline in PDAI total score was -3.1 in the vedolizumab group and -1.4 in the placebo group, and at W34 the mean change from baseline was -3.9 in the vedolizumab group and -2.1 in the placebo group

- **Change from baseline in IBDQ**

Table 15.2.18.1.1
Inflammatory Bowel Disease Questionnaire (IBDQ) Total Score and Change from Baseline by Visit
Full Analysis Set

Visit	Placebo IV (N=51) Value At Visit	Placebo IV (N=51) Change From Baseline	Vedolizumab IV 300 mg (N=51) Value At Visit	Vedolizumab IV 300 mg (N=51) Change From Baseline
Baseline				
n	50		51	
Mean (SD)	131.5 (30.78)		137.9 (33.53)	
Median	131.0		137.0	
Min, Max	59, 193		67, 208	
Week 14 (Observed)				
n	44	43	46	46
Mean (SD)	149.0 (34.65)	16.7 (27.05)	159.7 (31.06)	21.1 (28.99)
Median	154.5	18.0	164.0	16.6
Min, Max	44, 200	-47, 83	91, 208	-46, 106
p-value *				0.669
WMW Odds Estimator * (95% CI)				1.11 (0.56, 1.66)
HL Estimate for Difference * (95% CI)				3.00 (-8.00, 14.00)
Week 22 (Observed)				
n	37	36	39	39
Mean (SD)	158.2 (27.00)	24.7 (27.64)	168.6 (28.53)	27.5 (31.06)
Median	157.0	25.0	168.0	23.0
Min, Max	93, 204	-29, 84	95, 218	-36, 114
p-value *				0.983
WMW Odds Estimator * (95% CI)				0.99 (0.46, 1.52)
HL Estimate for Difference * (95% CI)				0.00 (-13.00, 13.00)

Week 34 (Observed)				
n	30	29	35	35
Mean (SD)	156.3 (27.80)	23.1 (21.58)	172.9 (26.11)	33.1 (34.39)
Median	162.0	19.0	175.0	24.0
Min, Max	97, 208	-12, 89	119, 220	-27, 111
p-value *				0.370
WMW Odds Estimator * (95% CI)				1.30 (0.55, 2.06)
HL Estimate for Difference * (95% CI)				7.00 (-8.00, 23.00)

*p-value from Wilcoxon rank-sum test, Wilcoxon-Mann-Whitney (WMW) odds estimator and Hodges-Lehmann (HL) estimate.
Note 1: IBDQ total score was calculated by summing the scores from each domain.
Note 2: Baseline is defined as the last observation prior to the first dose of study medication.

- **Change from baseline in CGQL**

Table 15.2.19.1
Cleveland Global Quality of Life (CGQL) Fazio Score and Change from Baseline by Visit
Full Analysis Set

	Placebo IV (N=51)		Vedolizumab IV 300 mg (N=51)	
Visit	Value At Visit	Change From Baseline	Value At Visit	Change From Baseline
Baseline				
n	49		50	
Mean (SD)	0.522 (0.1953)		0.556 (0.1626)	
Median	0.567		0.578	
Min, Max	0.07, 0.91		0.07, 0.93	
Week 14 (Observed)				
n	43	42	46	45
Mean (SD)	0.607 (0.1487)	0.066 (0.1559)	0.662 (0.1497)	0.106 (0.1671)
Median	0.633	0.044	0.700	0.078
Min, Max	0.13, 0.83	-0.19, 0.63	0.27, 0.93	-0.33, 0.57
p-value *				0.125
WMW Odds Estimator * (95% CI)				1.47 (0.73, 2.20)
HL Estimate for Difference * (95% CI)				0.04 (-0.01, 0.11)
Week 22 (Observed)				
n	35	34	37	36
Mean (SD)	0.656 (0.1364)	0.108 (0.1474)	0.698 (0.1321)	0.133 (0.1489)
Median	0.689	0.067	0.689	0.117
Min, Max	0.30, 0.88	-0.11, 0.51	0.37, 0.97	-0.13, 0.60
p-value *				0.391
WMW Odds Estimator * (95% CI)				1.27 (0.56, 1.99)
HL Estimate for Difference * (95% CI)				0.03 (-0.03, 0.10)
Week 34 (Observed)				
n	30	29	34	33
Mean (SD)	0.657 (0.1388)	0.105 (0.1361)	0.687 (0.1354)	0.135 (0.1826)
Median	0.667	0.100	0.717	0.078
Min, Max	0.30, 0.94	-0.12, 0.47	0.41, 0.91	-0.28, 0.50
p-value *				0.425
WMW Odds Estimator * (95% CI)				1.27 (0.52, 2.02)
HL Estimate for Difference * (95% CI)				0.03 (-0.04, 0.11)

*p-value from Wilcoxon rank-sum test, Wilcoxon-Mann-Whitney (WMW) odds estimator and Hodges-Lehmann (HL) estimate.
Note 1: The CGQL Fazio score was calculated by taking the average CGQL utility score from 3 days immediately prior to endoscopy (or bowel preparation for endoscopy) for each subject.
Note 2: Baseline is defined as the last observation prior to the first dose of study medication.

Both QoL endpoints (IBDQ and CGQL) failed to show statistically significant difference (change from baseline) between the groups, although the change was slightly greater in the vedolizumab than in the placebo group.

Additionally, the data are available for mPDAI remission, PDAI remission and partial mPDAI response (at W14 and W34 each) stratified by the type of pouchitis (tables A-C assembled by the Assessor):

Table A mPDAI Remission by the type of pouchitis at W14 and W34: (FAS-LOCF) **–** assembled by Assessor

	Week **14**		Week **34**	
	Placebo IV	Vedolizumab IV 300 mg	Placebo IV	Vedolizumab IV 300 mg
Chronic pouchitis	N = 25	N = 29	N = 25	N = 29
Number (%) of subjects achieving mPDAI remission	3 (12.0)	8 (27.6)	5 (20.0)	9 (31.0)
95% CI [a]	2.5, 31.2	12.7, 47.2	6.8, 40.7	15.3, 50.8
Difference, vedolizumab - placebo (pp)		15.6		11.0
95% CI [a]		-7.2, 37.2		-14.6, 34.5
Nominal p-value, vedolizumab vs placebo [b]		0.191		0.535
Recurrent pouchitis	N = 26	N = 22	N = 26	N = 22
Number (%) of subjects achieving mPDAI remission	2 (7.7)	8 (36.4)	4 (15.4)	9 (40.9)
95% CI [a]	0.9, 25.1	17.2, 59.3	4.4, 34.9	20.7, 63.6
Difference, vedolizumab - placebo (pp)		28.7		25.5
95% CI [a]		4.9, 53.1		-0.6, 50.2
Nominal p-value, vedolizumab vs placebo [b]		0.029		0.059

Table B PDAI Remission by the type of pouchitis at W14 and W34: (FAS-LOCF) – assembled by Assessor

	Week **14**		Week **34**	
	Placebo IV	Vedolizumab IV 300 mg	Placebo IV	Vedolizumab IV 300 mg
Chronic pouchitis	N = 25	N = 29	N = 25	N = 29
Number (%) of subjects achieving PDAI remission	3 (12.0)	9 (31.0)	4 (16.0)	9 (31.0)
95% CI [a]	2.5, 31.2	15.3, 50.8	4.5, 36.1	15.3, 50.8
Difference, vedolizumab - placebo (pp)		19.0		15.0
95% CI [a]		-3.9, 40.9		-8.9, 37.7
Nominal p-value, vedolizumab vs placebo [b]		0.113		0.223
Recurrent pouchitis	N = 26	N = 22	N = 26	N = 22
Number (%) of subjects achieving PDAI remission	2 (7.7)	9 (40.9)	5 (19.2)	10 (45.5)

Table B PDAI Remission by the type of pouchitis at W14 and W34: (FAS-LOCF) – assembled by Assessor

	Week **14**		Week **34**	
	Placebo IV	Vedolizumab IV 300 mg	Placebo IV	Vedolizumab IV 300 mg
95% CI [a]	0.9, 25.1	20.7, 63.6	6.6, 39.4	24.4, 67.8
Difference, vedolizumab - placebo (pp)		33.2		26.2
95% CI [a]		8.7, 56.7		-1.6, 51.8
Nominal p-value, vedolizumab vs placebo [b]		0.013		0.066

Table C Partial mPDAI response by the type of pouchitis at W14 and W34: (FAS-LOCF) – assembled by Assessor

	Week **14**		Week **34**	
	Placebo IV	Vedolizumab IV 300 mg	Placebo IV	Vedolizumab IV 300 mg
Chronic pouchitis	N = 25	N = 29	N = 25	N = 29
Number (%) of subjects achieving partial mPDAI response	10 (40.0)	18 (62.1)	8 (32.0)	14 (48.3)
95% CI [a]	21.1, 61.3	42.3, 79.3	14.9, 53.5	29.4, 67.5
Difference, vedolizumab - placebo (pp)		22.1		16.3
95% CI [a]		-5.3, 47.2		-10.9, 41.6
Nominal p-value, vedolizumab vs placebo [b]		0.106		0.225
Recurrent pouchitis	N = 26	N = 22	N = 26	N = 22
Number (%) of subjects achieving partial mPDAI response	7 (26.9)	14 (63.6)	7 (26.9)	12 (54.5)
95% CI [a]	11.6, 47.8	40.7, 82.8	11.6, 47.8	32.2, 75.6
Difference, vedolizumab - placebo (pp)		36.7		27.6
95% CI [a]		7.9, 61.1		-1.6, 53.1
Nominal p-value, vedolizumab vs placebo [b]		0.011		0.051

a The 95% CI of the percentages were calculated using the exact method.

b The p-value for the treatment difference in remission rates was obtained from the chi-squared test; if the number of responders or nonresponders in either of the 2 treatment groups was ≤5, the corresponding p-value from Fisher's Exact test is shown. All p-values are nominal as no adjustment for multiplicity was done.

c In the analysis of data with LOCF imputation applied, completely missing PDAI data at W14 was imputed using LOCF

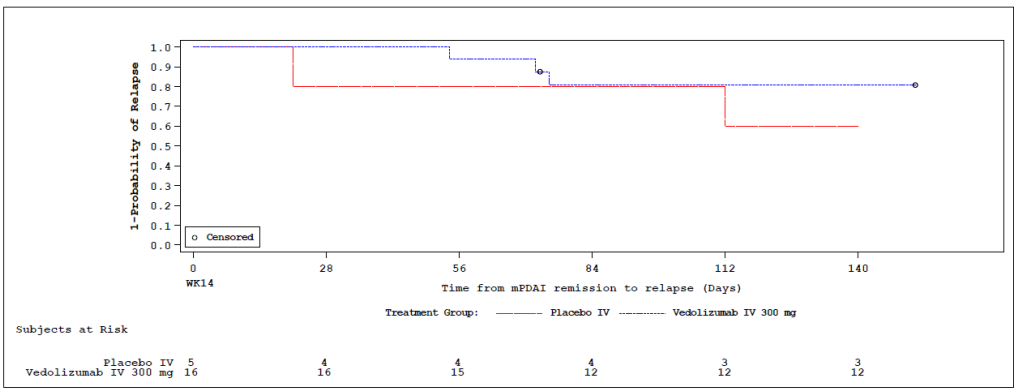
These data show better results for recurrent pouchitis but also the lack of statistical significance for the results of patients with chronic pouchitis.

Exploratory endpoints:

The results from most exploratory endpoints are only descriptive (mean, SD, median) and could be summarized as follows:

- **Change from baseline in RHI** (Robarts Histology Index) was greater in the vedolizumab group than in the placebo group as well as the rate of patients with histological remission and minimal histological activity
- **Change from baseline in FC**: Values of FC obtained during the study showed a high degree of variability between subjects within each treatment group; however, median reductions in FC levels were higher in the vedolizumab group than in the placebo group at W14 and at W34
- **Change from baseline in CRP**: No difference in the change from baseline in CRP was noted between placebo and vedolizumab groups at different time points
- **Time to relapse of pouchitis symptoms and number of relapses**

Figure 15.2.11.3
Kaplan Meier Plot of Time to Relapse of Pouchitis
Subjects with mPDAI Remission at Week 14
Full Analysis Set



mPDAI=Modified Pouchitis Disease Activity Index.
Note 1: Relapse of pouchitis is defined as a worsening in the pouchitis symptoms after previous mPDAI remission.
Note 2: Time to relapse of pouchitis was derived as the time between the day mPDAI remission was achieved and the day of relapse.
Note 3: Subjects who did not experience relapse of pouchitis during the study were censored at the time of the last subject visit (end of study or early discontinuation).

Table 15.2.11.1
Relapse of Pouchitis Symptoms after Week 14
Subjects with mPDAI Remission at Week 14
Full Analysis Set

	Placebo IV (N=5)	Vedolizumab IV 300 mg (N=16)
Relapse of Pouchitis Symptoms through End of Study (a)		
No (%) (95% CI)	3 (60.0) (14.7, 94.7)	11 (68.8) (41.3, 89.0)
Yes (%) (95% CI)	2 (40.0) (5.3, 85.3)	5 (31.3) (11.0, 58.7)
Difference, Vedolizumab - Placebo (p.p.) (95% CI)*		8.8 (-36.5, 56.8)
Time to First Relapse of Pouchitis Symptoms (days)		
n	2	5
Mean (SD)	66.5 (64.35)	120.6 (74.11)
Median	66.5	75.0
Min, Max	21, 112	54, 210
Number of Relapses of Pouchitis Symptoms		
n	2	5
Mean (SD)	2.5 (2.12)	1.6 (0.89)
Median	2.5	1.0
Min, Max	1, 4	1, 3

mPDAI=Modified Pouchitis Disease Activity Index; p.p.=percentage points.
*The 95% CI of the percentages were calculated using the exact method.
(a) End of Study includes through safety follow-up.
Note 1: Relapse of pouchitis is defined as a worsening in the pouchitis symptoms after previous mPDAI remission.
Note 2: Time to relapse of pouchitis was derived as the time between the day mPDAI remission was achieved and the day of relapse.
Note 3: Endpoint analyzed based on subjects from the full analysis set who experienced mPDAI remission at week 14.

Sixteen subjects in the vedolizumab group and 5 subjects in the placebo group had achieved clinical remission at W14. Five of 16 subjects (31.3%) in the vedolizumab group and 2 of 5 subjects (40%) in the placebo group experienced a worsening of pouchitis symptoms after W14. The median time to relapse was 66.5 days in the placebo group and 75 days in the vedolizumab group.

- **Changes in number of ulcers in the pouch, proportion of surface area in the pouch that is ulcerated, and SES-CD score in the pouch**: Changes in the total number of all ulcers and in the number of large (nonaphthous) ulcers at each visit were larger in the vedolizumab group than in the placebo group. More subjects in the vedolizumab group than in the placebo group had decreases in the proportion of the surface occupied by large ulcers.
- **SES-CD response**: The mean changes in SES-CD were more marked in the vedolizumab group than in the placebo group both at W14 (-1.7 vs 0), and at W34 (-1.3 vs -0.6). In addition, more subjects in the vedolizumab group than in the placebo group were recorded as being in endoscopic remission based on a SES-CD score ≤2: 20.8% versus 6.0% at W14 and 22.9% versus 10.0% at W34.
- **Change in stool frequency**: The tendency towards improved stool frequency with vedolizumab; the number of subjects with increased stool frequency at baseline who achieved their usual postoperative frequency and the number of subjects who had a reduction from ≥3 stools more than usual at baseline to ≤2 stools more than at baseline at W14 and W34 was slightly higher in the vedolizumab group than in the placebo group.
- **Sustained mPDAI remission**

Table 2.e Sustained Clinical (mPDAI) Remission at Week 14 and Week 34 (FAS)

	Placebo IV (N = 51)	**Vedolizumab IV 300 mg (N = 51)**
Week 14 and 34		
Number (%) subjects with sustained mPDAI remission	3 (5.9)	14 (27.5)

Table 2.e Sustained Clinical (mPDAI) Remission at Week 14 and Week 34 (FAS)

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)
95% CI [a]	1.2, 16.2	15.9, 41.7
Difference, vedolizumab minus placebo (pp)		21.6
95% CI [a]		6.5, 37.0

Subjects with missing data at a time point were considered not being in remission.

[a] The 95% CI of the percentages were calculated using the exact method.

Results for the PPS were supportive of the FAS analysis: the sustained remission rate in this population was 20.0 pp higher in the vedolizumab group than in the placebo group (95% CI: 2.6, 36.8). The other sensitivity analyses also showed higher clinical remission rates with vedolizumab than with placebo.

- **Sustained PDAI remission**

Table 2.h Sustained PDAI Remission at Week 14 and Week 34 (FAS)

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)
Week 14 and 34		
Number (%) subjects with sustained PDAI remission	4 (7.8)	16 (31.4)
95% CI [a]	2.2, 18.9	19.1, 45.9
Difference, vedolizumab minus placebo (pp)		23.5
95% CI [a]		8.0, 38.8
Nominal p-value, vedolizumab vs placebo [b]		0.005

Subjects with missing data at a time point were considered as not being in remission.
[a] The 95% CI of the percentages were calculated using the exact method.

[b] Nominal p-value for the treatment difference in remission rates was obtained from Fisher's Exact test (no adjustment done for multiplicity).

The PPS analysis, sensitivity using the LOCF and hybrid approach and analysis accounting for concomitant antibiotic before Week 14 all supported the superiority of vedolizumab over placebo in inducing PDAI remission at W14 and W34.

- **Corticosteroid-free mPDAI remission** and **corticosteroid-free PDAI remission** rates were both higher in vedolizumab group than in the placebo group, but the differences were statistically significant only at W14 but not at W34.
- **Change in PDAI components compared to baseline**:

1. Clinical Symptom Components:

- Stool frequency: see above
- Rectal bleeding: Among the small subset of subjects who had daily rectal bleeding at baseline (12 (23.5%) in the vedolizumab group and 8 (15.7%) in the placebo group), improvements, in terms of subjects reporting no rectal bleeding or only rare occurrences of bleeding at W14 and W34, were observed in a higher proportion of subjects treated with vedolizumab than in those treated with placebo.
- Fecal urgency or abdominal cramps: no difference between two groups at W14 and no major difference at W34. At W34, 20 of 36 subjects (55.6%) in the vedolizumab group had a score of 0 (no fecal urgency or abdominal pain) vs 12 of 31 subjects (38.7%) in the placebo group.
- Fever: present only in 2 patients of placebo group at baseline, none at W14 and in 1 patient in vedolizumab group at W34

2. Endoscopic components:

- Ulceration: Of the subjects who had large ulcers at baseline 11 of 40 subjects (27.5%) in the vedolizumab group had no large ulcers at W14 or at W34 compared with 5 of 36 (13.9%) and 7 of 36 (19.4%) in the placebo group who had no large ulcers at W14 and W34, respectively
- Friability: more subjects in the vedolizumab group than in the placebo group had absence of friability reported at W14 (22 of 45 subjects, 48.9% vs 9 of 40 subjects, 22.5%) and W34 (20 of 33 subjects, 60.6% vs 13 of 32 subjects, 40.6%).
- Edema: At W14, edema was reported as absent in 9 of 45 subjects (20%) in the vedolizumab group and in 3 of 40 subjects (7.5%) in the placebo group, and at W34, edema was reported as absent in 10 of 33 subjects (30.3%) in the vedolizumab group and 7 of 32 subjects (21.9%) in the placebo group.
- Loss of vascular pattern: no major difference between the groups at W14 and W34. At Baseline, 1 subject (2.0%) in the vedolizumab group had visible vasculature compared with 5 subjects (9.8%) in the placebo group. At W14, 7 of 45 subjects (15.6%) in the vedolizumab group had visible vasculature vs 3 of 40 subjects (7.5%) in the placebo group, and at W34, 9 of 33 subjects (27.3%) had visible vasculature in the vedolizumab group vs 6 of 32 subjects (18.8%) in the placebo group.

