

SUPPLEMENTAL MATERIALS

Intensity of Adverse Events

The intensity for each adverse event (AE) was defined by the study investigator as mild, moderate, or severe according to the following criteria:

- Mild: Awareness of sign or symptom, but easily tolerated
- Moderate: Discomfort enough to cause interference with normal daily activities
- Severe: Inability to perform normal daily activities

Progressive Multifocal Leukoencephalopathy Screening and Risk Estimation

All patients completed a standardised subjective checklist that evaluated the onset of new neurological symptoms at every visit before dosing. Patients were also asked to contact the study investigator immediately if they noticed any new neurological symptoms. The investigator performed a standardised neurological examination at each visit. If positive findings were identified on the subjective checklist, an objective checklist to evaluate neurological function was administered. Patients with abnormal findings on the objective checklist were referred to the site's study neurologist. If the neurologist was unable to exclude progressive multifocal leukoencephalopathy (PML), the case was reviewed by the independent adjudication committee (IAC). Diagnostic testing including magnetic resonance imaging and lumbar puncture to determine John Cunningham virus (JCV) viremia was performed during IAC assessment.

Regarding PML risk, the data set was stratified post hoc by the 3 known natalizumab PML risk factors—24 months treatment duration, prior immunosuppressive use, and positive JCV antibody status—which were derived from the published long-term experience with natalizumab, primarily from patients with multiple sclerosis and also those with Crohn's disease (CD).[1] Contemporaneous published PML incidence rates for patients positive for the anti-JCV antibody were 1.6 cases and 0.56 cases per 1000 person-years (PYs) with and without prior immunosuppressive use, respectively, for ≤24 months of natalizumab exposure and 11.1 cases and 4.6 cases per 1000 PYs with and without prior immunosuppressive use, respectively, for >24 months of natalizumab exposure.[1] JCV antibody testing was not performed in vedolizumab clinical trials owing to the lack of a commercially available assay.[2, 3] To account for this absence of testing, 50% of patients were assumed to have anti-JCV antibodies, a conservative assumption based on published rates in the literature, which includes patients with CD.[4, 5]

Patient Narratives

Serious Infusion-Related Reactions

Across the 6 clinical studies included in the overall safety population, 3 IRRs were considered serious. A CD patient enrolled in GEMINI 2 developed dyspnoea, bronchospasm, hives, flushing, rash, and increased blood pressure and heart rate that began 13 minutes after the start of her second vedolizumab infusion. Symptoms resolved about 3 hours later following vedolizumab discontinuation and treatment with oxygen, an antihistamine, and intravenous hydrocortisone. The patient was discontinued from the study because of the event. A second patient with CD experienced flushing, rash, vomiting, and swollen tongue about 30 minutes after the start of the patient's second vedolizumab infusion in the GEMINI Long-term Safety (LTS) study. Symptoms resolved within 5 hours with diphenhydramine treatment; however, the patient discontinued from the study as a result. One infusion-related reaction in an ulcerative colitis (UC) patient was considered serious. The patient, a 42-year-old female, had previous exposure to vedolizumab in a phase 2 study (M200-022) and developed anti-drug antibodies (titre not available) before enrolling in study C13004. She was administered prophylactic hydrocortisone before dosing, yet experienced throat tightness and nausea during her first vedolizumab infusion in C13004. The patient was subsequently found to have anti-drug antibodies (titre 1:625) and discontinued from the study.

Serious Hepatobiliary Events

Five hepatic events were considered serious, including 2 with potentially autoimmune etiology resulting in study drug discontinuation. A 20-year-old male with UC previously taking azathioprine/mercaptopurine was hospitalised for acute hepatitis without jaundice 2 months after his fifth vedolizumab infusion during GEMINI 1. Liver biopsy showed substantial lobular inflammatory infiltrates consistent with chronic autoimmune hepatitis. Treatment with corticosteroids resulted in resolution of symptoms and near normalization of liver transaminases. The second patient was a 36-year-old female with UC who had enrolled in GEMINI LTS from GEMINI 1, also previously treated with mercaptopurine. Her liver enzymes became elevated after her 34th infusion of vedolizumab. She received an additional dose of study drug before presenting with weakness, nausea, pruritus, and jaundice. She was treated with steroids with near normalization of liver enzymes. Approximately 2 months later, the patient was admitted to a dermatology hospital for subacute cutaneous lupus erythematosus, which was confirmed based on clinical, serologic, and histopathological findings, and may represent a potential alternative etiology of her transaminase elevation.