3. Histologic components:

- PMNL infiltration: At W14, 23 of 45 subjects (51.1%) in the vedolizumab group compared with 12 of 41 subjects (29.3%) in the placebo group had no infiltration or mild PMNL infiltration. Similarly, at W34, a higher proportion of subjects in the vedolizumab group (20 of 35; 57.2%) than in the placebo group (10 of 32; 31.3%) had no infiltration or mild infiltration of PMNLs.
- Ulceration: similar proportions of subjects were histologically ulcer free at baseline: 68.0% in the vedolizumab group and 64.7% in the placebo group; At W14, 77.8% of subjects in the vedolizumab group and 68.3% in the placebo group had no histologic evidence of pouch ulceration and at W34, 80% of subjects in the vedolizumab group and 68.8% in the placebo group had no histologic evidence of ulceration in the pouch.

Ancillary analyses

N/A

Summary of main study(ies)

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial Vedolizumab-4004

Title: A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)			
Study identifier	Vedolizumab-4004 (EARNEST); EudraCT 2015-003472-78; NCT 02790138 (clinicaltrials.gov)		
Design	Multicentre, parallel, randomized, double-blind, placebo-controlled efficacy and safety study		
	Duration of main phase:		34 weeks
Hypothesis	Superiority of Vedolizumab versus Placebo		
Treatments groups	Vedolizumab		Vedolizumab IV 300 mg administered Day 1, Weeks 2, 6, 14, 22, 30 (51 subjects randomized) Subjects also received ciprofloxacin 500 mg twice daily through Week 4
	Placebo		Placebo IV administered Day 1, Weeks 2, 6, 14, 22, 30 (51 subjects randomized] Subjects also received ciprofloxacin 500 mg twice daily through Week 4
Endpoints and definitions	Primary endpoint	mPDAI remission (W14)	Clinically relevant mPDAI remission at Week 14. Clinically relevant remission defined as an mPDAI score <5 and a reduction in overall score by ⩾2 points from baseline.
	Secondary endpoint	mPDAI remission (W34)	Clinically relevant mPDAI remission at Week 34. (defined as for W14)
	Secondary endpoint	PDAI remission (W14 and W34)	PDAI remission at Week 14 and Week 34. PDAI remission defined as score <7 and a reduction of overall score by ⩾3 points from baseline.
	Secondary endpoint	Partial mPDAI response (W14 and W34)	Partial mPDAI response at Week 14 and Week 34. Partial mPDAI response defined as a decrease in mPDAI score by ⩾2 points from baseline.
	Exploratory endpoint	Sustained mPDAI remission	mPDAI remission at both W14 and W34
	Exploratory endpoint	Sustained PDAI remission	PDAI remission at both W14 and W34
Database lock	16 Feb 2021		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (all randomized subjects who received at least 1 dose of study medication) Week 14 /week 34		
Descriptive statistics and estimate variability	Treatment group	Placebo	Vedolizumab
	Number of subject	51	51
	mPDAI remission W14 %	9.8	31.4
	Number of subject	51	51
	mPDAI remission W34 %	17.6	35.3
	Number of subject	51	51
	PDAI remission W14 %	9.8	35.3
	Number of subject	51	51
	PDAI remission W34 %	17.6	37.3
	Number of subject	51	51
	Partial mPDAI response W14 %	33.3	62.7
	Number of subject	51	51
	Partial mPDAI response W34 %	29.4	51
	Number of subject	51	51
	Sustained mPDAI remission %	5.9	27.5
	Number of subject	51	51
	Sustained PDAI remission %	7.8	31.4
Effect estimate per comparison	Primary endpoint mPDAI remission (W14)	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	21.6

		95% CI	4.9, 37.5
		P-value	0.013
	Secondary endpoint mPDAI remission (W34)	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	17.6
		95% CI	0.3, 35.1
		nominal P-value	0.043
	Secondary endpoint PDAI remission (W14)	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	25.5
		95% CI	8.0, 41.4
		nominal P-value	0.004
	Secondary endpoint PDAI remission (W34)	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	19.6
		95% CI	1.9, 37.0
		nominal P-value	0.027
	Secondary endpoint Partial mPDAI response (W14)	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	29.4
		95% CI	8.0, 47.6
		P-value	0.003
	Secondary endpoint Partial mPDAI response (W34)	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	21.6

		95% CI	1.9, 39.8
		P-value	0.026
	Exploratory endpoint Sustained mPDAI remission	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	21.6
		95% CI	6.5, 37.0
		P-value	0.007
	Exploratory endpoint Sustained PDAI remission	Comparison groups	Vedolizumab IV 300mg vs Placebo
		% difference in response rate	23.5
		95% CI	8.0, 38.8
		P-value	0.005

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

N/A

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the sought indication the MAH is providing evidence from one pivotal study only, Vedolizumab-4004, a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vedolizumab IV 300 mg in the treatment of adult subjects who had a proctocolectomy and IPAA for treatment of UC and had developed chronic refractory or recurrent

pouchitis. Therefore, the relevant guideline (POINTS TO CONSIDER ON APPLICATION WITH 1. META-ANALYSES; 2. ONE PIVOTAL STUDY, CPMP/EWP/2330/99) applies in this context.

The study design included a 30-week double-blind treatment period, with a final safety follow-up visit at W48. All subjects received concomitant antibiotic treatment with ciprofloxacin (considered a companion antibiotic) 500 mg twice daily through W4. The design of the pivotal study is acceptable, as per the EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1).

The study included subjects with active pouchitis (defined as mPDAI score ≥5 assessed as the average from 3 days immediately before the baseline endoscopy and a minimum endoscopic subscore of 2), that have recurrent pouchitis (≥3 recurrent episodes within 1 year before the screening period treated with ≥2 weeks of antibiotic or other prescription therapy), or chronic refractory pouchitis (requiring maintenance antibiotic therapy taken continuously for ≥4 weeks immediately before the baseline endoscopy visit). The MAH has clarified that in the definition of the recurrent pouchitis "other prescription therapy" was referred to treatments other than antibiotics used in the clinical practice. The two subtypes of pouchitis could have a different clinical course and expected response to antibiotic treatment, and therefore potentially a heterogeneous response to vedolizumab, therefore the MAH's choice to mix these subtypes in the study is not seen as the preferred choice although it is recognized that could be challenging to perform separate studies. Randomization was stratified by the type of pouchitis (recurrent or chronic). Overall inclusion and exclusion criteria are considered adequate for selecting a target population with a diagnosis of idiopathic chronic pouchitis. Secondary aetiologies are excluded. However, the MAH was asked to provide some clarification on exclusion of secondary causes of pouchitis such as CMV infection and pelvic sepsis. The claimed indication was revised, as requested, to reflect the setting investigated and subject's characteristics including severity of the disease (moderate to severe) and exclusion of patients intolerant to antibiotics.

Criteria for defining concomitant allowed or prohibited therapies and stable doses are considered acceptable. However, since two different subtypes of pouchitis are included, one responsive to antibiotics and the other not, the role of companion antibiotic and the potential impact on efficacy at week 14 could be potentially different. However, from further data provided by the MAH the efficacy in both subgroups seems not to be influenced by the companion antibiotic. The use of the companion antibiotic (4 weeks of concomitant ciprofloxacin) in both subgroups was added in 4.2 section of the SmPC upon request.

Clarification has been received for the chronic refractory pouchitis on fulfilment of ECCO guidelines 2017 criteria on the first line therapy, these are met by a majority of patients particularly when an extended (alternative) approach compared to more stringent one was used.

The study endpoints are aimed at assessing the efficacy of vedolizumab on symptoms, endoscopic and histological findings and could be overall acceptable. However, the selection of the primary estimand (mPDAI) lacking histology assessment as compared to the Pouchitis Disease Activity Index (PDAI) is not fully in line with the relevant EMA GL. The selection was not discussed within a SA. The EMA Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006 Rev.1) highlights the importance on demonstrating efficacy in terms of symptoms as well as mucosal healing (including histological assessment) (defined as co-primary endpoints). The relevant GL also reports that the 18-point PDAI, combining all three aspects (symptoms, macro- and microscopic appearance of mucosa) has been used to measure disease activity and response. However, this instrument is not fully validated and there are no generally accepted definitions of response and remission. Nevertheless, the use of PDAI is considered acceptable provided that response and remission are convincingly defined and provided that clinically

relevant effects in each of the main components of the score (symptoms as well as macro- and microscopic appearance of mucosa) are demonstrated (EMA GL CHMP/EWP/18463/2006 Rev.1).

The definition of the primary endpoint of the study was changed from PDAI to mPDAI clinically relevant remission, based on a claimed similar sensitivity and specificity of the mPDAI when compared with the PDAI (Shen 2003). However, it should be noted that this study refers only to an acute setting and therefore these results could not be simply translated on a chronic setting. Supportive data of a similar sensitivity and specificity of the mPDAI when compared with the PDAI in the setting of chronic pouchitis was provided, however this analysis was done only using data from this study. Therefore, although the concordance of PDAI and mPDAI scores in this study is relevant, the result could not be used to validate these tools. The primary evaluation for induction of efficacy was set at week 14 which is considered acceptable; evaluation of duration of efficacy was set at week 34, four weeks after the last dose of vedolizumab. From data coming from the study is not possible to gain information on when treatment could be stopped or when retreatment could be considered. The MAH addressed the point of stopping treatment (i.e. if no evidence of therapeutic benefit is observed by 14 weeks of treatment) but did not provide data on potential retreatment. SmPC was updated to reflect this information which is acceptable.

The assumptions made for the sample size calculation raised concerns. The original sample size was based on the observed remission rate in GEMINI 1 study conducted in subjects with moderate to severe UC (200 patients). However, since pouchitis is different from UC a new assessment using published data [Ferrante 2010, Barreiro-de Acosta 2012] was made (Amendment 3 of the Study Protocol), and the sample size was redefined (total of 98 evaluable subjects were required to provide 80% power to detect a 25% difference in clinical remission rates between placebo (15%) and vedolizumab (40%) at the 2-sided significance level of 0.05). However, the placebo rate does not seem to be supported by the two proposed published studies since both of them are retrospective uncontrolled studies; moreover, the average rate of clinical remission with infliximab from those studies (32% and 21%) could not be considered as the expected difference from placebo. The MAH justified the sample size calculation by assuming the optimistic (compared with infliximab) mPDAI remission rate at W14 of 40% for vedolizumab in conjunction with the conservative assumption of a high placebo remission rate of 15%, and therefore a treatment difference of 25% for vedolizumab relative to placebo. Although this treatment difference was not achieved in the results of Study Vedolizumab-4004 (placebo around 10% and vedolizumab around 31%) the treatment effect estimate, that can be considered around 20%, was statistically significant and confirmed by several sensitivity analyses.

Methodological aspects: the primary analysis was conducted on FAS population under the ITT principle. The study was powered for the difference in the primary estimand, and the analysis of the two populations (chronic and recurrent pouchitis) for the primary estimand was considered as sensitivity analysis. Therefore, the analysis does not follow the EMA guideline on covariates (EMA/CHMP/295050/2013) by omitting stratification variables. No multiplicity adjustment for inferential testing of the secondary and exploratory endpoints was considered; therefore, p-values were presented as nominal p-values only. In order to rely on more robust data, the MAH has provided new analyses that takes into account for multiple testing on the main secondary endpoints. The hybrid approach for handling missing data was questioned, and results after imputing missing data as LOCF or as non-responder have been presented separately as well as a jump-to-reference imputation with tipping point analysis; these analyses were also applied to the main secondary endpoints for which sensitivity analyses have been performed. Considering the analysis applied for secondary endpoints looking at Change from baseline as in PDAI endoscopic subscore, in PDAI histologic subscore, and in Total PDAI score, an analysis of covariance (ANCOVA) model was considered more appropriate and has been performed using the baseline score as covariate, and including the treatment and the

stratification stratum as explicative factors. Analysis of Time-To-Event Endpoints showing the Kaplan-Meier curves including the Log-rank test results to assess the difference between active treatment and placebo was performed.

One hundred and sixty-five patients with chronic or recurrent pouchitis were screened and a total of 102 eligible patients were randomised, treated and included in the FAS; 51 of them received vedolizumab 300mg IV. Patient's disposition was generally balanced across the study. However, it should be noted that a relevant number of patients discontinued the treatment (vedolizumab n= 15, placebo n= 19); the main reasons were: lack of efficacy, voluntary withdrawal and PTE/AE (pre-treatment event/adverse event). Moreover, due to a relevant number of major protocol violations (including missing w14 mPDAI values), the PPS included only 38 patients in the placebo arm and 43 patients in the vedolizumab arm. The enrolment sites across EU were adequately represented.

Two most substantial amendments occurred, namely the change of the primary endpoint from PDAI to mPDAI clinical remission and the reduction of the sample size from 200 to 110 subjects. These changes occurred early during study conduct, the MAH has specified that a total of 19 of 102 subjects (18.6%) have been enrolled before implementation of PA3; 9 of 102 subjects (8.8%) had completed their W14 assessments before PA3. Concerning the change of the inclusion criteria in the PA3 8 subjects (5 placebo, 3 vedolizumab) would not satisfy either the modified definition for chronic or recurrent (subsequently classified as recurrent). There was a high rate of significant protocol deviations: 39 subjects (38.2 %) had at least 1 study-specific significant protocol deviation (20 and 19 subjects in the placebo and vedolizumab IV groups, respectively). The most frequently reported were: concomitant medications in 11 subjects (21.6%) in each group; and procedure not performed per protocol in 10 subjects (19.6% placebo group) and 4 subjects (7.8% vedolizumab), respectively.

Overall, the majority of subjects (68.6%) were male, mean age 41.9 years, most of them with ≥7 years from IPAA likely representing a population that could suffer from idiopathic chronic pouchitis. Subject were randomized by type of pouchitis with an equal distribution 1:1. During the blind data review the definitions were revisited and therefore the pouchitis was classified as chronic in 49.0% of patients in the placebo arm and in 56.9% in the vedolizumab arm; accordingly, recurrent pouchitis was present in 51.0% of placebo and 43.1% of vedolizumab arm patients. To better characterize the population included in the study the MAH was asked to provide the duration of the disease i.e. time since pouchitis diagnosis for both subgroups however this information was not collected. Moreover, according to the Pouchitis Related Baseline Characteristics, ten patients were classified as recurrent pouchitis, although having only 1 or 2 episodes of pouchitis in the last 12 months. Satisfactory clarification of this issue was provided.

Disease activity: the mean baseline total mPDAI score was 8.0 (SD = 1.68): 62% of subjects had a moderately active disease (baseline score between 5 and 8) and 36.3% as severely active (score of 9 to 12); and 2 subjects had an mPDAI score <5 (excluded from the PPS). The distribution of subjects between treatment groups was similar. Looking at PDAI the mean value was 10.5 (SD 2.33) and 80% had moderate (7-12) and 18% severe (13-18) activity according to score system. Therefore, the majority of enrolled population had moderately active disease and the claimed indication has been revised to reflect the setting investigated and the characteristics of patients.

Considering PDAI clinical criteria the majority of subjects had 3 or more stools/day > postoperative usual, presented fecal urgency or abdominal cramps but remarkably most of them presented no/rare rectal bleeding and no fever. Considering the endoscopic inflammation PDAI criteria, these were present in most of the study subjects although data on granularity and mucus exudates are missing. Considering the acute histologic inflammation PDAI criteria, PMNL infiltration was moderate in the 56.4% and severe in the 21.8% of the study population, well balanced between two groups; instead, the mild infiltration was present in more subjects in the placebo group (21.6%) than in the

vedolizumab group (16%); the percentage of subjects being histologically ulcer free at baseline was 68.0% in the vedolizumab group and 64.7% in the placebo group. When pouchitis is diagnosed endoscopically, histological evidence of acute inflammation is invariably present [Tytgat, 1988].

Considering prior anti-TNF medications history for pouchitis, around one third of the study population was anti-TNF naïve (both pre- and post-colectomy) and only 27.5% of patients were treated with anti-TNF therapy post-colectomy. According to the previous response to antibiotic therapy around 15% of patients reported inadequate response for each type of antibiotics while only 3% each reported loss of response; the intolerance was not reported and the majority of patients reported "other" as a reason for discontinuation of antibiotic therapy. The claimed indication was revised excluding patients who were intolerant to antibiotic therapy. Even if the concomitant antibiotic therapy was not permitted until the end of the W14, it should be noted that 22.2% patients in the vedolizumab group (10 of 45 patients) and 20.0% in the placebo group (8 of 40 patients) were receiving concomitant antibiotic therapy at W14. Furthermore, there were more patients in the vedolizumab arm (7 of 33, 21.2%) than in the placebo arm (4 of 32, 12.5%) receiving the concomitant antibiotic therapy at W34. This deviation is taken into account by the sensitivity analysis with concomitant antibiotic therapy. Considering the importance of concomitant antibiotic therapy particularly for patients with recurrent pouchitis, the MAH has provided the rate of use of concomitant antibiotics by type of pouchitis, at W14 and W34 timepoints for both arms showing that a greater proportion of subjects in the VDZ group were administered concomitant antibiotics as compared with the PBO group. This trend was consistent in each of the 2 pouchitis subgroups however could be more relevant for the recurrent type. Only a minority of patients (more in the placebo arm (8 patients (15.7%)) than in the vedolizumab arm (5 patients (9.8%)) had concomitant use of corticosteroids at baseline. There was some difference between concomitant corticosteroid use rate at D1 (13.7% in the placebo and 7.8% in the vedolizumab group).

Efficacy data and additional analyses

Primary endpoint: a statistically significant higher proportion of patients in the vedolizumab IV 300mg group reached mPDAI remission at week 14 in comparison to the placebo group (31.4% vs 9.8% respectively), with a treatment difference of 21.6% (95% CI: 4.9, 37.5) p=0.013 on FAS analysis. The observed effect size does not support the planned difference of 25% between vedolizumab and placebo raising concerns on the clinical relevance of vedolizumab effect. Moreover, the effect size on the primary estimand appears different between chronic (15.6%, 95% CI -5.1, 36.2) and recurrent pouchitis (28.7%, 95% CI 6.1, 51.2) and wide confidence intervals were detected. From a clinical perspective a smaller effect size could be expected in subjects with chronic antibiotic refractory pouchitis with a more difficult to treat disease and from a methodological perspective small sample size of the subgroups is seen as a limitation.

Based on the predefined randomization scheme and on the results of the primary endpoint showing different effects per type of pouchitis, the FAS analysis of the primary estimand using the Chi-squared test was not considered methodologically adequate and the MAH was asked to focus the analysis on stratified analyses using the CMH test on the primary and main secondary outcomes including the Breslow-Day test to assess differences between chronic and recurrent pouchitis. Moreover, the imputation approach for the primary estimand including imputing missing data both as LOCF and non-responder was considered suboptimal and a more comprehensive approach had been requested i.e. imputing missing data as non-responders comprehensive and a jump-to-reference imputation with tipping point analysis at least; however, other suitable methods could be proposed in addition.

From a regulatory perspective in view of the criteria to be fulfilled in case of one pivotal trial, the lack of internal consistency between these pre-specified sub-populations was seen as concern overall

questioning the generalizability of the benefit/risk to both subpopulations. To support the homogeneity of vedolizumab effect between strata the MAH provided results of CMH test including level of significance. Although a higher treatment effect was detected among recurrent as compared to chronic pouchitis patients, differences were not statistically significant. However, given the limited dataset and the small size of subgroups, the absence of a significant difference between the subpopulations could not be seen as conclusive on the comparability of the treatment effect.

To justify the vedolizumab benefit for the claimed indication the MAH provided further analyses: these analyses confirmed a treatment difference for mPDAI remission of around 21% (statistically significant) at week 14 (primary endpoint), and of around 17-18% (statistically significant for the primary analysis) at week 34.