Two additional CD patients discontinued study drug because of a serious AE (SAE) of increased transaminases after 2 infusions of vedolizumab in GEMINI 2. A 23-year-old female was hospitalised with pulmonary embolism and hepatitis, both of which resolved with treatment. Sulfasalazine-induced hepatitis was confirmed by diagnosis in a 35-year-old female who had received sulfasalazine for 4 months; medical history included intermittent abnormal liver enzymes. The patient was treated with prednisone resulting in resolution. The fifth patient—a 28-year-old female enrolled in GEMINI 1—with an SAE of increased transaminases was 15 weeks pregnant when diagnosed with autoimmune hepatitis by liver biopsy 7 months after receiving her last dose of vedolizumab. The patient improved following methylprednisolone therapy.

Table S1: Clinical Trials of Vedolizumab Included in the Integrated Safety Summary

Study IDs	Patient population	Phase	Duration	Treatment arms (Dose)	Dosing regimen (IV infusions)	Citation
Randomised, double-blind, placebo-controlled studies						
C13002 NCT01177228	<ul style="list-style-type: none"> Mild UC Partial Mayo score 1-7 Endoscopic and/or histopathological evidence of disease extending proximal to the rectum Age 18-70 years 	2	253 days	VDZ 2 mg/kg VDZ 6 mg/kg VDZ 10 mg/kg PBO	Days 1, 15, 29, and 85	Parikh et al, 2012[6]
GEMINI 1 NCT00783718	<ul style="list-style-type: none"> Moderately to severely active UC Mayo score 6-12 and endoscopic subscore ≥ 2 $\leq 50\%$ had previous exposure to anti-TNFs Age 18-80 years 	3	Induction 6 weeks	VDZ 300 mg PBO	Weeks 0 and 2	Feagan et al, 2013[2]
			Maintenance 46 weeks	VDZ 300 mg PBO	Q4W or Q8W	
GEMINI 2 NCT00783692	<ul style="list-style-type: none"> Moderately to severely active CD CDAI score 220-450 $\leq 50\%$ had previous exposure to anti-TNFs Age 18-80 years 	3	Induction 6 weeks	VDZ 300 mg PBO	Weeks 0 and 2	Sandborn et al, 2013[3]
			Maintenance 46 weeks	VDZ 300 mg PBO	Q4W or Q8W	
GEMINI 3 NCT01224171	<ul style="list-style-type: none"> Moderately to severely active CD CDAI score 220-400 Inadequate response to, loss of response to, or intolerance to CS (except in the US), IS, and/or anti-TNFs within the previous 5 years Age 18-80 years 	3	10 weeks	VDZ 300 mg PBO	Weeks 0, 2, and 6	Sands et al, 2014[7]
Open-label extension studies						
C13004	<ul style="list-style-type: none"> UC and CD 	2	78 weeks	VDZ 2 mg/kg	Days 1, 15, and 43	Parikh et al,

NCT00619489	<ul style="list-style-type: none"> • Rollover patients from study C13002 • VDZ-naïve patients aged 18-75 years and partial Mayo score of 2-7 (UC) or CDAI score of 220-450 (CD) 			VDZ 6 mg/kg	and then Q8W	2013[8]
GEMINI LTS NCT00790933 (ongoing ^a)	<ul style="list-style-type: none"> • UC and CD • Rollover patients from studies C13004, GEMINI 1, GEMINI 2, and GEMINI 3 • VDZ-naïve patients aged 18-80 years and partial Mayo score 3-9 (UC) or HBI score 8-18 (CD) 	3	46+ months	VDZ 300 mg	Q4W	Feagan, et al 2014; Hanauer, et al 2014[9, 10]

Abbreviations: anti-TNF, tumour necrosis factor α antagonist; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CS, corticosteroids; HBI, Harvey Bradshaw Index; IS, immunosuppressive; IV, intravenous; LTS, long-term safety; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; UC, ulcerative colitis; US, United States; VDZ, vedolizumab.

^aIncludes data collected from May 22, 2009 to June 27, 2013.

Table S2. Common Index Used for Disease Activity in Cox Predictor Model for Combined UC and CD Phase 3 Safety Populations

HBI score	Partial Mayo score	Common index
0-2	0	0
3-4	1	1
5	2	2
6-7	3	3
8	4	4
9-10	5	5
11-12	6	6
13-15	7	7
16-18	8	8
≥19	9	9

Abbreviations: HBI, Harvey-Bradshaw Index.