The effect was confirmed for sustained mPDAI remission (20-21%), mPDAI response at week 14 (25%), PDAI remission at week 14 (24%), and sustained PDAI remission (23%); conversely, treatment difference for mPDAI response at week 34 (15-16%) and PDAI remission at week 34 (17-18%) were not statistically significant. Therefore, results confirmed a significant effect of vedolizumab on the primary estimand (mPDAI remission at week 14) as well as on the secondary endpoints mPDAI response week 14, sustained mPDAI remission, PDAI remission week 14, sustained PDAI remission.

The MAH was asked to substantiate the clinical efficacy of vedolizumab in respect of clinical symptoms and endoscopic evaluation. A comprehensive discussion of the expected clinical differences between the subpopulations was not performed but the chronic pouchitis population was considered as an unique population differentiated between the two pouchitis groups by only referring to 'the pattern of antibiotic usage'. Furthermore, the MAH did not discuss supportive evidence from published/literature data on vedolizumab benefit for the treatment of both pouchitis subtypes. Effect was mainly driven by endoscopic subscore (see below).

The primary analysis is supported by results from two sensitivity analyses (LOCF and hybrid approach), while PPS analysis (delta 19.4, 95% CI 0.4, 37.4, p=0.064) and that accounting for concomitant use of antibiotics before week 14 (delta 15.7, 95% CI 0.7, 31.4, p=0.067) did not reach the statistical significance. Therefore, treatment with a concomitant antibiotic (excluding ciprofloxacin as companion) positively affected vedolizumab efficacy.

The analysis of mPDAI clinical remission at W14 in some pre-defined subgroups showed inconsistent results, although the small sample size and the wide CI hamper any firm conclusion. Better results on mPDAI clinical remission at W14 were observed in the subgroup of severely active disease (difference of 22.2, 95% CI 2.3, 47.6) as compared to the moderate one (difference 18.2, 95% CI -3.9, 39.3); similar trend was seen at week 34 with an increased difference in treatment effect between groups (28.1 versus 8.6, respectively). It seems also that vedolizumab acts better for subgroups anti-TNF not used post-colectomy (vs anti-TNF failure) but also for anti-TNF experienced (UC or pouchitis) (vs anti-TNF naïve).

The MAH clarified that in more than two-thirds of patients in the study the anti-TNF were not used for pouchitis (75.9% in chronic stratum and 68.8% in recurrent stratum). Among patients naïve to anti-TNF for pouchitis, mPDAI remission and PDAI remission treatment effects at W14 were higher in the recurrent compared to chronic subgroup. The same trend was seen at W34 only with mPDAI remission endpoint. In the small subgroup of patients with anti-TNF failure for pouchitis a heterogeneous response was seen between the two pouchitis subtypes and also at the two timepoints (W14 and W34), so no conclusion can be drawn.

Different **secondary endpoints**, not controlled for multiplicity, were selected by MAH.

Secondary endpoints: mPDAI remission rate was a secondary endpoint when measured at W34. At this longer time point a smaller difference in mPDAI remission rate was seen from placebo (delta of 17, CI 0.3-35, p=0.043) therefore showing a slight decrease up to 8 months (34 weeks) but overall the effect was maintained. Sensitivity analyses are supportive of this result however, as per week 14 endpoint, PPS analysis was not (p=0.112). Remission rates at week 14 and 34 (both secondary endpoints) as measured by PDAI were consistent with the rates measured by using the mPDAI score, providing some reassurance on the use of mPDAI. Same figure is seen for the sensitivity analyses. Results on PDAI clinical remission at W14 and week 34 on severe/moderate subgroup seem to have the same trend of those seen using mPDAI score but the very limited sample size (and very wide CI) somewhat hamper conclusions. Partial mPDAI response at W14 and W34 also showed better results with vedolizumab with a treatment difference of 29.4% and 21.6%, respectively; supported by the sensitivity analyses (except for Concomitant Antibiotic sensitivity analysis at W14 and PPS at W34). No difference between the placebo and vedolizumab groups were observed for mPDAI clinical remission, as well as for PDAI remission, in patients with baseline PMNL none/mild. A revised indication statement clarifying that vedolizumab is intended for use in patients with moderately to severely active chronic pouchitis has been added which addresses the issue.

As reported in the methods section, in order to rely on more robust data, the MAH was asked to perform a new analysis that accounts for multiple testing on the main secondary endpoints. Applying more conservative approaches like Bonferroni and Bonferroni stepdown (Holm), 4 of the 7 endpoints remain significant (PDAI remission W14, mPDAI response W14, Sustained mPDAI remission, and Sustained PDAI remission), whereas endpoints evaluated at week 34 (mPDAI remission, PDAI remission, mPDAI response) became not significant, in line with the jump-to-reference analysis, the further sensitivity analyses required and reported above. In the results of 2 other multiple testing approaches requested (Hochberg and Hommel), the p-values remained significant (<0.05) across all 7 variables.

Results from the composite Total PDAI score (change from baseline) favoured vedolizumab at W14 (nominal p=0.025), however when the different PDAI domains were analysed, only the endoscopic subscore at week 14 showed a greater treatment difference in the vedolizumab group (not seen at week 34) therefore implying that results on the total score are mainly driven by the endoscopic subscore. An analysis of covariance (ANCOVA) model has been requested on these results confirming that only for total PDAI and Endoscopic Inflammation scores the treatment effect was statistically significant.

Importantly, results on QoL endpoints (IBDQ and CGQL) do not clearly support vedolizumab effect over placebo questioning the benefits of vedolizumab as perceived by the patients.

Results by type of pouchitis from available secondary endpoints i.e. mPDAI 34 week, PDAI remission as well as in the partial mPDAI response at week 14 and 34 confirm those seen for the primary endpoint showing a greater response difference for vedolizumab over placebo group in the recurrent pouchitis group as compared to the chronic one.

Exploratory endpoints: some selected endpoints evaluate histologic (RHI), endoscopic (SES-CD) scores other than PDAI score. The results of histologic endpoint (RHI) and endoscopic ulcer endpoints (number, surface, SES-CD) showed better results with vedolizumab compared to placebo.

Of importance, results related to sustained mPDAI and PDAI remission (both at W14 and W34), clinically relevant endpoints, support a benefit of vedolizumab over placebo with a difference of 21.6 pp (95% CI 6.5, 37.0) for sustained mPDAI remission and 23.5 pp (95% CI 8.0, 38.8) for sustained PDAI remission, therefore supporting a maintenance of the effect in terms of disease activity control

with a clinically mindful effect size over placebo. However, a multiplicity analysis was performed confirming the robustness of the results.

On the other hand, the biomarkers showed little (FC) or no improvement (CRP) with vedolizumab compared to placebo, not supporting their use as useful clinical measures of vedolizumab response.

Time to relapse, as well as number of relapses, could be considered as an important endpoint for both types of pouchitis; however, the analysis found only a modest difference between the rates with vedolizumab (31.3%) and placebo (40%). The MAH has provided the Kaplan-Meier curves for time to relapse, both for overall population and for the subgroups of subjects classified as having recurrent or chronic pouchitis, these were not statistically significant between vedolizumab and placebo.

Although the composite scores mPDAI and PDAI show better results with vedolizumab compared with placebo, analysis of change in PDAI components compared to baseline are inconsistent and total scores seems to be mainly driven by endoscopic subscore, raising concerns about the clinical relevance of the observed effect. The MAH has discussed the different pattern of ulceration seen at PDAI endoscopic (present at baseline in the 70.6% of placebo arm and 78.4% of vedolizumab arm) and PDAI histologic assessment (absent at baseline in 68.0% in the vedolizumab group and 64.7% in the placebo) concluding that the endoscopic evaluation represents the true level of ulceration in the pouch and that the difference in pattern of ulceration between endoscopic and histologic assessment is secondary to targeting biopsies at inflamed mucosa rather than at sites of ulceration. The endoscopic subscore drives the effect. Moreover, the baseline values for granularity and mucus exudates within the endoscopic subscore of PDAI have been provided.

The clinical relevance of these results, considering that the current EMA GL highlights that clinically relevant effects in each of the main components of the PDAI score (symptoms as well as macro- and microscopic appearance of mucosa) is not supported by all components of the score but the endoscopic one is regarded as objective and clinically important.

A favourable effect of vedolizumab seems to be exerted on corticosteroid-free mPDAI remission and corticosteroid-free PDAI remission rates at 14 week, the same figure is not seen at a longer time point (week 34) and it is referred to a small subset of subjects taking concomitant corticosteroids treatment at baseline (7.8% in the vedolizumab group and 13.7% in the placebo group on Day 1) making an specific claim not possible.

2.4.3. Conclusions on the clinical efficacy

The use of vedolizumab for the treatment of pouchitis is sufficiently supported by available evidence and analyses as the estimand strategy provide confirmatory evidence of efficacy.

2.5. Clinical safety

Introduction

The safety evaluation of vedolizumab focuses on the analysis of safety results from Study Vedolizumab-4004 to establish whether the safety profile in pouchitis is similar to that observed in subjects with ulcerative cholitis (UC) and Crohn's disease (CD). The safety data from Study Vedolizumab-4004 are supported by the extensive safety profile of vedolizumab IV through an Integrated Summary of Safety (ISS) which includes phase 3 completed clinical studies in subjects with moderately to severely active UC or CD previously submitted to support marketing applications for these indication targets. This provides a comparison of safety between pouchitis and inflammatory

bowel disease (IBD) populations. Indeed, this submission is to support a new pouchitis indication and references combined safety data with vedolizumab IV in subjects with moderately to severely active UC or CD as previously provided in an ISS prepared in 2013.

Study Vedolizumab-4004 (EARNEST)

Study Vedolizumab-4004 (EARNEST) was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of vedolizumab IV 300 mg over a 34-week treatment period (with the last dose at Week 30) in subjects who had a proctocolectomy and IPAA for UC, who had developed chronic or recurrent pouchitis. To participate in the study, adult subjects were required to have active pouchitis that inadequately responded to antibiotics; these subjects were randomized into treatment groups (vedolizumab IV 300 mg or placebo IV) based on pouchitis classification (chronic or recurrent).

To date, Study Vedolizumab-4004 is the only placebo-controlled clinical study to evaluate the safety of vedolizumab IV in subjects with pouchitis. Efficacy endpoints included assessments of clinical remission, clinical response, quality of life, and improvement in clinical symptoms, endoscopic appearance, and pouch histopathology.

The dosing and administration regimen of vedolizumab IV was consistent with that approved in the vedolizumab IV label for patients with UC and CD. Randomized subjects received study drug (vedolizumab IV 300 mg or placebo IV) at Weeks 0, 2, 6, 14, 22, and 30. Final efficacy assessments were measured 4 weeks after the last study dose at Week 34 (W34), with a final safety follow-up visit at Week 48 (W48), 18 weeks after the last dose of study drug. All subjects were expected to complete a long-term follow-up safety survey by telephone, 26 weeks after the last dose of study drug.

Integrated Summary of Safety (ISS)

The ISS presents an analysis of safety experience in 3326 subjects, i.e., 1279 subjects with UC; 1850 subjects with CD; and 197 healthy subjects, who received at least 1 dose of vedolizumab IV. Of the total number of subjects in this analysis, 903 subjects, with either UC or CD, received ≥24 infusions with 4 weeks of follow-up, and 415 received ≥36 infusions with 4 weeks of follow-up. The focus of this ISS was the analysis of safety from the vedolizumab IV phase 3 program, which consisted of 3 completed studies (Studies C13006, C13007, and C13011), in addition to interim data from an uncontrolled open-label extension (OLE) safety study (Study C13008):

- Study C13006 was a pivotal, phase 3 study that demonstrated induction and maintenance efficacy of vedolizumab IV in the treatment of subjects with active UC. Subjects from the induction phase who achieved a clinical response at Week 6 were randomized to receive vedolizumab IV 300 mg every 4 weeks (Q4W) or every 8 weeks (Q8W), or placebo Q4W starting at Week 6 and ending at Week 52.

- Study C13007 was a pivotal, phase 3 study that demonstrated induction and maintenance efficacy of vedolizumab IV in the treatment of subjects with active CD. Subjects from the induction phase who achieved a clinical response at Week 6 were randomized to receive vedolizumab IV 300 mg Q4W or Q8W, or placebo Q4W starting at Week 6 and ending at Week 52.

- Study C13011 was a phase 3, randomized, placebo-controlled, blinded, multicenter study of the induction of clinical response and remission by vedolizumab IV in subjects with moderate to severe CD with prior failure of tumor necrosis factor alpha (TNF-α) antagonists.

- Study C13008 was an open-label, single-arm, long-term extension study where subjects were administered vedolizumab IV 300 mg Q4W to evaluate long-term safety and efficacy in subjects with UC or CD who rolled over from phase 3 studies C13006, C13007, and C13011 (including rollover from

phase 2 studies C13002 and C13004 and de novo subjects). C13008 data contained in the ISS are from the interim clinical study report (CSR) (dated 14 March 2013) completed 4 years after study start. Cumulative adverse event (AE) and exposure data of this safety report are included from the final C13008 CSR (>8 years of vedolizumab IV exposure).

The safety data from the phase 3 studies in the ISS (C13006 and C13007) and the OLE study (C13008) referenced in this safety evaluation (to provide context and aid the review of new safety data from Study Vedolizumab-4004) focuses specifically on the combined vedolizumab groups (Q4W and Q8W). The combined vedolizumab group includes subjects who responded to vedolizumab induction treatment and were randomized to receive double-blind vedolizumab Q4W or Q8W dosing in the maintenance phase; subjects who did not respond to vedolizumab induction treatment were assigned to open label vedolizumab Q4W dosing in the maintenance phase. This latter group provides important information on safety in subjects who may not respond initially to induction treatment but continue with vedolizumab treatment as they may respond with additional dosing. Thus, the combined vedolizumab group represents the range of subjects with moderately to severely active disease who may be administered vedolizumab in the clinic.

Because vedolizumab IV is approved for use as a chronic treatment for UC and CD, the safety report makes specific reference to the safety data from Study C13006, and the combined safety data from Studies C13006 and C13007 presented in the ISS. In addition, this report makes specific reference to the safety data from the final CSR for OLE Study C13008.

The established safety profile from the vedolizumab IV clinical program is reflected in approved product labeling for Entyvio (vedolizumab) for IV infusion. Since the launch of Entyvio (vedolizumab) for IV infusion, cumulative worldwide exposure (as of 31 March 2021) was approximately 722,703 patient-years, with no new major safety issues identified to date from the postmarketing data (Risk Management Plan, Version 7.0). The postmarketing safety data was consistent with that summarized in the ISS.

Patient exposure

Vedolizumab-4004

Per protocol, 6 IV infusions of study drug (vedolizumab IV 300 mg or placebo IV) were planned for all randomized subjects at Weeks 0, 2, 6, 14, 22, and 30. The duration of study drug exposure was calculated as the total number of days on study drug (date of last dose - date of first dose + 1). For vedolizumab, the calculated duration of exposure accounts for 5 times the half-life of vedolizumab and, therefore, includes an additional 126 days (date of last dose - date of first dose + 1 + 126).

All 6 planned infusions were administered to 32 of 51 subjects (62.7%) in the placebo group and 36 of 51 subjects (70.6%) in the vedolizumab group. Of those subjects, 1 subject in the vedolizumab group was reported to have had 1 incomplete infusion at Week 2. Among subjects who received fewer than 6 infusions, all study drug infusions were complete.

The mean (SD) duration of exposure was 157.6 (76.43) days in the placebo group and 297.0 (69.80) days in the vedolizumab group, which accounted for the established vedolizumab half life. The maximum duration of exposure to vedolizumab was ≥48 weeks in 30 subjects (58.8%). In the placebo group, 31 subjects (60.8%) were reported with a duration of exposure between 24 to <32 weeks, which included the planned duration of 30 weeks.

Table 12.a Study Drug Exposure (SAF)

	Placebo IV (N = 51)	Vedolizumab IV 300 mg (N = 51)
Subject who received a total of 6 IV infusions, n (%)	32 (62.7)	36 (70.6)
Subjects who received any incomplete infusions n([%]) [a]	0	1 (2.0)
Total vedolizumab dose received during study duration (mg)		
n	0	51
Mean (SD)	- (-)	1564.7 (412.71)
Median	-	1800.0
Minimum, maximum	-, -	300, 1800
Duration of exposure (days) [b]		
Mean (SD)	157.6 (76.43)	297.0 (69.80)
Median	210.0	337.0
Minimum, maximum	13, 225	127, 351
Duration of exposure (categorized) (n[%]) [a]		
<20 Weeks	17 (33.3)	2 (3.9)
20 to <24 Weeks	2 (3.9)	0
24 to <32 Weeks	31 (60.8)	8 (15.7)
32 to <40 Weeks	1 (2.0)	3 (5.9)
40 to <48 Weeks	0	8 (15.7)
≥48 Weeks	0	30 (58.8)

Source: Table 15.1.14.1.

IV: intravenous; SAF: safety analysis set.

[a] Percentages are based on the total number of subjects in the SAF (per column).

[b] Duration of exposure to vedolizumab IV is defined as date of last dose – date of first dose + 1 + 126 to account for 5*half-life of vedolizumab and duration of exposure to placebo is defined as date of last dose – date of first dose + 1.

Reference IBD Studies

The ISS presents an analysis of safety experience in 1434 subjects (620 subjects with UC and 814 subjects with CD) who were administered vedolizumab IV 300 mg for up to a total of 52 weeks in the phase 3 studies, C13006 and C13007. The final CSR of Study C13008 presents an analysis of safety experience in 2243 subjects (894 subjects with UC and 1349 subjects with CD) who were administered vedolizumab IV 300 mg in OLE Study C13008 (C13008 final CSR).

In the combined vedolizumab groups of Study C13006 and C13007, 287 subjects and 312 subjects, respectively, completed all 14 planned infusions of vedolizumab IV in each study (ISS). In the final CSR of Study C13008, of the 2243 total subjects, 1350 (60%) completed ≥24 infusions (2 years of exposure), with a similar percentage of subjects with UC or CD (64% and 58%, respectively); more than half (52%) completed ≥36 infusions (3 years of exposure); and one-fourth (25%) completed ≥72 infusions (6 years of exposure). Five subjects (<1%) with UC received ≥116 infusions (≥9.5 years of exposure) (C13008 Final CSR).

The mean exposure (SD) to vedolizumab was 258.5 (117.98) and 246.8 (112.42) in Study C13006 and C13007, respectively (ISS), and 1174.9 (887.57) days in Study C13008 (C13008 Final CSR). The reported duration of exposure takes the vedolizumab half-life into account.

Demographic and Other Characteristics of Study Population

Disposition and Baseline Demographics

A total of 102 subjects were randomized into Study Vedolizumab-4004 with even distribution to the placebo and vedolizumab-treated groups (51 subjects in each group). Overall, the baseline demographics were similar for subjects in the 2 treatment groups. The majority of subjects (70 subjects [68.6%]) were male, 34 subjects (61.8%) were aged 35 to <65 years, and 86 subjects (87.8%) were white and 9 subjects (9.2%) were Asian. The means of weight and calculated body mass index were similar between treatment groups. Smoking, considered a risk factor for pouchitis, was reported in a total of 11 subjects (10.8%).

Baseline Disease Characteristics

Based on case report form (CRF)-reported data, 54 subjects (52.9%) were classified as having chronic pouchitis and 48 subjects (47.1%) as having recurrent pouchitis.

Subjects were also required to have undergone proctocolectomy and IPAA that was completed at least 12 months before the first dose of study drug. In the SAF, a mean of 11.5 years (range: 1.5 to 32.3 years) had elapsed from IPAA to enrollment, with 65 subjects (63.7%) having ≥7 years since IPAA, 27 subjects (26.5%), 3 to <7 years; and 10 subjects (9.8%), 1 to <3 years. The distribution of subjects was similar between vedolizumab and placebo-treated groups in each category.