Table S3. Adverse Events by Months of Vedolizumab Exposure in the Overall Safety Population

Adverse event	0 to <3 months (n = 2830)	3 to <6 months (n = 2718)	6 to <12 months (n = 2432)	12 to <18 months (n = 1632)	18 to <24 months (n = 1288)	24 to <36 months (n = 1030)	36 to <48 months (n = 551)	≥48 months (n = 61)
	Patients, n (%)							
Any AE	1824 (64)	1512 (56)	1460 (60)	963 (59)	722 (56)	665 (65)	220 (40)	20 (33)
Any SAE	251 (9)	212 (8)	242 (10)	126 (8)	63 (5)	93 (9)	29 (5)	1 (2)
Common AEs (≥30 patients in any month category)								
Headache	250 (9)	112 (4)	110 (5)	67 (4)	40 (3)	41 (4)	12 (2)	1 (2)
Arthralgia	160 (6)	118 (4)	119 (5)	70 (4)	47 (4)	54 (5)	18 (3)	0
Nasopharyngitis	154 (5)	139 (5)	187 (8)	120 (7)	95 (7)	101 (10)	36 (7)	5 (8)
Exacerbation of CD	153 (5)	144 (5)	132 (5)	70 (4)	51 (4)	35 (3)	6 (1)	1 (2)
Nausea	145 (5)	76 (3)	80 (3)	53 (3)	32 (2)	30 (3)	10 (2)	0
Pyrexia	127 (4)	81 (3)	73 (3)	37 (2)	28 (2)	28 (3)	6 (1)	1 (2)
Fatigue	108 (4)	37 (1)	43 (2)	28 (2)	24 (2)	22 (2)	3 (<1)	0
Abdominal pain	101 (4)	76 (3)	106 (4)	61 (4)	57 (4)	62 (6)	19 (3)	0
Upper respiratory tract infection	95 (3)	69 (3)	102 (4)	68 (4)	47 (4)	49 (5)	20 (4)	1 (2)
Vomiting	80 (3)	48 (2)	48 (2)	35 (2)	29 (2)	26 (3)	5 (<1)	0
Dizziness	70 (2)	19 (<1)	32 (1)	20 (1)	12 (<1)	23 (2)	6 (1)	0
Cough	59 (2)	50 (2)	45 (2)	34 (2)	28 (2)	24 (2)	10 (2)	2 (3)
Anaemia	58 (2)	35 (1)	53 (2)	36 (2)	19 (1)	26 (3)	2 (<1)	0
Exacerbation of UC	57 (2)	73 (3)	98 (4)	56 (3)	28 (2)	38 (4)	8 (1)	1 (2)
Urinary tract infection	53 (2)	35 (1)	39 (2)	28 (2)	17 (1)	23 (2)	3 (<1)	0
Influenza like illness	51 (2)	25 (<1)	34 (1)	19 (1)	16 (1)	18 (2)	10 (2)	2 (3)
Oropharyngeal pain	51 (2)	25 (<1)	25 (1)	22 (1)	16 (1)	14 (1)	4 (<1)	0
Diarrhoea	43 (2)	47 (2)	48 (2)	38 (2)	38 (3)	34 (3)	14 (3)	2 (3)
Bronchitis	40 (1)	40 (1)	49 (2)	24 (1)	21 (2)	36 (3)	6 (1)	0
Lymphopenia	38 (1)	10 (<1)	9 (<1)	5 (<1)	2 (<1)	5 (<1)	0	0
Back pain	37 (1)	39 (1)	45 (2)	26 (2)	24 (2)	38 (4)	11 (2)	1 (2)
Abdominal pain, upper	37 (1)	16 (<1)	35 (1)	14 (<1)	16 (1)	16 (2)	2 (<1)	0
Rash	36 (1)	30 (1)	22 (<1)	20 (1)	15 (1)	12 (1)	7 (1)	0
Pruritus	35 (1)	33 (1)	14 (<1)	9 (<1)	6 (<1)	10 (<1)	0	0
Sinusitis	34 (1)	38 (1)	55 (2)	35 (2)	26 (2)	37 (4)	9 (2)	0
Influenza	34 (1)	37 (1)	43 (2)	29 (2)	25 (2)	34 (3)	6 (1)	0
Oedema peripheral	34 (1)	26 (<1)	25 (1)	12 (<1)	4 (<1)	10 (<1)	1 (<1)	0
Myalgia	33 (1)	18 (<1)	25 (1)	18 (1)	10 (<1)	16 (2)	2 (<1)	1 (2)
Insomnia	31 (1)	20 (<1)	23 (<1)	15 (<1)	10 (<1)	11 (1)	3 (<1)	0
Pain in extremity	31 (1)	16 (<1)	27 (1)	10 (<1)	13 (1)	9 (<1)	1 (<1)	0
Hypoaesthesia	30 (1)	19 (<1)	18 (<1)	7 (<1)	9 (<1)	10 (<1)	2 (<1)	0
Paraesthesia	30 (1)	11 (<1)	18 (<1)	12 (<1)	6 (<1)	6 (<1)	2 (<1)	0
Gastroenteritis	26 (<1)	38 (1)	51 (2)	38 (2)	24 (2)	37 (4)	7 (1)	1 (2)
Common SAEs (≥10 patients in any month category)								
Exacerbation of CD	82 (3)	81 (3)	64 (3)	30 (2)	20 (2)	11 (1)	2 (<1)	0
Exacerbation of UC	28 (<1)	29 (1)	43 (2)	17 (1)	8 (<1)	11 (1)	3 (<1)	0
Anal abscess	15 (<1)	5 (<1)	7 (<1)	6 (<1)	3 (<1)	0	2 (<1)	0
Abdominal pain	9 (<1)	3 (<1)	9 (<1)	6 (<1)	0	10 (<1)	4 (<1)	0
Small intestinal obstruction	7 (<1)	1 (<1)	13 (<1)	4 (<1)	1 (<1)	3 (<1)	0	0