The distribution of subjects with anti-TNF exposure (pre- and postcolectomy), and reasons for anti-TNF failures postcolectomy, were well-balanced across treatment groups.

Adverse events

The Table below reports an overview of TEAEs in Study Vedolizumab-4004.

Table 3.a Overview of TEAEs, Including Serious TEAEs (Vedolizumab-4004 SAF)

	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
	#Events	Subjects n (%)	#Events	Subjects n (%)	#Events	Subjects n (%)
TEAEs	171	44 (86.3)	191	47 (92.2)	362	91 (89.2)
Mild	98	11 (21.6)	120	15 (29.4)	218	26 (25.5)
Moderate	64	28 (54.9)	68	29 (56.9)	132	57 (55.9)
Severe	9	5 (9.8)	3	3 (5.9)	12	8 (7.8)
Related	19	11 (21.6)	17	12 (23.5)	36	23 (22.5)
Not related	152	33 (64.7)	174	35 (68.6)	326	68 (66.7)
Leading to study drug Discontinuation	5	5 (9.8)	1	1 (2.0)	6	6 (5.9)
Serious TEAEs	4	4 (7.8)	3	3 (5.9)	7	7 (6.9)
Related	1	1 (2.0)	0	0	1	1 (1.0)
Not related	3	3 (5.9)	3	3 (5.9)	6	6 (5.9)
Leading to study drug Discontinuation	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Source: Vedolizumab-4004 Table 15.3.1.1.1.

AE: adverse event; IV: intravenous; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

A TEAE is defined as an AE where date of onset occurs after first dose of study drug up to end of follow-up (18 weeks after last dose).

Number of events = number of TEAEs reported per class/term and TEAE attribute (intensity/relationship to study drug/leading to discontinuation). Subjects = number of subjects with a TEAE per class/term and highest TEAE attribute level reported; a subject is counted only once within a class/term with the most severe intensity or highest reported relationship.

Percentages are based on the total number of subjects in the SAF for each treatment group.

The summary table below reports a comparison of the TEAE overview between UC/CD and pouchitis.

Table 3.b Overall Summary of AEs and SAEs for UC, CD, and Pouchitis (SAF)

	C13006	C13006 and C13007	C13008	Vedolizumab-4004
Adverse Event Category, n (%)	UC [a] Vedolizumab IV N = 620	Combined UC/CD [b] Vedolizumab IV N = 1434	Combined UC/CD [c] Vedolizumab IV N = 2243	Pouchitis Vedolizumab IV N = 51
Any AE	497 (80)	1203 (84)	2125 (95)	47 (92)
Drug-related AE	200 (32)	517 (36)	978 (44)	12 (24)
AE resulting in study discontinuation	36 (6)	127 (9)	366 (16)	1 (2)
Serious AE	77 (12)	276 (19)	825 (37)	3 (6)
Serious infection AE	12 (2)	57 (4)	207 (9)	1 (2)
Drug-related serious AE	13 (2)	48 (3)	116 (5)	0
Serious AE resulting in study discontinuation	16 (3)	75 (5)	213 (9)	0
Deaths	1 (<1)	5 (<1)	10 (<1)	0

Source: Vedolizumab-4004 Table 15.3.1.1.1 and Table 15.3.1.1.12; C13006 Table 14.4.1.1M; ISS Table 18.2.2.1A; C13008 Final Table 14.4.1.1.

AE: adverse event; CD: Crohn's disease; IV: intravenous; OLE: open-label extension; Q4W: every 4 weeks; Q8W: every 8 weeks; SAE: serious adverse event; SAF: safety analysis set; UC: ulcerative colitis.

[a] UC safety population who received vedolizumab IV (Q4W and Q8W) during the induction and maintenance phase of the study.

[b] Combined UC/CD safety population from Study C13006 and C13007 who received vedolizumab IV (Q4W and Q8W) during the induction and maintenance phase of the studies.

[c] Combined UC/CD safety population in OLE Study C13008 (Final) who received vedolizumab IV (Q4W) during the study. Includes >8 years of cumulative AE data from previous rollover studies and AEs from Study C13008.

To account for the different subject durations on-study, and therefore, different durations of exposure to study drug, exposure-adjusted analysis rates for AE incidence were calculated for Study Vedolizumab-4004 and C13008.

Table 3.c Exposure-Adjusted Incidence Rates for Vedolizumab IV 300 mg in UC, CD, and Pouchitis (SAF)

	C13008 [a]				Vedolizumab-4004	
	UC Vedolizumab IV N = 894		CD Vedolizumab IV N = 1349		Pouchitis Vedolizumab IV N = 51	
Mean (SD) duration of exposure (days)	1278 (913.3)		1107 (863.7)		297 (69.8)	
	# Subjects	IR	# Subjects	IR	# Subjects	IR
Subjects with at least 1 AE	829	1220	1296	1799	47	1133
Subjects with at least 1 SAE	277	91	548	147	3	72

Source: Vedolizumab-4004 Table 15.3.1.1.3 and Table 15.3.1.1.11; C13008 Final Table 14.1.1.11B, Table 14.4.1.26A, and Table 14.4.1.26C.

AE: adverse event; CD: Crohn's disease; IR: exposure-adjusted incidence per 1000 subject years; IV: intravenous; SAE: serious adverse event; UC: ulcerative colitis.

Exposure adjusted incidence rates in Study Vedolizumab-4004 were originally derived per 100 subject years and have been converted to per 1000 subject years.

Exposure adjusted incidence rates were not reported for Study C13006 and C13007.

[a] Study C13008 Final includes >8 years of cumulative exposure and AE data from previous rollover studies and Study C13008.

Common AEs

The Table below reports an overall summary of TEAEs by SOC in the Study Vedolizumab-4004.

Table 12.d Overall Summary of TEAEs by SOC (SAF)

SOC	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
	#Events	Subjects n(%)	#Events	Subjects n(%)	#Events	Subjects n(%)
Subjects with any TEAE	**171**	**44 (86.3)**	**191**	**47 (92.2)**	**362**	**91 (89.2)**
Gastrointestinal disorders	54	32 (62.7)	67	36 (70.6)	121	68 (66.7)
Infections and infestations	26	15 (29.4)	41	24 (47.1)	67	39 (38.2)
Musculoskeletal and connective tissue disorders	25	15 (29.4)	17	12 (23.5)	42	27 (26.5)
Nervous system disorders	7	5 (9.8)	17	15 (29.4)	24	20 (19.6)
General disorders and administration site conditions	9	7 (13.7)	8	7 (13.7)	17	14 (13.7)
Investigations	10	7 (13.7)	7	5 (9.8)	17	12 (11.8)
Respiratory, thoracic and mediastinal disorders	9	6 (11.8)	3	3 (5.9)	12	9 (8.8)
Metabolism and nutrition disorders	6	5 (9.8)	3	3 (5.9)	9	8 (7.8)
Skin and subcutaneous tissue disorders	4	4 (7.8)	4	4 (7.8)	8	8 (7.8)
Injury, poisoning and procedural complications	3	2 (3.9)	8	5 (9.8)	11	7 (6.9)
Eye disorders	1	1 (2.0)	6	5 (9.8)	7	6 (5.9)
Psychiatric disorders	5	5 (9.8)	1	1 (2.0)	6	6 (5.9)
Blood and lymphatic system disorders	1	1 (2.0)	4	4 (7.8)	5	5 (4.9)
Renal and urinary disorders	5	3 (5.9)	1	1 (2.0)	6	4 (3.9)
Vascular disorders	2	2 (3.9)	1	1 (2.0)	3	3 (2.9)
Hepatobiliary disorders	1	1 (2.0)	1	1 (2.0)	2	2 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2 (3.9)	0	0	2	2 (2.0)
Cardiac disorders	0	0	1	1 (2.0)	1	1 (1.0)
Endocrine disorders	1	1 (2.0)	0	0	1	1 (1.0)
Pregnancy, puerperium and perinatal conditions	0	0	1	1 (2.0)	1	1 (1.0)

Source: Table 15.3.1.1.2.1.

AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

A TEAE is defined as an AE where date of onset occurred after first dose of study drug up to end of follow-up (18 weeks after last dose).

Subjects with more than 1 TEAE within a MedDRA level are counted only once in that level.

Percentages are based on the total number of subjects in the SAF for each treatment group.

MedDRA Version 23.0 was used for coding AEs.

The Table below reports the most frequent (≥5%) PT in the Study Vedolizumab-4004.

Table 3.d Most Frequent TEAEs (≥5% in Any Treatment Group) by PT (Vedolizumab-4004 SAF)

	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
PT	#Events	Subjects n (%)	#Events	Subjects n (%)	#Events	Subjects n (%)
Subjects with any most frequent TEAE	74	36 (70.6)	88	42 (82.4)	162	78 (76.5)
Pouchitis	25	20 (39.2)	33	24 (47.1)	58	44 (43.1)
Arthralgia	11	9 (17.6)	7	7 (13.7)	18	16 (15.7)
Headache	4	3 (5.9)	11	10 (19.6)	15	13 (12.7)
Nasopharyngitis	9	6 (11.8)	9	6 (11.8)	18	12 (11.8)
Nausea	6	5 (9.8)	5	5 (9.8)	11	10 (9.8)
Abdominal pain	3	3 (5.9)	5	4 (7.8)	8	7 (6.9)
Back pain	5	5 (9.8)	2	2 (3.9)	7	7 (6.9)
Frequent bowel movements	2	2 (3.9)	5	4 (7.8)	7	6 (5.9)
Upper respiratory tract infection	1	1 (2.0)	5	5 (9.8)	6	6 (5.9)
Gastroenteritis	3	3 (5.9)	2	2 (3.9)	5	5 (4.9)
Influenza	1	1 (2.0)	4	4 (7.8)	5	5 (4.9)
Dyspnoea	4	3 (5.9)	0	0	4	3 (2.9)

Source: Vedolizumab-4004 Table 15.3.1.1.4.

AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.

A TEAE is defined as an AE where date of onset occurs after first dose of study drug up to end of follow-up (18 weeks after last dose).

Only TEAEs with an incidence rate of at least 5% in any treatment group are shown.

Subjects with more than 1 TEAE within a MedDRA PT level are counted only once in that level.

Percentages are based on the total number of subjects in the SAF for each treatment group.

PTs are sorted in decreasing frequency based on the total number of subjects with TEAEs.

MedDRA Dictionary (Version 23.0) was used for coding AEs.

As showed by the Table below, the most frequent TEAEs reported in the vedolizumab group in Study Vedolizumab-4004 are overall consistent with the known vedolizumab IV safety profile established in subjects with IBD or are related to the underlying disease of pouchitis.

Table 3.e Most Frequent TEAEs With Vedolizumab IV (≥4% in Study Vedolizumab-4004) by PT in Subjects With UC, CD, and Pouchitis (SAF)

	C13006		C13006 and C13007		C13008		Vedolizumab-4004	
	UC [a] Vedolizumab IV		Combined UC/CD [b] Vedolizumab IV		Combined UC/CD [c] Vedolizumab IV		Pouchitis Vedolizumab IV	
PT	#Events	Subjects n (%)	#Events	Subjects n (%)	Events [d]	Subjects n (%)	Events	Subjects n (%)
Subjects with any most frequent AE	2388	497 (80)	6161	1203 (84)	-	2124 (95)	88	42 (82.4)
Pouchitis	-	-	-	-	-	-	33	24 (47)
Headache	151	80 (13)	287	177 (12)	-	454 (20)	11	10 (20)
Arthralgia	65	56 (9)	210	166 (12)	-	484 (22)	7	7 (14)
Nasopharyngitis	108	80 (13)	232	180 (13)	-	594 (26)	9	6 (12)
Nausea	55	38 (6)	175	128 (9)	-	336 (15)	5	5 (10)
Upper respiratory tract infection	72	52 (8)	134	106 (7)	-	379 (17)	5	5 (10)
Abdominal pain	43	35 (6)	148	114 (8)	-	420 (19)	5	4 (8)
Frequent bowel movements	-	-	-	-	-	-	5	4 (8)
Influenza	33	30 (5)	54	51 (4)	-	210 (9)	4	4 (8)
Gastroenteritis	22	19 (3)	38	35 (2)	-	229 (10)	2	2 (4)
Back pain	27	24 (4)	65	62 (4)	-	241 (11)	2	2 (4)

Source: Vedolizumab-4004 Table 15.3.1.1.4; ISS Table 18.2.2.2A, Table 18.2.2.5A, and Table 18.2.2.3B; C13008 Final Table 14.4.1.3.

AE: adverse event; CD: Crohn's disease; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; OLE: open-label extension; PT: Preferred Term; Q4W: every 4 weeks; Q8W: every 8 weeks; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event; UC: ulcerative colitis.

Only TEAEs with an incidence rate of at least 5% in Study Vedolizumab-4004 are shown.

Subjects with more than one TEAE within a MedDRA PT level are counted only once in that level.

[a] UC safety population who received vedolizumab IV (Q4W and Q8W) during the induction and maintenance phase of the study.

[b] Combined UC/CD safety population from Studies C13006 and C13007 who received vedolizumab IV (Q4W and Q8W) during the induction and maintenance phase of the studies.

[c] Combined UC/CD safety population in OLE Study C13008 (Final) who received vedolizumab IV (Q4W) during the study. Includes >8 years of cumulative AE data from previous rollover studies and AEs from Study C13008.

[d] Number of events not reported in Study C13008.

Intensity of AEs

The majority of TEAEs in Study Vedolizumab-4004 were considered by the investigator to be mild to moderate in intensity (see the Table below).

Table 12.f Summary of TEAEs and Drug-Related TEAEs by Intensity (SAF)

	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
PT	#Events	Subjects n(%)	#Events	Subjects n(%)	#Events	Subjects n(%)
Subjects with any TEAE						
Mild	98	11 (21.6)	120	15 (29.4)	218	26 (25.5)
Moderate	64	28 (54.9)	68	29 (56.0)	132	57 (55.9)
Severe	9	5 (9.8)	3	3 (5.9)	12	8 (7.8)
Overall	171	44 (86.3)	191	47 (92.2)	362	91 (89.2)
Subjects with any drug-related TEAE						
Mild	10	6 (11.8)	12	8 (15.7)	22	14 (13.7)
Moderate	7	3 (5.9)	5	4 (7.8)	12	7 (6.9)
Severe	2	2 (3.9)	0	0	2	2 (2.0)
Overall	19	11 (21.6)	17	12 (23.5)	36	23 (22.5)

Source: Table 15.3.1.1.7 and Table 15.3.1.1.8.

AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

A TEAE is defined as an AE where date of onset occurred after first dose of study drug up to end of follow-up (18 weeks after last dose).

Number of events = number of TEAEs reported per class/term and intensity. Subjects = number of subjects with TEAE per class/term and most severe intensity; a subject is counted only once within a class/term with the most severe intensity.

Percentages are based on the total number of subjects in the SAF for each treatment group.

MedDRA Version 23.0 was used for coding AEs.

The Table below reports a summary of severe AEs by the different indications and studies.

Table 3.f Summary of Severe AEs: UC, CD, and Pouchitis (SAF)

	C13006	C13006 and C13007	C13008	Vedolizumab-4004
AE Category, n (%)	UC [a] Vedolizumab IV N = 620	UC/CD Combined [b] Vedolizumab IV N = 1434	UC/CD Combined [c] Vedolizumab IV N = 2243	Pouchitis Vedolizumab IV N = 51
Subjects with at least 1 severe AE	64 (10)	219 (15)	630 (28)	3 (6)

Source: Vedolizumab-4004 Table 15.3.1.1.7; C13006 Table 14.4.2.5M; ISS Table 18.2.2.4; C13008 Final Table 14.4.1.12.

AE: adverse event; CD: Crohn's disease; IV: intravenous; Q4W: every 4 weeks; Q8W: every 8 weeks; SAF: safety analysis set; UC: ulcerative colitis.

[a] UC safety population who received vedolizumab IV (Q4W and Q8W) during the induction and maintenance phase of the study.

[b] Combined UC/CD safety population from Studies C13006 and C13007 who received vedolizumab IV (Q4W and Q8W) during the induction and maintenance phase of the studies.

[c] Combined UC/CD safety population in Study C13008 (Final) who received vedolizumab IV (Q4W) during the study. Includes >8 years of cumulative AE data from previous rollover studies and AEs from Study C13008.

Drug-related AEs

The Table below reports the drug-related TEAEs (≥2.0% of subjects) by treatment group in Study Vedolizumab-4004.

Table 12.g Drug-Related TEAEs Reported in ≥2.0% Subjects in any Treatment Group (SAF)

	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
SOC PT	#Events	Subjects n(%)	#Events	Subjects n(%)	#Events	Subjects n(%)
Subjects with any drug-related TEAE	19	11 (21.6)	17	12 (23.5)	36	23 (22.5)
Infections and infestations	4	4 (7.8)	11	8 (15.7)	15	12 (11.8)
Nasopharyngitis	1	1 (2.0)	3	3 (5.9)	4	4 (3.9)
Upper respiratory tract infection	0	0	2	2 (3.9)	2	2 (2.0)
Gastrointestinal disorders	2	2 (3.9)	1	1 (2.0)	3	3 (2.9)
Pouchitis	2	2 (3.9)	1	1 (2.0)	3	3 (2.9)
Musculoskeletal and connective tissue disorders	3	3 (5.9)	0	0	3	3 (2.9)
Arthralgia	2	2 (3.9)	0	0	2	2 (2.0)

Source: Table 15.3.1.1.6.

AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

A TEAE is defined as an AE where date of onset occurred after first dose of study drug up to end of follow-up (18 weeks after last dose).

Subjects with more than 1 TEAE within a MedDRA level are counted only once in that level.

Percentages are based on the total number of subjects in the SAF for each treatment group.

SOCs and PTs are sorted in decreasing frequency based on the total number of subjects with TEAEs.

MedDRA Version 23.0 was used for coding AEs.

AESIs

In Study Vedolizumab-4004, AESI categories were predefined in the protocol based on the mechanism of action of vedolizumab and the known safety profile. The 5 AESI categories are hypersensitivity reactions including IRRs, PML, liver injury, malignancies, and serious infections.

The Table below reports the AESIs by SOC and PT.

Table 12.h All AESIs by SOC and PT (SAF)

SOC	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
PT	#Events	Subjects n(%)	#Events	Subjects n(%)	#Events	Subjects n(%)
Subjects with any AESI	10	7 (13.7)	6	5 (9.8)	16	12 (11.8)
Hypersensitivity reactions including IRRs	**3**	**2 (3.9)**	**4**	**3 (5.9)**	**7**	**5 (4.9)**
Gastrointestinal disorders	0	0	1	1 (2.0)	1	1 (1.0)
Mouth ulceration	0	0	1	1 (2.0)	1	1 (1.0)
General disorders and administration site conditions	2	2 (3.9)	1	1 (2.0)	3	3 (2.9)
Swelling	1	1 (2.0)	0	0	1	1 (1.0)
Oedema peripheral	1	1 (2.0)	0	0	1	1 (1.0)
Chest discomfort	0	0	1	1 (2.0)	1	1 (1.0)
Renal and urinary disorders	0	0	1	1 (2.0)	1	1 (1.0)
Acute kidney injury	0	0	1	1 (2.0)	1	1 (1.0)
Respiratory, thoracic and mediastinal disorders	1	1 (2.0)	0	0	1	1 (1.0)
Obstructive airways disorder	1	1 (2.0)	0	0	1	1 (1.0)
Vascular disorders	0	0	1	1 (2.0)	1	1 (1.0)
Flushing	0	0	1	1 (2.0)	1	1 (1.0)
Liver Injury	**5**	**3 (5.9)**	**1**	**1 (2.0)**	**6**	**4 (3.9)**
Investigations	5	3 (5.9)	1	1 (2.0)	6	4 (3.9)
Gamma-glutamyltransferase increased	2	2 (3.9)	0	0	2	2 (2.0)
Alanine aminotransferase increased	1	1 (2.0)	0	0	1	1 (1.0)
Aspartate aminotransferase increased	1	1 (2.0)	0	0	1	1 (1.0)
Hepatic enzyme increased	0	0	1	1 (2.0)	1	1 (1.0)
Liver function test increased	1	1 (2.0)	0	0	1	1 (1.0)
Malignancies	**2**	**2 (3.9)**	**0**	**0**	**2**	**2 (2.0)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2 (3.9)	0	0	2	2 (2.0)
Benign neoplasm of testis	1	1 (2.0)	0	0	1	1 (1.0)
Basal cell carcinoma	1	1 (2.0)	0	0	1	1 (1.0)
Serious Infections	**0**	**0**	**1**	**1 (2.0)**	**1**	**1 (1.0)**
Infections and infestations	0	0	1	1 (2.0)	1	1 (1.0)
Gastroenteritis	0	0	1	1 (2.0)	1	1 (1.0)

Source: Table 15.3.1.1.12.