Abbreviations: AE, adverse event; CD, Crohn's disease; SAE, serious adverse event; UC ulcerative colitis.

Table S4. Risk Factors and Treatment Outcomes of Patients With Malignancies

Malignancy (preferred term)	Age/Sex	IBD history	Relevant risk factors	Treatment	Outcome^a
Gastrointestinal malignancies					
Colon cancer	73.7/M	14 y UC	Former smoker; prior IS therapy	Resection	Resolved
Colon cancer	32.7/M	8 y UC	Severe inflammation at site of cancer; prior IS therapy	Total colectomy; chemotherapy	Death
Colon cancer	45.5/F	18 y CD	PSC; former smoker; prior IS therapy	Ileocolectomy	Resolved
Metastases to peritoneum	44.1/M	16 y UC	PSC; prior IS therapy	Chemotherapy	Death
Hepatic neoplasm malignant	51.1/F	4 y CD	Family history of hepatic cancer (father) ; prior IS therapy	Hospitalised; referred to oncology	Death
Carcinoid tumour of the appendix	20.7/F	11 y CD	Prior IS therapy	Appendectomy	Resolved
Genitourinary malignancies					
Transitional cell carcinoma	40.5/M	4 y UC	History of haematuria and dysuria; prior IS therapy	TURP	Resolved
Renal cancer	50.4/M	7 y UC	Smoking history, obesity	Nephrectomy	Resolved
Haematological malignancies					
B-cell lymphoma	42.9/M	4 y CD	Prior IS therapy	Chemo- and radiotherapy	Unresolved
Pulmonary malignancies					
Lung neoplasm malignant	75.3/F	17 y UC	Former smoker; prior IS therapy	Resection; lobectomy	Resolved
Lung neoplasm malignant (Hepatic neoplasm malignant)	69/F	20 y CD	Current smoker; history of lung cancer; prior IS therapy	Chemotherapy	Unresolved
Breast cancer					
Breast cancer	45.2/F	25 y CD	Smoking history; prior IS therapy	Tumourectomy; chemotherapy	Unresolved
Breast cancer in situ	63.5/M	26 y UC	Prior IS therapy	Mastectomy	Unresolved
Dermatological malignancies					
Malignant melanoma	47.4/M	5 y UC	Smoking history; prior IS therapy	Excision	Resolved
Malignant melanoma	70.2/M	7 y UC	Actinic keratosis, skin age spots; smoking history; prior IS therapy	Excision	Resolved
Squamous cell carcinoma	52.1/F	19 y CD	History of basal cell carcinoma, seborrheic keratosis, HPV, smoking, extensive sun exposure w/o sun screen; prior IS therapy	Excision	Resolved
Squamous cell carcinoma	49.7/M	3 y CD	Prior IS therapy	Excision	Resolved
Basal cell carcinoma	46.8/M	29 y CD	Skin lesions (groin), positive HPV lesions, lung nodule; prior IS therapy	Excision	Resolved
Basal cell carcinoma Squamous cell carcinoma	70.7/F	13 y UC	Smoking history, history of basal cell carcinoma, hysterectomy, prior IS therapy ^b	Excision	Resolved

Abbreviations: CD, Crohn's disease; F, female; HPV, human papillomavirus; IBD, inflammatory bowel disease; IS, immunosuppressive; M, male; PSC, primary sclerosing cholangitis; TURP, transurethral resection of the prostate; UC, ulcerative colitis; w/o; without; y, years.