AE: adverse event; AESI: adverse event of special interest; IRR: infusion-related reaction; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.

An AESI is defined as an AE of scientific and medical concern specific to the program or compound.

Subjects with more than 1 AESI within a MedDRA level are counted only once in that level.

Percentages are based on the total number of subjects in the SAF for each treatment group.

SOCs are sorted using alphabetical order and PTs are sorted in decreasing frequency based on the total number of subjects with AEs.

MedDRA Version 23.0 was used for coding AEs.

Hypersensitivity Reactions, including Infusion-Related Reactions

As with any biologic therapy, there exists the potential for infusion-related or hypersensitivity like reactions. Hypersensitivity reactions, including IRRs, were reported in 2 subjects (3.9%) in the placebo group and 3 subjects (5.9%) in the vedolizumab group. All events in this AESI category were considered by the investigator to be not related to study drug, with the exception of 1 subject in the vedolizumab group who experienced a related AESI of chest discomfort and recovered on the same day. The event was considered by the investigator to be mild in intensity, and the subject completed the study. There were no events specifically reported as IRRs.

Liver Injury

Liver injury AESIs were reported in 3 subjects (5.9%) in the placebo group and 1 subject (2.0%) in the vedolizumab group. One subject in the placebo-treated group experienced 3 related AESIs: increased aspartate aminotransferase increased, alanine aminotransferase increased, and gamma glutamyl transferase increased. The events began after the subject had stopped study drug. In each case, the events were moderate in intensity; however, the events had not resolved at the time of the subject's

last study visit. The AESI of hepatic enzyme increase in 1 subject in the vedolizumab treated group was assessed to be mild in intensity, and the subject recovered from the event during the study.

Malignancies

Two subjects (3.9%) in the placebo group (and none in the vedolizumab group) had AESIs of malignancy, including basal cell carcinoma and benign neoplasm of testis. The event of basal cell carcinoma began >30 days posttreatment. The event was considered to be an SAE. The subject had a previous medical history of basal cell carcinoma. The event of benign neoplasm of testis occurred >30 days posttreatment. The subject recovered from the event, and the investigator considered the event to be unrelated to study drug and mild in intensity. The subject discontinued study drug due to a separate drug-related TEAE of insomnia.

Serious Infections

One subject (2.0%) in the vedolizumab group (and none in the placebo group) experienced a serious infection AESI of gastroenteritis. The subject was hospitalized for observation and the event was reported as an SAE. The investigator considered the event to be not related to study drug and severe in intensity. The subject recovered from the event and completed the study.

PML

There were no cases of PML.

Summary of AESIs

Overall, there were no apparent trends or events that were of clinical concern among the AESIs reported in subjects with pouchitis. AESIs were consistent with those previously reported in the ISS in subjects with IBD.

Exposure-Adjusted AEs

Because AE rates are influenced by subject duration on study, exposure-adjusted analyses were performed to adjust for differences in overall exposure between treatment groups. Rates of AEs were expressed in terms of exposure-adjusted incidence rates (e.g., per 100 subject-years) to accommodate variable subject follow-up time. Incidence rates in both vedolizumab and placebo groups were similar (113.3 and 111.1 per 100 subject-years, respectively).

TEAEs Related to a Flare

The Table below reports an overview of TEAEs related to a flare in Study Vedolizumab-4004.

Table 3.i Overview of TEAEs and Serious TEAEs Related to a Flare of Pouchitis (Vedolizumab-4004 SAF)

	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
	#Events	Subjects n(%)	#Events	Subjects n(%)	#Events	Subjects n(%)
Treatment-emergent flare AE	32	24 (47.1)	51	29 (56.9)	83	53 (52.0)
Mild	7	4 (7.8)	22	13 (25.5)	29	17 (16.7)
Moderate	23	18 (35.3)	27	14 (27.5)	50	32 (31.4)
Severe	2	2 (3.9)	2	2 (3.9)	4	4 (3.9)
Related	3	3 (5.9)	1	1 (2.0)	4	4 (3.9)
Not related	29	21 (41.2)	50	28 (54.9)	79	49 (48.0)
Leading to study drug discontinuation	2	2 (3.9)	1	1 (2.0)	3	3 (2.9)
Serious treatment-emergent flare AE	1	1 (2.0)	2	2 (3.9)	3	3 (2.9)
Related	1	1 (2.0)	0	0	1	1 (1.0)
Not related	0	0	2	2 (3.9)	2	2 (2.0)
Leading to study drug discontinuation	0	0	0	0	0	0

Source: Vedolizumab-4004 Table 15.3.1.2.1.

AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

A TEAE is defined as an AE where date of onset occurred after first dose of study drug up to end of follow-up (18 weeks after last dose).

Number of events = number of TEAEs reported per class/term and intensity. Subjects = number of subjects with TEAE per class/term and most severe intensity; a subject is counted only once within a class/term with the most severe intensity.

Percentages are based on the total number of subjects in the SAF for each treatment group.

TEAEs related to a flare refer to any AE related to worsening of pouchitis.

MedDRA Version 23.0 was used for coding AEs.

In Study Vedolizumab 4004, at least 1 TEAE related to a pouchitis flare was reported in 24 subjects (47.1%) in the placebo group and 29 subjects (56.9%) in the vedolizumab group. Pouchitis was the most frequently reported PT related to a flare, reported in 19 subjects (37.3%) in the placebo group and 24 subjects (47.1%) in the vedolizumab group.

A total of 53 subjects reported a total of 83 TEAE events related to a flare, the majority of which (79 events [95.2%]) were reported to be mild or moderate in intensity. TEAEs related to a flare that were considered by the investigator to be severe in intensity were reported in 4 subjects, with 2 in each treatment group.

A higher percentage of TEAEs related to a flare (specifically with PT of pouchitis) were reported in subjects in the vedolizumab group. An in-depth review of the TEAEs related to a flare showed that multiple episodes of pouchitis in a given subject was also higher in the vedolizumab group. One subject in the vedolizumab group had 5 episodes of pouchitis, 1 subject had 3 episodes, and 3 subjects had 2 episodes each, whereas, in the placebo group, only 1 subject experienced 3 episodes of pouchitis and no subjects experienced >3 episodes. Among events reported in the vedolizumab group, 2 were considered severe, 1 event was considered treatment-related, and 1 event led to discontinuation of treatment. Approximately half of the pouchitis events in the vedolizumab group occurred before Week 14, and 6 events occurred after W34. No specific trends were observed between the time of treatment and onset of the event or the duration of the event.

TEAEs related to a flare that were considered to be related to study drug were reported in 3 subjects (5.9%) in the placebo group and 1 subject (2.0%) in the vedolizumab group. One TEAE related to flare and related to study drug was reported in a. placebo-treated subject as an SAE and is described further in the SAE section. The other TEAEs related to flare and considered study drug related are briefly described as follows:

- A TEAE of pouchitis in a placebo-treated subject began on Day 33 and was assessed as related to treatment. The subject withdrew from the study on Day 142 and the outcome of the. event was unknown.

- A TEAE of arthralgia in a placebo-treated subject began on Day 3 and was assessed as related to treatment and severe in intensity. The subject discontinued study drug on Day 17 as. a result of the TEAE and recovered from the event on Day 61. The subject's last visit occurred on Day 150.

- A TEAE of pouchitis in a vedolizumab-treated subject began on Day 44 and was assessed as related to treatment and moderate in intensity. The subject recovered from the event on Day 47 and the subject completed the study on Day 332.

TEAEs related to a flare that led to study drug discontinuation were reported in 2 subjects (3.9%) in the placebo group and 1 subject (2.0%) in the vedolizumab group.

Serious adverse event/deaths/other significant events

SAEs

SAEs in Study Vedolizumab-4004 are presented by SOC and PT in the Table below.

Table 3.g Serious TEAEs in Pouchitis by SOC and PT (Vedolizumab-4004 SAF)

SOC	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
PT	#Events	Subjects n (%)	#Events	Subjects n (%)	#Events	Subjects n (%)
Subjects with any serious TEAE	4	4 (7.8)	3	3 (5.9)	7	7 (6.9)
Gastrointestinal disorders	3	3 (5.9)	2	2 (3.9)	5	5 (4.9)
Abdominal pain	1	1 (2.0)	0	0	1	1 (1.0)
Pouchitis	1	1 (2.0)	2	2 (3.9)	3	3 (2.9)
Intestinal obstruction	1	1 (2.0)	0	0	1	1 (1.0)
Infections and infestations	0	0	1	1 (2.0)	1	1 (1.0)
Gastroenteritis	0	0	1	1 (2.0)	1	1 (1.0)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1	1 (2.0)	0	0	1	1 (1.0)
Basal cell carcinoma	1	1 (2.0)	0	0	1	1 (1.0)

Source: Vedolizumab-4004 Table 15.3.1.1.10.1.
AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAF: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
A TEAE was defined as an AE where date of onset occurred after first dose of study drug up to end of follow-up (18 weeks after last dose).
Subjects with more than one serious TEAE within a MedDRA level are counted only once in that level.
Percentages are based on the total number of subjects in the SAF for each treatment group.
SOC terms are sorted using alphabetical order and PTs are sorted in decreasing frequency based on the total number of subjects with AEs.
MedDRA Dictionary (Version 23.0) was used for coding AEs.

Exposure-adjusted SAEs

The incidence rate of SAEs was reported as 7.2 per 100 subject-years in the vedolizumab group and 10.1 per 100 subject-years in the placebo group. Pouchitis was reported as 4.8 per 100 subject-years in the vedolizumab group and 2.5 per 100 subject-years in the placebo group.

SAEs Related to a Flare

SAEs related to a flare are presented in the Table below.

Table 15.3.1.2.6
Serious Treatment-Emergent Adverse Events Related to a Flare by System Organ Class, High Level Term and Preferred Term
Safety Analysis Set

System Organ Class High Level Term Preferred Term	Placebo IV (N=51)		Vedolizumab IV 300 mg (N=51)		Total (N=102)	
	#Events	Subjects n(%)	#Events	Subjects n(%)	#Events	Subjects n(%)
Subjects with Any Serious TEAE Related to a Flare	1	1 (2.0)	2	2 (3.9)	3	3 (2.9)
Gastrointestinal disorders	1	1 (2.0)	2	2 (3.9)	3	3 (2.9)
Gastrointestinal inflammatory disorders NEC	1	1 (2.0)	2	2 (3.9)	3	3 (2.9)
Pouchitis	1	1 (2.0)	2	2 (3.9)	3	3 (2.9)

Note 1: A treatment-emergent adverse event (TEAE) is defined as an adverse event where date of onset occurs after first dose of study drug up to end of follow-up (18 weeks after last dose).
Note 2: Subjects with more than one serious TEAE related to Flare within a MedDRA level are counted only once in that level.
Note 3: Percentages are based on the total number of subjects in the safety analysis set for each treatment group.
Note 4: System organ classes and high level terms are sorted using alphabetical order and preferred terms are sorted in decreasing frequency based on the total number of subjects with AEs.
Note 5: Adverse events related to a flare refer to any adverse event related to worsening of pouchitis.
Note 6: MedDRA Dictionary (Version 23.0) was used for coding adverse events.

Serious PTEs

One subject (2.0%) in the placebo group experienced a serious PTE (pre-treatment events) of pyrexia before administration of study drug. The event was considered by the investigator to be related to a pouchitis flare and was described as being severe in intensity. The subject recovered from the event prior to first administration of study drug.

Deaths

No deaths occurred in Study Vedolizumab-4004.

Laboratory findings

No clinically significant changes in clinical laboratory parameters were noted in Study Vedolizumab-4004.

Serum chemistry

No clinically significant differences between the treatment groups in mean changes from baseline at any time point were observed for any chemistry parameter.

Hematology

No clinically significant differences between the treatment groups in mean changes from baseline at any time point were observed for any hematology parameter.

Urinalysis

No clinically significant differences between the treatment groups in mean changes from baseline at any time point were observed for any urinalysis parameter.

Individual Clinically Significant Abnormalities

A laboratory value was considered markedly abnormal if it met the predefined criteria. Few subjects met the criteria for a marked laboratory abnormality. The most common marked laboratory abnormality was high GGT. During treatment, high GGT was observed in 5 subjects (9.8%) in the placebo group and 3 subjects (5.9%) in the vedolizumab group. No apparent clinically significant trends were observed.

Vital signs

No clinically significant findings were noted regarding mean changes from baseline in vital signs, including blood pressure, pulse rate, respiratory rate, temperature, and body weight.

Immunogenicity

Immunogenicity was not specifically evaluated in Study Vedolizumab-4004. Antibodies to vedolizumab may develop during vedolizumab treatment, most of which are neutralizing. IRRs after vedolizumab infusion have been reported in subjects with anti-vedolizumab antibodies. The immunogenicity of vedolizumab IV has been evaluated in patients with IBD; the immunogenicity profile is reflected in the approved product labeling for Entyvio (vedolizumab) for IV infusion.

Safety in special populations

Safety in special groups and situations was not specifically studied.

Use in Pregnancy and Lactation

The safety of vedolizumab in pregnant or lactating women has not been evaluated in clinical studies.

In Study Vedolizumab-4004, one subject in the vedolizumab group experienced a pregnancy during the study, which was confirmed by a urine test on Day 197. On the same day, the subject underwent an elective termination and recovered from the event on Day 200. The subject completed the study on Day 346.

Overdose

No information on overdose became available during the clinical development of vedolizumab IV. There were no reports of overdose in the clinical study setting.

Drug Abuse

The potential for abuse and dependence with vedolizumab has not been evaluated in clinical studies. There were no reports of abuse in the clinical study setting.

Withdrawal and Rebound

The potential for AEs related to withdrawal and rebound was not assessed.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No specific data were collected during clinical development to assess the impact of vedolizumab on the ability to drive or operate machinery or impairment of mental ability.

Safety related to drug-drug interactions and other interactions

No specific interaction or pharmacokinetic studies have been performed in patients with pouchitis. In Study Vedolizumab-4004 vedolizumab has been co-administered with antibiotics. The pharmacokinetics of vedolizumab is expected to be similar to that in patients with moderate to severely active ulcerative colitis or Crohn’s disease. Sections 4.5 and 5.2 of the SmPC have been updated accordingly

Discontinuation due to adverse events

The Table below reports the TEAEs leading to discontinuation by SOC and PT in Study Vedolizumab-4004.

Table 3.h TEAEs Leading to Study Drug Discontinuation by SOC and PT (Vedolizumab-4004 SAF)

SOC	Placebo IV (N = 51)		Vedolizumab IV 300 mg (N = 51)		Total (N = 102)	
PT	#Events	Subjects n (%)	#Events	Subjects n (%)	#Events	Subjects n (%)
Subjects with any TEAE leading to study drug discontinuation	5	5 (9.8)	1	1 (2.0)	6	6 (5.9)
Gastrointestinal disorders	2	2 (3.9)	1	1 (2.0)	3	3 (2.9)
Crohn's disease	1	1 (2.0)	0	0	1	1 (1.0)
Pouchitis	1	1 (2.0)	1	1 (2.0)	2	2 (2.0)
Infections and infestations	1	1 (2.0)	0	0	1	1 (1.0)
Epstein-Barr virus infection reactivation	1	1 (2.0)	0	0	1	1 (1.0)
Musculoskeletal and connective tissue disorders	1	1 (2.0)	0	0	1	1 (1.0)
Arthralgia	1	1 (2.0)	0	0	1	1 (1.0)
Psychiatric disorders	1	1 (2.0)	0	0	1	1 (1.0)
Insomnia	1	1 (2.0)	0	0	1	1 (1.0)

Source: Vedolizumab-4004 Table 15.3.1.1.9.1.
AE: adverse event; IV: intravenous; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAF: safety analysis set; SOC: system organ class; TEAE: treatment-emergent adverse event.
A TEAE was defined as an AE where date of onset occurs after first dose of study drug up to end of follow-up (18 weeks after last dose).
Subjects with more than one TEAE leading to study drug discontinuation within a MedDRA level are counted only once in that level.
Percentages are based on the total number of subjects in the SAF for each treatment group.
SOC terms are sorted using alphabetical order and PTs are sorted in decreasing frequency based on the total number of subjects with AEs.
MedDRA Dictionary (Version 23.0) was used for coding AEs.

Post marketing experience

Vedolizumab has been marketed since 2014 and is approved for UC and CD in over 70 countries. Since the launch of Entyvio (vedolizumab) for IV infusion, cumulative worldwide patient exposure as of 31 March 2021 was approximately 722,703 patient-years and no new major safety issues have been identified to date from the postmarketing data (Risk Management Plan, Version 7.0)

The MAH stated that i) the safety of vedolizumab has been well-characterized from postmarketing data; the recent periodic benefit-risk evaluation report (PBRER) did not identify any new safety concerns, and the safety data was found to be consistent with the known safety profile of the drug. ii) There were no new trends or changes in clinical importance seen for IRRs, infections, malignancies, or hepatic events, and no cases of PML were reported. iii) The current risk mitigation measures provide sufficient information to allow for the safe use of vedolizumab. iv) In addition, ongoing studies will provide additional information to further characterize risks and address missing information. v) The safety profile of vedolizumab is well established, and the overall benefit-risk profile for vedolizumab continues to remain positive. vi) Literature searches revealed no significant safety findings associated with vedolizumab IV in patients with pouchitis.

2.5.1. Discussion on clinical safety

The safety evaluation of vedolizumab is based on data obtained from Study Vedolizumab-4004 (the randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of

vedolizumab IV 300 mg over a 34-week treatment period in subjects who had a proctocolectomy and IPAA for ulcerative cholitis [UC], who had developed chronic or recurrent pouchitis) and supported by the Integrated Safety of Summary (ISS) which includes phase 3 completed clinical studies (Studies C13006, C13007, and C13011) in subjects with moderately to severely active UC or Chron's Disease (CD) previously submitted for the marketing applications for these indication targets. In addition, interim data (dated 14 March 2013) from an uncontrolled open-label extension (OLE) safety study (Study C13008), including subjects with UC or CD who rolled over from phase 3 studies C13006, C13007, and C13011, were taken into account.

This safety dataset is considered acceptable and appropriate, because it provides a comparison of safety between pouchitis and inflammatory bowel disease (IBD) populations to establish whether the safety profile in subjects with pouchitis is similar to that observed in subjects with UC and CD.

Besides the patients enrolled in Study Vedolizumab-4004, the ISS presents an analysis of safety experience in 3326 subjects, i.e., 1279 subjects with UC; 1850 subjects with CD; and 197 healthy subjects, who received at least 1 dose of vedolizumab IV. Of the total number of subjects in this analysis, 903 subjects, with either UC or CD, received ≥24 infusions with 4 weeks of follow-up, and 415 received ≥36 infusions with 4 weeks of follow-up.

IV infusion of study drug was completed in 36 of 51 subjects (70.6%) in the vedolizumab group. One subject in the vedolizumab group received an incomplete infusion. However, the safety data from Study Vedolizumab-4004 are supported by phase 3 completed clinical studies in subjects with moderately to severely active UC or CD previously submitted to support marketing applications for these indications.

Therefore, the overall size of the safety database can be considered sufficient for the assessment and adequate for regulatory purposes.

Exposure

In the Vedolizumab-4004 Study, overall, the treatment with all 6 IV infusion of study drug (vedolizumab IV 300 mg or placebo IV) at Week 0, 2, 6, 14, 22, and 30) were administered to 36/51 (70.6%) subjects in the vedolizumab group and 32/51 (62.7%) subjects in the placebo group (1 of the vedolizumab subjects had 1 incomplete infusion at Week 2).

The mean (SD) duration of exposure is considered adequate (297.0 [69.80] days [approximately 10 months in the vedolizumab group] and 157.6 [76.43] days [approximately 5 months] in the placebo group) and the majority of subjects (58.8%) had the maximum duration of exposure to vedolizumab (≥48 weeks).

Concerning the reference IBD studies as comparison, vedolizumab IV 300 mg for up a total of 52 weeks (approximately, 13 months) was administered to 1434 subjects (620 with UC and 814 with CD) in the phase studies C13006 and C13007 and 2243 subjects (894 with UC and 1349 with CD) in the OLE study C13008. In the OLE study C13008, 1350 subjects (60%) completed ≥24 infusions (2 years of exposure); 52% of subjects completed ≥36 infusions (3 years); 25% of subjects completed ≥72 infusions (6 years). Only 5 subjects (<1%) with UC received ≥116 infusions (≥9.5 years). The mean exposure (SD) to vedolizumab was 258.5 (117.98) (approximately 8.5 months) and 246.8 (112.42) (approximately 8 months) in Study C13006 and C13007, respectively (ISS) -therefore, comparable with the mean exposure to vedolizumab in Study Vedolizumab-4004-, and 1174.9 (887.57) days (approximately 39 months [i.e., around 3 years]) in Study C13008.

In Study Vedolizumab-4004, a total of 102 subjects (51 in vedolizumab and placebo groups each) were enrolled. ***Baseline and demographic characteristics*** were overall balanced between the two treatment groups. The mean (SD) age was 41.9 (12.44) years (40.8 years in the vedolizumab group vs. 42.9 years in the placebo group) with a range from 19 to 68 years. The majority of patients (61.8%)

was aged 25 to <65 years. 54 (approximately 53%) and 48 (approximately 47%) subjects were classified as having chronic and recurrent pouchitis, respectively. A mean of 11.5 years (range: 1.5 to 32.3 years) had elapsed from IPAA to enrollment. The distribution of subjects with anti-TNF exposure (pre- and postcolectomy), and reasons for anti-TNF failures postcolectomy, were overall balanced across treatment groups.

Adverse events

Overall, in Study Vedolizumab-4004, around 92% of patients treated with vedolizumab experienced at least 1 TEAEs compared with approximately 86% of subjects receiving placebo.

In the comparison with UC/CD patient populations, AEs of any type and severity were reported less frequently in the pouchitis group than in the UC study C13006, the combined UC/CD studies C13006 and C13007, and the combined UC/CD OLE study C13008 (drug-related AEs: 24% vs. 32%, 36%, and 44%, respectively; AEs leading to discontinuation: 2% vs. 6%, 9%, 16%; SAEs: 6% vs. 12%, 19%, 37%; serious infection AEs: 2% vs. 2%, 4%, 9%; drug-related SAEs: 0 vs. 2%, 3%, 5%; SAEs leading to discontinuation: 0 vs. 3%, 5%, 9%; deaths: 0 vs. <1% for the remaining groups).

No significant differences were observed when comparing the overall exposure-adjusted incidence rates between Study Vedolizumab-4004 and Study C13008.

Common AEs

The SOC with the higher frequency of TEAEs in the vedolizumab group compared with the placebo group were GI disorders (70.6% vs. 62.7%; with pouchitis being the most frequent AE in this SOC: 47.1% [n=24] vs. 39.2% [n=20]); Infections and Infestations (47.1% vs. 29.4%; with nasopharyngitis being the most frequently reported AE in this SOC: 6 subjects in each treatment group); Nervous system disorder (29.4% vs. 9.8%; with headache being the most frequent AE in this SOC: 19.6% [n=10] vs. 5.9% [n=3]); Injury, poisoning and procedural complications (9.8% vs. 3.9%); Eye disorders (9.8% vs. 2.0%); Blood and lymphatic system disorders (7.8% vs. 2.0%).

Overall, pouchitis (reported as related to a flare or worsening of pouchitis) was the most frequent TEAE occurring in a higher number of subjects (24, [47.1%]) in the vedolizumab group compared with the placebo group (20 subjects [39.2%]) suggesting a potential loss of efficacy. The other most frequent TEAEs in the vedolizumab group were (in order of frequency by the percentage of subjects who experienced the event): headache, arthralgia, nasopharyngitis, nausea, upper respiratory tract infection, influenza, frequent bowel movement, and abdominal pain.

TEAEs occurring more frequently with vedolizumab treatment as compared to placebo and occurring in at least ≥4% of subjects in the vedolizumab group (in order of frequency) were pouchitis -as mentioned above-, headache (19.6% [n=10] vs. 5.9% [n=3]), upper respiratory tract infection (9.8% [n=5] vs. 2.0% [n=1]), abdominal pain (7.8% vs. 5.9%), influenza (7.8% [n=4] vs. 2.0% [n=1]), and frequent bowel movements (7.8% [n=4] vs. 3.9% [n=2]).

Other AEs which occurred in the vedolizumab group in at least 2 subjects (3.9%) versus none in the placebo group were: anaemia, gastroesophageal reflux disease, rectal hemorrhage, musculoskeletal pain, asthenia, and chest discomfort (for all, 3.9% [n=2] vs. 0).

In the comparison with UC/CD patient populations, AEs of any type and severity were reported less frequently in the pouchitis group than in the UC study C13006, the combined UC/CD studies C13006 and C13007, and the combined UC/CD OLE study C1300. The overall summary of TEAEs by SOC in Vedolizumab-4004 were consistent with those presented in the ISS in subjects with IBD. As would be expected in subjects with pouchitis or IBD, GI disorders were the most frequently reported TEAEs.

Although in terms of most frequent AEs, the safety profile of vedolizumab in the pouchitis group is overall similar to that reported for the other indications, there are some TEAEs that occurred more frequently with vedolizumab treatment as compared to placebo such as abdominal pain and frequent bowel movements (with a difference of approximately 2% and 4%, respectively), which are not reported in the section 4.8 of the current SmPC. As requested, the MAH made a thorough review of the AEs abdominal pain and bowel movements. The difference in terms of absolute numbers between vedolizumab and placebo group was of 1 subject (4 vs. 3) for "abdominal pain" and of 2 subjects (4 vs. 2) for "bowel movements". Given the small number of patients included in the study even an apparent small difference can become clinically relevant; it is however acknowledged that all events in the vedolizumab group were reported as nonserious, mild or moderate in intensity, not considered related to study drug with the majority of them having a relatively short duration and resolving. Furthermore, most of the subjects with "abdominal pain" had also received multiple concomitant medications during the time of the event that could have contributed to abdominal pain. Regarding "bowel movements", all events in the vedolizumab group recovered in the timeframe from 4 to 66 days before the end of the study; furthermore, as for "abdominal pain", concomitant medications could have contributed to the event. Neither "abdominal pain" nor "bowel movements" led to treatment discontinuation. No significant differences in the observed clinical characteristics between subjects in either treatment groups were found. The MAH pointed out that these two symptoms could be related to the underlying disease (pouchitis), particularly because none of the subjects were in remission at the moment when these AEs occurred. This could be agreed. It is noted that other ADRs included in section 4.8 of the SmPC, particularly in the SOC Gastrointestinal disorders, can be due to the underlying diseases. PTs included in the ADR Table in section 4.8 of the SmPC under the SOC Grastrointestinal disorders, such as abdominal distension, dyspepsia, constipation, flatulence, can include abdominal pain and bowel movements as symptoms. In conclusion, given the above, the MAH did not consider that inclusion of abdominal pain and bowel movements in Section 4.8 of the SmPC was warranted as there was insufficient evidence to establish a strong causal association between the events and vedolizumab. Overall, this was agreed particularly due to the small difference in the incidence of these AEs between vedolizumab and placebo groups, the absence of remarkable differences in the characteristics of these AEs between the two treatment groups, and the multiple concomitant medications during the time of the event that could have contributed to their occurrence.

Other AEs which occurred in the vedolizumab group in at least 2 subjects (3.9%) versus none in the placebo group were: anaemia, gastroesophageal reflux disease, rectal hemorrhage, musculoskeletal pain, asthenia, and chest discomfort (for all, 3.9% [n=2] vs. 0). Therefore, for the above-mentioned AEs, the MAH was required to discuss whether they (or at least some of them) could be due to lack of efficacy and whether they should have been added in the ADR table of the 4.8 section of the SmPC. Based on the analyses made by the MAH, most of these events were mild or moderate in intensity, nonserious, recovered, did not lead to discontinuation, and were not considered related to study drug by the investigator. For some of these events (i.e., anaemia, gastroesophageal reflux disease, and musculoskeletal pain), a conclusion on the causal relationship with vedolizumab treatment cannot be drawn. For the remaining AEs: a) in the absence of confounding factors, the MAH was asked to include rectal hemorrhage AEs, which were not even associated with pouchitis events or the absence of remission status, in the ADR Table in section 4.8 of the SmPC; b) in the presence of a clear temporal relationship with IRR, asthenia and chest discomfort were requested to be included in the already existing list of signs and symptoms of infusion-related reactions reported under the SOC General disorders and administration site conditions in the table of section 4.8 and asthenia should have been included for consistency in the new text of the subsection "Infusion-related reactions" (see below the Discussion on the AESIs). The MAH agreed and implemented these changes to the PI.

In order to better understand the safety profile of vedolizumab in different subgroup populations, the MAH was asked to provide safety data in terms of AEs, AESIs, SAEs, drug-related AEs, AEs leading to discontinuation, stratified by: a) chronic vs. recurrent pouchitis; b) anti-TNFalfa naïve vs. experienced status, c) baseline clinical severity, d) concomitant use of antibiotics excluding ciprofloxacin as companion (first 4 weeks). Based on the data submitted by the MAH, given the small numbers, conclusions from these subgroup analyses are limited. More AEs occurred in subjects who were anti-TNF naïve, had severely active pouchitis at baseline, and who did not use any concomitant antibiotics before W34, with a higher frequency of SAE in the recurrent pouchitis subgroup compared with the chronic subgroup. However, no relevant difference vedolizumab and placebo arms were observed.

The majority of the AEs reported in the Vedolizumab-4004 Study was mild or moderate in intensity in both treatment groups (mild: vedolizumab 29.4% vs. placebo 21.6%; moderate: 56% vs. 54.9%). A lower proportion of vedolizumab-treated patients experienced a TEAE that was considered by the investigator to be severe in intensity (5.9% [n=3] vs. 9.8% [n=5] in the placebo group). Most severe TEAEs occurred in the GI disorders SOC (6 subjects, 5.9%) with pouchitis (reported as related to a flare or worsening of pouchitis) being the most common severe TEAE, reported in 1 subject (2.0%) in the placebo group and 2 subjects (3.9%) in the vedolizumab group, as mentioned above. The pouchitis event occurred in the placebo group was considered as a SAE and related to the study drug by the investigator while the 2 severe events of pouchitis occurred in the vedolizumab groups were not deemed to be drug-related and only 1 was considered to be a SAE.

Severe events reported in the IBD studies occurred only within the GI disorders SOC and included events of CD, abdominal pain, and colitis ulcerative.

Drug-related AEs

In Study Vedolizumab-4004, drug-related TEAEs were reported with a slightly higher frequency in the vedolizumab group compared with the placebo group (23.5% [n=12] vs. 21.6% [n=11]), in particular, in the SOC Infections and Infestations (15.7% [n=8] vs. 7.8% [n=4]). In this SOC, the following drug-related AEs occurred more frequently in the vedolizumab group: nasopharyngitis (5.9% [n=3] vs. 2.0% [n=1]), upper respiratory tract infection (3.9% [n=2] vs. 0). These AEs are already listed in the ADR Table of the SmPC section 4.8. The AEs of pouchitis were reported as drug-related in only 1 (2.0%) subject treated with vedolizumab and in 2 (3.9%) subjects receiving placebo.

The same was also observed in subjects with IBD, where the majority of drug-related AEs were reported within the SOC of infections and infestations (ISS).

AESIs

AESI categories were predefined in the protocol of Study Vedolizumab-4004, based on the mechanism of action of vedolizumab and the known safety profile. The 5 AESI categories are hypersensitivity reactions including IRRs, PML, liver injury, malignancies, and serious infections. A total of 16 AESI events were reported with a lower proportion in the vedolizumab group compared with the placebo group (9.8% [n=6] vs. 13.7% [n=10]), which is reassuring.

Most frequently reported AESIs were ***hypersensitivity reactions including IRRs*** that occurred in 3 subjects (5.9%) in the vedolizumab group and in 2 subjects (3.9%) in the placebo group. None of these events were specifically reported as IRRs. All events in this AESI category were considered by the investigator to be not related to study drug, with the exception of an event of chest discomfort, considered related to study drug and mild in intensity, that occurred in 1 subject in the vedolizumab group. The event occurred on Day 155 and was reported as recovered on the same day; the subject completed the study on Day 339.

Liver injury AESIs were reported in 1 subject (2.0%) in the vedolizumab group and in 3 subjects (5.9%) in the placebo group. The AESI of hepatic enzyme increase in 1 subject in the vedolizumab treated group was assessed to be mild in intensity, and the subject recovered from the event during the study.

AESIs of ***malignancies*** were reported in 2 subjects (3.9%) in the placebo group and in none in the vedolizumab group, including basal cell carcinoma and benign neoplasm of testis.

Regarding ***serious infections***, 1 subject (2.0%) in the vedolizumab group (and none in the placebo group) experienced a serious infection AESI of gastroenteritis. The subject was hospitalized for observation, recovered from the event and completed the study; the event was reported as a SAE and the investigator considered it to be not related to study drug and severe in intensity.

No cases of ***PML*** were reported.

It is acknowledged that, overall, there were no apparent trends or events that were of clinical concern among the AESIs reported in subjects with pouchitis treated with vedolizumab. AESIs seems to be consistent with those previously reported in the ISS in subjects with IBD. However, in the section 4.8 of the SmPC, the MAH was asked to update the paragraph on "Description of selected adverse reactions" with the specific results of the Study Vedolizumab-4004. As requested, the MAH agrees to the addition of AESI information from Study Vedolizumab-4004 to section 4.8 of the SmPC. New text has been added to the subsections "Infusion-related reactions" and "Infections". IRRs were reported in 3 subjects (5.9%) in the vedolizumab group and in 2 subjects (3.9%) in the placebo group. The individual PTs included mouth ulceration, swelling, oedema peripheral, chest discomfort, acute kidney injury, obstructive airway disorder and flushing. All events were mild to moderate in intensity, nonserious, did not lead to study discontinuation, and were considered not related to study drug by the investigator except for one event of chest discomfort. The wording of the new text can be considered acceptable, however, as mentioned above, there were 3 AEs of asthenia reported in 2 vedolizumab subjects occurred during drug infusions. Given the temporal relationship with the vedolizumab infusion in terms of onset and duration, the MAH pointed out that these events were most likely an infusion-related reaction consistent with the known ADR of vedolizumab. The causality is likely and, therefore, as mentioned above, the MAH agreed to include asthenia in the new text of the SmPC 4.8. subsection "Infusion-related reactions".

The new text in the subsection "Infections" can be considered acceptable outlining that a serious infection of AESI was reported in 1 subject (2.0%) in the vedolizumab group and in none in the placebo group. The subject was hospitalized and the event was severe in intensity, not considered related to study drug by the investigator, and recovered. The MAH specified that in Study Vedolizumab-4004 there was no trend of infections in relation to BMI and no higher risk of infections in patients who had prior exposure to TNF-alfa antagonist therapy. Therefore, the current statement in the SmPC is referred only to UC and CD studies and not to pouchitis. This is acceptable.

No changes were necessary for the text of the subsection "Malignancies".

Exposure-adjusted analyses were performed to adjust for differences in overall exposure between treatment groups. Overall, exposure-adjusted incidence rates in both vedolizumab and placebo groups were similar (113.3 and 111.1 per 100 subject-years, respectively). However, differences persisted between the treatment groups in terms of a higher incidence rates in the vedolizumab group compared with the placebo group of the following AEs: pouchitis (57.8 per 100 subject-years [n=24] vs. 50.5 per 100 subjects-years [n=20]), headache (24.1 [n=10] vs. 7.6 [n=3]), upper respiratory tract infection (12.0 [n=5] vs. 2.5 [n=1]), influenza and frequent bowel movements (for both, 9.6 [n=4] vs. 2.5 [n=1]), anaemia, gastroesophageal reflux disease, rectal hemorrhage, asthenia, chest discomfort, and musculoskeletal pain (for all, 4.8 [n=2] vs. 0). As reported above the MAH provided the requested

clarifications and included rectal hemorrhage, asthenia, chest discomfort in section 4.8 of the SmPC as requested.

TEAEs Related to a Flare

A total of 53 subjects reported 83 TEAE events related to a flare; as mentioned above, at least 1 TEAE related to a pouchitis flare was reported in a higher proportion of patients treated with vedolizumab than in the placebo group (56.9% [n=29] vs. 47.1% [n=24]). Pouchitis was the most frequently reported PT related to a flare and with a higher frequency in vedolizumab subjects (47.1% [n=24] vs. 37.3% [n=19] in the placebo group).

Multiple episodes of pouchitis in a given subject was also higher in the vedolizumab group. One subject in the vedolizumab group had 5 episodes of pouchitis, 1 subject had 3 episodes, and 3 subjects had 2 episodes each, whereas, in the placebo group, only 1 subject experienced 3 episodes of pouchitis and no subjects experienced >3 episodes. Among events reported in the vedolizumab group, 2 were considered severe, 1 event was considered treatment-related, and 1 event led to discontinuation of treatment. Approximately half of the pouchitis events in the vedolizumab group occurred before Week 14, and 6 events occurred after Week 34. No specific trends were observed between the time of treatment and onset of the event or the duration of the event.

The majority of TEAEs related to flare (79 events [95.2%]) were reported to be mild (25.5% [n=13] in the vedolizumab group vs. 7.8%. [n=4] in the placebo group) or moderate (27.5% [n=14] vs. 35.3% [n=18]) in intensity; severe events were reported in 4 subjects, with 2 in each treatment group. TEAEs related to flare were considered related to study drug in only 1 (2.0%) subject in the vedolizumab group and in 3 (5.9%) subjects receiving placebo. The TEAE of pouchitis in the vedolizumab-treated subject began on Day 44 and was assessed as related to treatment and moderate in intensity; the subject recovered from the event on Day 47 and completed the study on Day 332. One TEAE related to flare and related to study drug was reported in a placebo-treated subject as a SAE and is described further in the SAE section, herein.

TEAEs related to flare that led to discontinuation occurred in 1 (2.0%) vedolizumab subject and in 2 (3.9%) placebo subjects.

SAEs

A slightly lower proportion of SAEs was reported in patients treated with vedolizumab compared with placebo (5.9% [n=3] vs. 7.8% [n=4]). Pouchitis was the SAE that occurred more frequently in the vedolizumab group (3.9% [n=2] vs. 2.0% [n=1]), however, only the event occurred in the placebo group was considered related to study drug by the investigators. One vedolizumab patient had a SAE of gastroenteritis. No SAEs led to study drug discontinuation.

Two SAEs (basal cell carcinoma in the placebo group and gastroenteritis in the vedolizumab group) were also reported as AESIs under the categories of malignancies and serious infections, respectively.