^aAt last patient contact.

^bHad received 3 placebo and no vedolizumab infusions during GEMINI 1 when event occurred

Table S5. Exposure-Adjusted Incidence Rates of Hepatobiliary Adverse Events in the Overall Safety Population

Adverse event	UC				CD				UC and CD			
	Placebo		Vedolizumab		Placebo		Vedolizumab		Placebo		Vedolizumab	
	UC (n = 149) ^a		UC (n = 1107) ^b		CD (n = 355) ^c		CD (n = 1723) ^d		UC and CD (n = 504) ^e		UC and CD (n = 2830) ^f	
	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)
Hepatocellular damage and hepatitis NEC	0	0.0 (0.0-3.7)	3	0.1 (0.0-0.3)	0	0.0 (0.0-2.3)	13	0.5 (0.2-0.7)	0	0.0 (0.0-1.4)	16	0.3 (0.2-0.5)
Hepatic steatosis	0	0.0 (0.0-3.7)	2	0.1 (0.0-0.2)	0	0.0 (0.0-2.3)	7	0.3 (0.1-0.4)	0	0.0 (0.0-1.4)	9	0.2 (0.1-0.3)
Cytolytic hepatitis	0	0	0	0	0	0.0 (0.0-2.3)	3	0.1 (0.0-0.2)	0	0.0 (0.0-1.4)	3	0.1 (0.0-0.1)
Hepatitis	0	0	0	0	0	0.0 (0.0-2.3)	2	0.1 (0.0-0.2)	0	0.0 (0.0-1.4)	2	<0.1 (0.0-0.1)
Hepatitis acute	0	0.0 (0.0-3.7)	1	<0.1 (0.0-0.1)	0	0	0	0	0	0.0 (0.0-1.4)	1	<0.1 (0.0-0.1)
Hepatotoxicity	0	0	0	0	0	0.0 (0.0-2.3)	1	<0.1 (0.0-0.1)	0	0.0 (0.0-1.4)	1	<0.1 (0.0-0.1)
Hepatic enzymes and function abnormalities	0	0.0 (0.0-3.7)	4	0.2 (0.0-0.4)	0	0.0 (0.0-2.3)	2	0.1 (0.0-0.2)	0	0.0 (0.0-1.4)	6	0.1 (0.0-0.2)
Hypertransaminasaemia	0	0.0 (0.0-3.7)	4	0.2 (0.0-0.4)	0	0	0	0	0	0.0 (0.0-1.4)	4	0.1 (0.0-0.2)
Hepatic function abnormal	0	0	0	0	0	0.0 (0.0-2.3)	2	0.1 (0.0-0.2)	0	0.0 (0.0-1.4)	2	<0.1 (0.0-0.1)
Hepatic failure and associated disorders	0	0.0 (0.0-3.7)	1	<0.1 (0.0-0.1)	0	0	0	0	0	0.0 (0.0-1.4)	1	<0.1 (0.0-0.1)
Hepatic failure	0	0.0 (0.0-3.7)	1	<0.1 (0.0-0.1)	0	0	0	0	0	0.0 (0.0-1.4)	1	<0.1 (0.0-0.1)

Abbreviations: CD, Crohn's disease; CI, confidence interval; NEC, not elsewhere classified; PY, person-years; UC ulcerative colitis.

Exposure-adjusted incidence rates for each AE were calculated by dividing the number of patients experiencing the event by the total PYs, multiplied by 100. PYs were calculated as the sum of each patient's contribution, calculated from the days of exposure (ie, AE onset date minus the date of first dose plus 1 day). For each AE, the PYs were truncated after a patient experienced the AE and each AE was counted only once per patient. Patients who were randomised to placebo and then rolled over into an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. When the number of events = 0, the 95% CI was calculated based on rule of 3 (ie, [0, 3/total PYs]*100).

^aIncludes patients from GEMINI 1.

^bIncludes patients from studies C13002, C13004, GEMINI 1, and GEMINI LTS.