Consistent with underlying disease, the majority of SAEs were reported within the GI disorders SOC, reported in a total of 5 of 7 subjects (4.9%). This is also consistent with the SAEs observed in the IBD populations where Crohn's disease, colitis ulcerative, and anal abscess were among the most frequently reported SAEs, consistent with the underlying conditions in the IBD populations.

The incidence rate of SAEs was reported as 7.2 per 100 subject-years in the vedolizumab group and 10.1 per 100 subject-years in the placebo group. Pouchitis was reported as 4.8 per 100 subject-years in the vedolizumab group and 2.5 per 100 subject-years in the placebo group.

SAE related to flare

Regarding the SAE related to a flare, the 2 subjects experiencing events of pouchitis in the vedolizumab group, which was not considered related to study drug, were both hospitalized due to worsening of pouchitis.

In particular, one subject was hospitalized on Day 8; the event was also considered severe in intensity and recovered on Day 14; the subject discontinued study drug on Day 43 due to lack of efficacy and attended the end of study visit on Day 347. The second subject was hospitalized on Day 48 after the subject had discontinued study drug on Day 43 due to worsening pouchitis that was considered moderate in intensity; the subject recovered from the event on Day 62 and completed an end of study visit on Day 72.

Regarding the event of pouchitis in the placebo-treated subject, considered by the investigator to be related to study drug and severe in intensity, it began on Day 68 (>30 days posttreatment); the subject was hospitalized for a laparotomy ileostomy, recovered from the event on Day 76 and attended the end of study visit on Day 272.

Taking into account the details of the narratives of the pouchitis SAEs occurred in Study Vedolizumab-4004, it seems that, overall, there are not specific differences between the event occurred in the placebo group and those occurred in the vedolizumab group. Both vedolizumab subjects discontinued the study drug. Furthernore, as mentioned above, pouchitis (reported as related to a flare or worsening of pouchitis) was the most frequently reported TEAE occurring in a higher proportion of vedolizumab-treated patients compared with the placebo group (47.1% [n=24] vs. 39.2% [n=20], with a difference of 7.9%), even though the majority of the events was of mild to moderate intensity. Given the above, i) the MAH was requested to provide information on the proportion of AEs of pouchitis which recovered and those which did not and the proportion of pouchitis events that needed additional treatments by severity intensity and by treatment groups. ii) Although vedolizumab is proposed for the treatment of pouchitis, the MAH was asked to elaborate on whether there is a possible biological rationale that this drug might exacerbate the pre-existing pouchitis or whether all the pouchitis events in terms of flare of pouchitis or worsening of the pre-esisting pouchitis, could be definitely considered as a consequence of lack of efficacy. iii) The MAH was requested to consider to include flare and worsening of pouchitis in the ADR Table of the SmPC section 4.8 with a corresponding warning in section 4.4. The MAH presented the requested data and discussion and based on i) the absence of clinically relevant differences between vedolizumab and placebo treatment groups in terms of pouchitis event outcome and the need of additional treatment; ii) the unlikelihood of vedolizumab causing exacerbation of pouchitis on the basis of its mechanism of action; iii) the absence of evident relationship between the occurrence of pouchitis events and achievement of mPDAI remission; and iv) the absence of relevant differences in terms of demographics and clinical characteristics between patients with and without pouchitis events, it was agreed with the MAH that there was no sufficient evidence to conclude for the inclusion of flare and worsening of pouchitis in section 4.8 or as a warning in section 4.4.

Deaths

No deaths occurred in Study Vedolizumab-4004.

Laboratory findings

No clinically significant changes in clinical laboratory parameters were noted in Study Vedolizumab-4004.

Few subjects met the criteria for a marked laboratory abnormality. The most common marked laboratory abnormality was high GGT that was observed in 5 subjects (9.8%) in the placebo group and 3 subjects (5.9%) in the vedolizumab group. No apparent clinically significant trends were observed.

Regarding immunogenicity, it was not specifically evaluated in Study Vedolizumab-4004. Antibodies to vedolizumab may develop during vedolizumab treatment, most of which are neutralizing. IRRs after

vedolizumab infusion have been reported in subjects with anti-vedolizumab antibodies. The immunogenicity of vedolizumab IV has been evaluated in patients with IBD; the immunogenicity profile is reflected in the approved product labeling for Entyvio (vedolizumab) for IV infusion, which is acceptable.

Special populations

Safety in special populations was not specifically studied.

In Study Vedolizumab-4004, the mean (SD) age was 41.9 (12.44) years (40.8 years in the vedolizumab group vs. 42.9 years in the placebo group) with a range from 19 to 68 years. The majority of patients (61.8%) was aged 25 to <65 years. The MAH was asked to clarify whether differences in safety of vedolizumab were observed by age categories between the treatment groups. The comparison by age categories had to be performed also with the data coming from the ISS on IBD. The same analyses by gender and race/ethnicity were requested. Based on the submitted data, it is agreed with the MAH that the assessments of safety by age categories (<25, 25 to 65, and >65 years), gender, race, and ethnicity are limited by the smaller sample sizes and subsequent uneven distribution among various subgroups, making it difficult draw strong clinical conclusions. In any case, from the presented analyses, it seems that there were no new or different safety signal also in the comparison with the UC/CD patient populations.

Safety related to drug-drug interactions and other interactions

No specific interaction studies have been performed in patients with pouchitis. The section 4.5 of the SmPC has been updated with information on Study Vedolizumab-4004 which is acceptable.

AEs leading to discontinuation

In Study Vedolizumab-4004, a lower proportion of patients treated with vedolizumab reported AEs that led to discontinuation (2.0% [n=1] vs. 9.8% [n=5]). The only AE that led to discontinuation in the vedolizumab group was pouchitis.

Three out of the total of 6 TEAEs leading to discontinuation were reported in the SOC of GI disorders (1 event of Crohn's disease and 2 events of pouchitis). This was consistent with events reported in the UC and CD Vedolizumab IV studies, where the majority of events leading to discontinuation were due to Crohn's disease and colitis ulcerative.

Post marketing experience

Vedolizumab has been marketed since 2014 and is approved for UC and CD in over 70 countries. Since the launch of Entyvio (vedolizumab) for IV infusion, cumulative worldwide patient exposure as of 31 March 2021 was approximately 722,703 patient-years and no new major safety issues have been identified to date from the postmarketing data. The safety of vedolizumab has been well-characterized from postmarketing data; the recent periodic benefit-risk evaluation report (PBRER) did not identify any new safety concerns, and the safety data was found to be consistent with the known safety profile of the drug. There were no new trends or changes in clinical importance seen for IRRs, infections, malignancies, or hepatic events, and no cases of PML were reported.

2.5.2. Conclusions on clinical safety

The safety profile of vedolizumab in subjects with pouchitis is considered to be acceptable, manageable, and overall similar to and consistent with the known safety profile observed in previous vedolizumab IV UC and CD studies in the IBD populations.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Safety Specification

Epidemiology of the indications and target population

Addition of data for new indication of Pouchitis. The section is approvable.

Clinical trial exposure

Addition of data from study vedolizumab-4004, MLN0002SC-3031 and MLN0002SC-3030. The section is approvable.

Post-authorisation experience

Update of the section with post marketing data till DLP 31 March 2021. The section is acceptable.

Identified and potential risks

The information on risks have been amended according to current knowledge and experience.

Annexes

The annex 8 has been updated appropriately.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.0 is acceptable.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Entyvio is already authorised for the treatment of ulcerative colitis (UC) and Crohn's disease (CD) and the pharmaceutical forms available for these indications are: 300 mg powder for concentrate for solution for infusion and 108 mg solution for injection in pre-filled syringe. The user test has been performed at the time of the first MA (2013) and within the X/40 application (2019) aiming to introduce a new pharmaceutical form (solution for injection), associated with a new strength (108 mg) and a new route of administration (subcutaneous use).

The new proposed indication in pouchitis foresees the use of 300 mg powder for concentrate for solution for infusion dosing regimen with the same posology approved for UC/CD. As per UC and CD, Entyvio as IV infusion, should be administered by the HCP. The safety profile in the current population is similar to that already established for Entyvio in UC/CD. No major changes are proposed to the PIL as a result of the new indication, nor to the PIL layout/instructions for use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The Applicant is seeking the addition of a new therapeutic indication for Vedolizumab:

Treatment of adult patients with pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with, lost response to, or were intolerant to antibiotic therapy.

Vedolizumab is a gut selective immunosuppressive biologic. It is a humanized immunoglobulin G1 monoclonal antibody that selectively inhibits the interaction of the α4β7 integrin on memory T and B cells with mucosal addressin cell adhesion molecule-1 expressed on the vascular endothelium in the gut.

Primary efficacy has been evaluated in terms of response rates with a composite endpoint clinically relevant mPDAI remission after 14 weeks of treatment. Clinically relevant remission is defined as an mPDAI score <5 and a reduction of overall score by ≥2 points from baseline at W14.

3.1.2. Available therapies and unmet medical need

Pouchitis is considered by clinical experts to be an independent medical entity of IBD and is a distinct target disease separable from UC and CD, the current authorized conditions approved for vedolizumab.

Currently, there are no approved therapies for pouchitis in the EU, United Kingdom (UK), or US. Because pouchitis represents a disease spectrum ranging from acute antibiotic responsive to chronic antibiotic-refractory, optimal treatment regimens will vary. This condition is largely treated empirically with only small, predominantly retrospective studies having been conducted. Initial treatment of pouchitis focuses on correction of the perceived bacterial dysbiosis, with patients commonly prescribed antibiotics (metronidazole, ciprofloxacin, or rifaximin) as first-line treatment. Patients who develop chronic pouchitis either become dependent on antibiotics for symptom relief or have continuous symptoms despite chronic antibiotic therapy.

3.1.3. Main clinical studies

One pivotal study was conducted for the assessment of efficacy and safety.

Study Vedolizumab-4004 (EARNEST): a randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vedolizumab IV 300 mg in the treatment of adult subjects who had a proctocolectomy and IPAA for treatment of UC and had developed chronic or recurrent pouchitis.

The primary efficacy analysis was at 14 weeks and the secondary analysis at W34 (4 weeks after the last dose of study drug), with a final safety follow-up visit at W48. All subjects were expected to complete a long-term follow-up safety survey by telephone at W56, 26 weeks after the last dose of study drug.

3.2. Favourable effects

Primary endpoint: a statistically significant higher proportion of patients in the vedolizumab IV 300mg group reached mPDAI remission at week 14 in comparison to the placebo group (31.4% vs 9.8% respectively), with a treatment difference of 21.6% (95% CI: 4.9, 37.5) p=0.013 on FAS analysis.

The primary analysis is supported by results from two sensitivity analyses (LOCF and hybrid approach), while PPS analysis and that accounting for concomitant use of antibiotics before week 14 did not.

The efficacy (remission rate) of vedolizumab at week 34 was overall maintained although with a smaller difference from placebo (delta of 17, CI 0.3-35, p 0.043).

PDAI Remission rates at week 14 and 34 (both secondary endpoints) as measured by PDAI were consistent with the rates measured by using the mPDAI score, excluding histologic assessment, providing reassurance on the use of mPDAI as primary estimand.

Moreover, consistent results favouring vedolizumab were seen using a less stringent clinical endpoint i.e. partial mPDAI response at W14 and W34 (treatment difference of 29.4% and 21.6%, respectively).

Results by type of pouchitis from primary estimand and available secondary endpoints i.e. mPDAI 34 week, PDAI remission as well as in the partial mPDAI response at week 14 and 34 show a greater response difference for vedolizumab over placebo group in the recurrent pouchitis group as compared to the chronic one.

Importantly, results coming from clinically relevant endpoints i.e. sustained mPDAI and PDAI remission (both at W14 and W34) support a benefit of vedolizumab over placebo with a difference of 21.6 pp (95% CI 6.5, 37.0) for sustained mPDAI remission and 23.5 pp (95% CI 8.0, 38.8) for sustained PDAI remission, therefore a maintenance of the effect in terms of disease activity control with a clinically mindful effect size over placebo is observed.

Other endpoints are in favour of vedolizumab effect (change in Total PDAI score, nominal p 0.025) and time to relapse/number of relapses (modest difference between the rates with vedolizumab 31.3% and placebo 40%).

Results of histologic endpoint (RHI) and endoscopic ulcer endpoints (number, surface, SES-CD) showed better results with vedolizumab compared to placebo. The biomarkers showed little (FC) or no improvement (CRP) with vedolizumab compared to placebo, not supporting their use as useful clinical measures of vedolizumab response.

A favourable effect of vedolizumab seems to be exerted on corticosteroid-free mPDAI remission and corticosteroid-free PDAI remission rates at 14 weeks, the same figure is not seen at a longer time point (week 34) and it is referred to a small subset of subjects taking concomitant corticosteroids treatment at baseline (7.8% in the vedolizumab group and 13.7% in the placebo group on Day 1).

3.3. Uncertainties and limitations about favourable effects

The selected primary endpoint is not validated and the preferable one would have been PDAI clinically relevant remission; supportive data of a similar sensitivity and specificity of the mPDAI when compared with the PDAI in the setting of chronic pouchitis was provided, however this analysis was done only using

data from this study. Therefore, although the concordance of PDAI and mPDAI scores in this study is relevant, the result could not be used to validate these tools.

Although a statistically significant higher proportion of patients in the vedolizumab IV 300mg group reached mPDAI remission at week 14 in comparison to the placebo group, the observed effect size does not support the planned difference of 25% between vedolizumab and placebo raising concerns on the clinical relevance of vedolizumab effect. The assumptions made for the sample size calculation were justified by assuming the optimistic (compared with infliximab) mPDAI remission rate at W14 of 40% for vedolizumab in conjunction with the conservative assumption of a high placebo remission rate of 15%, and therefore a treatment difference of 25% for vedolizumab relative to placebo. Although this treatment difference was not achieved in the results of Study Vedolizumab-4004 (placebo around 10% and vedolizumab around 31%) the treatment effect estimate, that can be considered around 20%, was statistically significant and confirmed by several sensitivity analyses.

Moreover, the effect size on the primary estimand appears different between the two subtypes chronic (15.6%, 95% CI -5.1, 36.2) and recurrent pouchitis (28.7%, 95% CI 6.1, 51.2) and wide confidence intervals were detected.

Support was provided on the homogeneity of vedolizumab effect between strata: although a higher treatment effect was detected among recurrent as compared to chronic pouchitis patients, differences were not statistically significant (CHM test). However, given the limited dataset and the small size of subgroups, the absence of a significant difference between the subpopulations could not be seen as conclusive on the comparability of the treatment effect. Further reassurance was gained on the results using a more conservative imputation approach for the primary estimand i.e. imputing missing data as non-responders and for the jump-to-reference case, the missing cases in both treatment arms were imputed as responders according to the observed placebo response rate.

Therefore, the use of vedolizumab for the treatment of pouchitis is sufficiently supported by available evidence and analyses. It should be mentioned that some inconsistency is noted i.e. sensitivity analysis or subgroup analyses but the small sample size and the wide CI hamper any firm conclusion.

New analysis taking into account for multiple testing (Bonferroni and Bonferroni stepdown, Holm) on the main secondary endpoints (i.e. PDAI remission, Partial mPDAI response, Sustained mPDAI remission, Sustained PDAI remission) show that 4 of the 7 endpoints remain significant (PDAI remission W14, mPDAI response W14, Sustained mPDAI remission, and Sustained PDAI remission), whereas endpoints evaluated at week 34 (mPDAI remission, PDAI remission, mPDAI response) became not significant also in line with the jump-to-reference analysis. In the results of 2 other multiple testing approaches requested (Hochberg and Hommel), the p-values remained significant (<0.05) across all 7 variables.

Therefore, reassurance on the effect of induction treatment (week 14) is gained and uncertainties persist on maintenance of the effect (week 34). Discontinuation of treatment at week 14 if no evidence of therapeutic benefit is observed has been added to section 4.2. of the SmPC.

Other secondary endpoints are in favour of vedolizumab effect however when the different PDAI domains were analysed, only the endoscopic subscore at week 14 showed a greater treatment difference in the vedolizumab group (not seen at week 34) therefore implying that results on the total score are mainly driven by the endoscopic subscore. A covariance (ANCOVA) model on these results confirmed that only for total PDAI and Endoscopic Inflammation scores the treatment effect was statistically significant.

The clinical relevance of these results, considering that the current EMA GL highlights that clinically relevant effects in each of the main components of the PDAI score (symptoms as well as macro- and microscopic appearance of mucosa) is not supported by all components of the score but the endoscopic one is regarded as objective and clinically important.

Time to relapse, as well as number of relapses, could be considered as an important endpoint for both types of pouchitis; however, the analysis found only a modest difference between the rates with vedolizumab (31.3%) and placebo (40%). The Kaplan-Meier curves for time to relapse, both for overall population and for the subgroups of subjects classified as having recurrent or chronic pouchitis were not statistically significant between vedolizumab and placebo.

Importantly, results on QoL endpoints (IBDQ and CGQL) do not clearly support vedolizumab effect over placebo questioning the benefits of vedolizumab as perceived by the patients.

Biomarkers data showed little (FC) or no improvement (CRP) with vedolizumab compared to placebo, not supporting their use as useful clinical measures of vedolizumab response.

A favourable effect of vedolizumab seems to be exerted on corticosteroid-free mPDAI remission and corticosteroid-free PDAI remission rates at 14 weeks, however on later time points (week 34) the advantage is not seen and importantly the potential advantage is only referred to a small subset of subjects taking concomitant corticosteroids treatment at baseline (7.8% in the vedolizumab group and 13.7% in the placebo group on Day 1) making any claim not possible.

The two chronic pouchitis subgroups, as defined in the study, appear to correspond to the following classification reported in the literature: 'Chronic' as defined in the present study to Chronic Antibiotic-Refractory Pouchitis (CARP), while 'recurrent' to Chronic Antibiotic-Dependent Pouchitis (CADP). In this context, the use of a clear identification of the two subgroups in the 4.1 and 5.1 sections of the SmPC is considered of clinical importance. The target population enrolled as per protocol inclusion criteria (IC) and as reflected in the pouchitis-related baseline characteristics had moderately to severe chronic pouchitis, patient intolerant to antibiotics were not included. Accordingly the MAH proposed during the procedure a revised wording of the indication: "Entyvio is indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy".

The target population including the setting investigated, the characteristics of patients, response to antibiotic therapy, and eventually, considering the new analyses are now reflected in the wording of the indication.

3.4. Unfavourable effects

Overall, in Study Vedolizumab-4004, around 92% of patients treated with vedolizumab experienced at least 1 TEAE compared with approximately 86% of subjects receiving placebo.

In the comparison with UC/CD patient populations, **TEAEs** of any type and severity were reported less frequently in the pouchitis group than in the UC study C13006, the combined UC/CD studies C13006 and C13007, and the combined UC/CD OLE study C13008 No significant differences were observed when comparing the overall exposure-adjusted incidence rates between Study Vedolizumab-4004 and the UC/CD OLE Study C13008.

The SOC with the higher frequency of TEAEs in the vedolizumab group compared with the placebo group were GI disorders (70.6% vs. 62.7%; with pouchitis being the most frequent AE in this SOC: 47.1% [n=24] vs. 39.2% [n=20]); Infections and Infestations (47.1% vs. 29.4%; with nasopharyngitis being the most frequently reported AE in this SOC: 6 subjects in each treatment group); Nervous system disorder (29.4% vs. 9.8%; with headache being the most frequent AE in this SOC: 19.6% [n=10] vs.

5.9% [n=3]); Injury, poisoning and procedural complications (9.8% vs. 3.9%); Eye disorders (9.8% vs. 2.0%); Blood and lymphatic system disorders (7.8% vs. 2.0%).

Overall, pouchitis (reported as related to a flare or worsening of pouchitis) was the **most frequent TEAE** occurring in a higher number of subjects (24, [47.1%]) in the vedolizumab group compared with the placebo group (20 subjects [39.2%]) suggesting a potential loss of efficacy.

The other most frequent TEAEs in the vedolizumab group were (in order of frequency by the percentage of subjects who experienced the event): headache, arthralgia, nasopharyngitis, nausea, upper respiratory tract infection, influenza, frequent bowel movement, and abdominal pain.

TEAEs occurring more frequently with vedolizumab treatment as compared to placebo and occurring in at least ≥4% of subjects in the vedolizumab group (in order of frequency) were pouchitis -as mentioned above-, headache (19.6% [n=10] vs. 5.9% [n=3]), upper respiratory tract infection (9.8% [n=5] vs. 2.0% [n=1]), abdominal pain (7.8% vs. 5.9%), influenza (7.8% [n=4] vs. 2.0% [n=1]), and frequent bowel movements (7.8% [n=4] vs. 3.9% [n=2]).

The overall summary of TEAEs by SOC in Vedolizumab-4004 were consistent with those presented in the ISS in subjects with IBD. As would be expected in subjects with pouchitis or IBD, GI disorders were the most frequently reported TEAEs.

In terms of most frequent AEs, the safety profile of vedolizumab in the pouchitis group is overall similar to that reported for the other indications.

The majority of the AEs reported in the Vedolizumab-4004 Study was mild or moderate in intensity in both treatment groups %). A lower proportion of vedolizumab-treated patients experienced a TEAE that was considered by the investigator to be severe in intensity (5.9% [n=3] vs. 9.8% [n=5] in the placebo group). Most severe TEAEs occurred in the GI disorders SOC (6 subjects, 5.9%) with pouchitis (reported as related to a flare or worsening of pouchitis) being the most common severe TEAE, reported in 1 subject (2.0%) in the placebo group and 2 subjects (3.9%) in the vedolizumab group, as mentioned above. The pouchitis event occurred in the placebo group was considered as a SAE and related to the study drug by the investigator while the 2 severe events of pouchitis occurred in the vedolizumab groups were not deemed to be drug-related and only 1 was considered to be a SAE.

Severe events reported in the IBD studies occurred only within the GI disorders SOC and included events of CD, abdominal pain, and colitis ulcerative.

In Study Vedolizumab-4004, **drug-related TEAEs** were reported with a slightly higher frequency in the vedolizumab group compared with the placebo group (23.5% [n=12] vs. 21.6% [n=11]), in particular, in the SOC Infections and Infestations (15.7% [n=8] vs. 7.8% [n=4]).

The same was also observed in subjects with IBD, where the majority of drug-related AEs were reported within the SOC of infections and infestations (ISS).

AESI categories were predefined in the protocol of Study Vedolizumab-4004, based on the mechanism of action of vedolizumab and the known safety profile. The 5 AESI categories are hypersensitivity reactions including IRRs, PML, liver injury, malignancies, and serious infections. A total of 16 AESI events were reported with a lower proportion in the vedolizumab group compared with the placebo group (9.8% [n=6] vs. 13.7% [n=10]), which is reassuring. Most frequently reported AESIs were *hypersensitivity reactions including IRRs* that occurred in 3 subjects (5.9%) in the vedolizumab group and in 2 subjects (3.9%) in the placebo group. None of these events were specifically reported as IRRs. All events in this AESI category were considered by the investigator to be not related to study drug, with the exception of an event of chest discomfort, considered related to study drug and mild in intensity, that occurred in 1 subject in the vedolizumab group. *Liver injury AESIs* were reported in 1 subject (2.0%) in the

vedolizumab group and in 3 subjects (5.9%) in the placebo group. The AESI of hepatic enzyme increase in 1 subject in the vedolizumab treated group was assessed to be mild in intensity, and the subject recovered from the event during the study. AESIs of *malignancies* were reported in 2 subjects (3.9%) in the placebo group and in none in the vedolizumab group, including basal cell carcinoma and benign neoplasm of testis. Regarding *serious infections*, 1 subject (2.0%) in the vedolizumab group (and none in the placebo group) experienced a serious infection AESI of gastroenteritis considered by the investigator to be not related to study drug. No cases of *PML* were reported.

A total of 53 subjects reported 83 **TEAE events related to a flare**; as mentioned above, at least 1 TEAE related to a pouchitis flare was reported in a higher proportion of patients treated with vedolizumab than in the placebo group (56.9% [n=29] vs. 47.1% [n=24]). Pouchitis was the most frequently reported PT related to a flare and with a higher frequency in vedolizumab subjects (47.1% [n=24] vs. 37.3% [n=19] in the placebo group).

Multiple episodes of pouchitis in a given subject was also higher in the vedolizumab group. One subject in the vedolizumab group had 5 episodes of pouchitis, 1 subject had 3 episodes, and 3 subjects had 2 episodes each, whereas, in the placebo group, only 1 subject experienced 3 episodes of pouchitis and no subjects experienced >3 episodes. Among events reported in the vedolizumab group, 2 were considered severe, 1 event was considered treatment-related, and 1 event led to discontinuation of treatment. Approximately half of the pouchitis events in the vedolizumab group occurred before Week 14, and 6 events occurred after Week 34. No specific trends were observed between the time of treatment and onset of the event or the duration of the event.

The majority of TEAEs related to flare were reported to be mild or moderate in intensity; severe events were reported in 4 subjects, with 2 in each treatment group. TEAEs related to flare were considered related to study drug in only 1 (2.0%) subject in the vedolizumab group and in 3 (5.9%) subjects receiving placebo. The TEAE of pouchitis in the vedolizumab-treated subject began on Day 44 and was assessed as related to treatment and moderate in intensity; the subject recovered from the event on Day 47 and completed the study on Day 332.

TEAEs related to flare that led to discontinuation occurred in 1 (2.0%) vedolizumab subject and in 2 (3.9%) placebo subjects.

A slightly lower proportion of **SAEs** was reported in patients treated with vedolizumab compared with placebo (5.9% [n=3] vs. 7.8% [n=4]). Pouchitis was the SAE that occurred more frequently in the vedolizumab group (3.9% [n=2] vs. 2.0% [n=1]), however, only the event occurred in the placebo group was considered related to study drug by the investigators. One vedolizumab patient had a SAE of gastroenteritis. No SAEs led to study drug discontinuation. Consistent with underlying disease and the other indications, the majority of SAEs were reported within the GI disorders SOC, reported in a total of 5 of 7 subjects (4.9%). The incidence rate of SAEs was reported as 7.2 per 100 subject-years in the vedolizumab group and 10.1 per 100 subject-years in the placebo group. Pouchitis was reported as 4.8 per 100 subject-years in the vedolizumab group and 2.5 per 100 subject-years in the placebo group.

Regarding the *SAE related to a flare*, the 2 subjects experiencing events of pouchitis in the vedolizumab group, which was not considered related to study drug, were both hospitalized due to worsening of pouchitis. In particular, one subject was hospitalized on Day 8; the event was also considered severe in intensity and recovered on Day 14; the subject discontinued study drug on Day 43 due to lack of efficacy and attended the end of study visit on Day 347. The second subject was hospitalized on Day 48 after the subject had discontinued study drug on Day 43 due to worsening pouchitis that was considered moderate in intensity; the subject recovered from the event on Day 62 and completed an end of study visit on Day 72. Regarding the event of pouchitis in the placebo-treated subject, considered by the investigator to be related to study drug and severe in intensity, it began on Day 68 (>30 days

posttreatment); the subject was hospitalized for a laparotomy ileostomy, recovered from the event on Day 76 and attended the end of study visit on Day 272.

In Study Vedolizumab-4004, a lower proportion of patients treated with vedolizumab reported **TEAEs that led to discontinuation** (2.0% [n=1] vs. 9.8% [n=5]). The only AE that led to discontinuation in the vedolizumab group was pouchitis.

3.5. Uncertainties and limitations about unfavourable effects

Although in terms of most frequent AEs, the safety profile of vedolizumab in the pouchitis group is overall similar to that reported for the other indications, there are some TEAEs that occurred more frequently with vedolizumab treatment as compared to placebo such as abdominal pain and frequent bowel movements (with a difference of approximately 2% and 4%, respectively), which are not reported in the section 4.8 of the current SmPC. Based on the thorough review of these two AEs made by the MAH, it was agreed that there was insufficient evidence to establish a strong causal association between the events and vedolizumab, given the small difference in the incidence of these AEs between vedolizumab and placebo groups, the absence of remarkable differences in the characteristics of these AEs between the two treatment groups, and the multiple concomitant medications during the time of the event that could have contributed to their occurrence.

Other AEs which occurred in the vedolizumab group in at least 2 subjects (3.9%) versus none in the placebo group were: anaemia, gastroesophageal reflux disease, rectal hemorrhage, musculoskeletal pain, asthenia, and chest discomfort (for all, 3.9% [n=2] vs. 0). Therefore, for the above-mentioned AEs, the MAH was asked to discuss whether they (or at least some of them) could be due to lack of efficacy and whether they should have been added in the ADR table of the 4.8 section of the SmPC. Based on the analyses made by the MAH, most of these events were mild or moderate in intensity, nonserious, recovered, did not lead to discontinuation, and were not considered related to study drug by the investigator. For some of these events (i.e., anaemia, gastroesophageal reflux disease, and musculoskeletal pain), a conclusion on the causal relationship with vedolizumab treatment cannot be drawn. For the remaining AEs: a) in the absence of confounding factors, the MAH was asked to include rectal hemorrhage AEs, which were not even associated with pouchitis events or the absence of remission status, in the ADR Table in section 4.8 of the SmPC; b) in the presence of a clear temporal relationship with IRR, asthenia and chest discomfort were requested by the CHMP to be included in the already existing list of signs and symptoms of infusion-related reactions reported under the SOC General disorders and administration site conditions in the table of section 4.8 and asthenia was requested by the CHMP to be included for consistency in the new text of the subsection "Infusion-related reactions" (see also below the discussion on the AESIs). The MAH agreed with these PI updates.

Exposure-adjusted analyses were performed to adjust for differences in overall exposure between treatment groups. Overall, exposure-adjusted incidence rates in both vedolizumab and placebo groups were similar (113.3 and 111.1 per 100 subject-years, respectively). However, differences persisted between the treatment groups in terms of a higher incidence rates in the vedolizumab group compared with the placebo group of the following AEs: pouchitis (57.8 per 100 subject-years [n=24] vs. 50.5 per 100 subjects-years [n=20]), headache (24.1 [n=10] vs. 7.6 [n=3]), upper respiratory tract infection (12.0 [n=5] vs. 2.5 [n=1]), influenza and frequent bowel movements (for both, 9.6 [n=4] vs. 2.5 [n=1]), anaemia, gastroesophageal reflux disease, rectal haemorrhage, asthenia, chest discomfort, and musculoskeletal pain (for all, 4.8 [n=2] vs. 0). As reported above and herein, for these AEs other than those already reported in the ADR Table of the SmPC section 4.8, the MAH provided the requested

clarifications and included rectal hemorrhage, asthenia, chest discomfort into SmPC section 4.as requested by the CHMP.

In order to better understand the safety profile of vedolizumab in different subgroup populations, the MAH was asked to provide safety data in terms of AEs, AESIs, SAEs, drug-related AEs, AEs leading to discontinuation, stratified by: a) chronic vs. recurrent pouchitis; b) anti-TNFalfa naïve vs. experienced status, c) baseline clinical severity, d) concomitant use of antibiotics excluding ciprofloxacin as companion (first 4 weeks). Based on the data submitted by the MAH, in general, given the small numbers reliable conclusions from these subgroup analyses can be drawn. More AEs occurred in subjects who were anti-TNF naïve, had severely active pouchitis at baseline, and who did not use any concomitant antibiotics before W34, with a higher frequency of SAE in the recurrent pouchitis subgroup compared with the chronic subgroup. However, no relevant difference vedolizumab and placebo arms were observed.

It is acknowledged that, overall, there were no apparent trends or events that were of clinical concern among the AESIs reported in subjects with pouchitis treated with vedolizumab. AESIs seems to be consistent with those previously reported in the ISS in subjects with IBD. However, in the section 4.8 of the SmPC, the MAH was asked to update the paragraph on "Description of selected adverse reactions" with the specific results of the Study Vedolizumab-4004. As requested, the MAH agrees to the addition of AESI information from Study Vedolizumab-4004 to section 4.8 of the SmPC. New text has been added to the subsections "Infusion-related reactions" and "Infections". IRRs were reported in 3 subjects (5.9%) in the vedolizumab group and in 2 subjects (3.9%) in the placebo group. The individual PTs included mouth ulceration, swelling, oedema peripheral, chest discomfort, acute kidney injury, obstructive airway disorder and flushing. All events were mild to moderate in intensity, nonserious, did not lead to study discontinuation, and were considered not related to study drug by the investigator except for one event of chest discomfort. The wording of the new text can be considered acceptable, however, as mentioned above, there were 3 AEs of asthenia reported in 2 vedolizumab subjects occurred during drug infusions. Given the temporal relationship with the vedolizumab infusion in terms of onset and duration, the MAH pointed out that these events were most likely an infusion-related reaction consistent with the known ADR of vedolizumab. The causality is likely and, therefore, as mentioned above, the MAH was requested to include asthenia in the new text of the subsection "Infusion-related reactions"; the MAH agreed to make these changes to the PI. The new text in the subsection "Infections" can be considered acceptable. A serious infection of AESI was reported in 1 subject (2.0%) in the vedolizumab group and in none in the placebo group. The subject was hospitalized and the event was severe in intensity, not considered related to study drug by the investigator, and recovered. The MAH specified that in Study Vedolizumab-4004 there was no trend of infections in relation to BMI and no higher risk of infections in patients who had prior exposure to TNF-alfa antagonist therapy. Therefore, the current statement in the SmPC is referred only to UC and CD studies and not to pouchitis. This is acceptable. No changes were necessary for the text of the subsection "Malignancies".

Overall, no specific differences between the event of pouchitis occurred in the placebo group and those occurred in the vedolizumab group. Both vedolizumab subjects discontinued the study drug. Furthernore, as mentioned above, pouchitis (reported as related to a flare or worsening of pouchitis) was the most frequently reported TEAE occurring in a higher proportion of vedolizumab-treated patients compared with the placebo group (47.1% [n=24] vs. 39.2% [n=20], with a difference of 7.9%), even though the majority of the events was of mild to moderate intensity. Given the above, i) the MAH was requested to provide information on the proportion of AEs of pouchitis which recovered and those which did not and the proportion of pouchitis events that needed additional treatments by severity intensity and by treatment groups. ii) Although vedolizumab is proposed for the treatment of pouchitis, the MAH was asked to elaborate on whether there is a possible biological rationale that this drug might exacerbate the pre-existing pouchitis or whether all the pouchitis events in terms of flare of pouchitis or worsening

of the pre-esisting pouchitis, could be definitely considered as a consequence of lack of efficacy. iii) The MAH was requested to consider to include flare and worsening of pouchitis in the ADR Table of the SmPC section 4.8 with a corresponding warning in section 4.4. The MAH presented the requested data and discussion and based on i) the absence of clinically relevant differences between vedolizumab and placebo treatment groups in terms of pouchitis event outcome and the need of additional treatment; ii) the unlikelihood of vedolizumab causing exacerbation of pouchitis on the basis of its mechanism of action; iii) the absence of evident relationship between the occurrence of pouchitis events and achievement of mPDAI remission; and iv) the absence of relevant differences in terms of demographics and clinical characteristics between patients with and without pouchitis events, it was agreed with the MAH that there was no sufficient evidence to conclude for the inclusion of flare and worsening of pouchitis in section 4.8 or as a warning in section 4.4.

Safety in special populations was not specifically studied. Concerning pregnancy, one case of pregnancy was reported in the Study Vedolizumab-4004 on pouchitis. In Study Vedolizumab-4004, the mean (SD) age was 41.9 (12.44) years (40.8 years in the vedolizumab group vs. 42.9 years in the placebo group) with a range from 19 to 68 years. The majority of patients (61.8%) was aged 25 to <65 years. Clarifications was needed on whether differences in safety of vedolizumab were observed by age categories between the treatment groups. The comparison by age categories had to be performed also with the data coming from the ISS on IBD. The same analyses by gender and race/ethnicity were requested. The assessments of safety by age categories, gender, race, and ethnicity were however limited by the smaller sample sizes and subsequent uneven distribution among various subgroups, making it difficult draw strong clinical conclusions. In any case, from the presented analyses, there appeared to be no new or different safety signal also in the comparison with the UC/CD patient populations.

Immunogenicity was not specifically evaluated in Study Vedolizumab-4004. Antibodies to vedolizumab may develop during vedolizumab treatment, most of which are neutralizing. The immunogenicity profile is reflected in the approved product labeling for Entyvio (vedolizumab) for IV infusion, which is acceptable.

3.6. Effects Table

Table 1. Effects Table for vedolizumab in the pouchitis indication

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
mPDAI remission W14	% patients achieving mPDAI remission at Week 14	%	31.4	9.8	Difference in response 21.6 (p=0.013)	Study Vedolizumab-4004
mPDAI remission W34	% patients achieving mPDAI remission at	%	35.3	17.6	No control for multiplicity (p=0.043)	Study Vedolizumab-4004

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	Week 34					
PDAI remission W14	% patients achieving PDAI remission at Week 14	%	35.3	9.8	No control for multiplicity (p=0.004)	Study Vedolizumab-4004
PDAI remission W34	% patients achieving PDAI remission at Week 34	%	37.3	17.6	No control for multiplicity (p=0.027)	Study Vedolizumab-4004
Partial mPDAI response W14	% patients achieving partial mPDAI response at Week 14	%	62.7	33.3	No control for multiplicity (p=0.003)	Study Vedolizumab-4004
Partial mPDAI response W34	% patients achieving partial mPDAI response at Week 34	%	51.0	29.4	No control for multiplicity (p=0.026)	Study Vedolizumab-4004
Unfavourable Effects						
Pouchitis (reported as flare or worsening of pouchitis)	Incidence	%	47.1	39.2	Impact on patient wellbeing	Study Vedolizumab-4004
Headache	Incidence	%	19.6	5.9	Impact on patient wellbeing	Study Vedolizumab-4004
Upper respiratory tract infection	Incidence	%	9.8 (as drug-related 3.9)	2.0 (as drug-related 0)	Impact on patient wellbeing	Study Vedolizumab-4004
Nasopharyngitis	Incidence	%	5.9 (as drug-related)	2.0 (as drug-related)	Impact on patient wellbeing	Study Vedolizumab-4004
Abdominal pain	Incidence	%	7.8	5.9	Impact on patient wellbeing	Study Vedolizumab-4004
Influenza	Incidence	%	7.8	2.0	Impact on patient wellbeing	Study Vedolizumab-4004

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Frequent bowel movements	Incidence	%	7.8	3.9	Impact on patient wellbeing	Study Vedolizumab-4004
Anaemia, gastroesophageal reflux disease, rectal hemorrhage, musculoskeletal pain, asthenia, and chest discomfort	Incidence	%	3.9	0	Impact on patient wellbeing	Study Vedolizumab-4004

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary estimand analysis showed a statistically significant higher proportion of patients in the vedolizumab IV 300mg group reached mPDAI remission at week 14 in comparison to the placebo group, several conservative analyses have supported the robustness of the results.

The safety profile of vedolizumab in subjects with pouchitis is considered to be acceptable, manageable, and overall similar to and consistent with the known safety profile observed in previous vedolizumab IV UC and CD studies in the IBD populations.

3.7.2. Balance of benefits and risks

The use of vedolizumab for the treatment of pouchitis is sufficiently supported by available evidence. Therefore, the benefits outweigh the risks.

3.8. Conclusions

The overall B/R of Entyvio is positive in the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB and IV

Extension of indication to include treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy for Entyvio; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC for Entyvio 300 mg are updated. The Package Leaflet is updated accordingly. The RMP is updated to version 7.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB, IV and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Entyvio-H-C-002782-II-0061