^cIncludes patients from GEMINI 2 and GEMINI 3.

^dIncludes patients from studies C13004, GEMINI 2, GEMINI 3, and GEMINI LTS.

^eIncludes patients from GEMINI 1, GEMINI 2, and GEMINI 3.

^fIncludes patients from all 6 studies.

Table S6. Exposure-Adjusted Incidence Rates of Liver Function Test Abnormalities

Adverse event	UC				CD				UC and CD			
	Placebo		Vedolizumab		Placebo		Vedolizumab		Placebo		Vedolizumab	
	UC (n = 149) ^a		UC (n = 1107) ^b		CD (n = 355) ^c		CD (n = 1723) ^d		UC and CD (n = 504) ^e		UC and CD (n = 2830) ^f	
	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)
Liver function analyses	5	6.4 (0.7-12.1)	45	2.2 (1.6-2.9)	1	0.8 (0.0-2.2)	51	1.9 (1.4-2.4)	6	2.8 (0.6-5.1)	96	2.1 (1.6-2.5)
ALT increased	2	2.5 (0.0-6.0)	19	0.9 (0.5-1.3)	1	0.8 (0.0-2.2)	20	0.7 (0.4-1.1)	3	1.4 (0.0-3.0)	39	0.8 (0.6-1.1)
AST increased	1	1.2 (0.0-3.7)	15	0.7 (0.4-1.1)	1	0.8 (0.0-2.2)	16	0.6 (0.3-0.9)	2	0.9 (0.0-2.2)	31	0.7 (0.4-0.9)
LFT abnormal	0	0.0 (0.0-3.7)	14	0.7 (0.3-1.0)	0	0.0 (0.0-2.3)	9	0.3 (0.1-0.5)	0	0 (0.0-1.4)	23	0.5 (0.3-0.7)
Hepatic enzyme increased	2	2.5 (0.0-6.0)	8	0.4 (0.1-0.7)	0	0.0 (0.0-2.3)	11	0.4 (0.2-0.6)	2	0.9 (0.0-2.2)	19	0.4 (0.2-0.6)
Transaminases increased	1	1.2 (0.0-3.7)	1	<0.1 (0.0-0.1)	0	0.0 (0.0-2.3)	8	0.3 (0.1-0.5)	1	0.5 (0.0-1.4)	9	0.2 (0.1-0.3)
Blood bilirubin increased	0	0.0 (0.0-3.7)	2	0.1 (0.0-0.2)	0	0.0 (0.0-2.3)	1	<0.1 (0.0-0.1)	0	0 (0.0-1.4)	3	0.1 (0.0-0.1)
GGT increased	0	0.0 (0.0-3.7)	1	<0.1 (0.0-0.1)	0	0.0 (0.0-2.3)	2	0.1 (0.0-0.2)	0	0 (0.0-1.4)	3	0.1 (0.0-0.1)
Bilirubin conjugated increased	0	0	0	0	0	0.0 (0.0-2.3)	1	<0.1 (0.0-0.1)	0	0 (0.0-1.4)	1	<0.1 (0.0-0.1)
Total bile acids increased	0	0	0	0	0	0.0 (0.0-2.3)	1	<0.1 (0.0-0.1)	0	0 (0.0-1.4)	1	<0.1 (0.0-0.1)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, Crohn's disease; CI, confidence interval; GGT, gamma-glutamyltransferase; LFT, liver function test; PY, person-years; UC ulcerative colitis.

Exposure-adjusted incidence rates for each AE were calculated by dividing the number of patients experiencing the event by the total PYs, multiplied by 100. PYs were calculated as the sum of each patient's contribution, calculated from the days of exposure (ie, AE onset date minus the date of first dose plus 1 day). For each AE, the PYs were truncated after a patient experienced the AE and each AE was counted only once per patient. Patients who were randomised to placebo and then rolled over into an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. When the number of events = 0, the 95% CI was calculated based on rule of 3 (ie, [0, 3/total PYs]*100).

^aIncludes patients from GEMINI 1.

^bIncludes patients from studies C13002, C13004, GEMINI 1, and GEMINI LTS.

^cIncludes patients from GEMINI 2 and GEMINI 3.

^dIncludes patients from studies C13004, GEMINI 2, GEMINI 3, and GEMINI LTS.

^eIncludes patients from GEMINI 1, GEMINI 2, and GEMINI 3.

^fIncludes patients from all 6 studies.

Table S7. Deaths Reported for the Overall Safety Population

Indication	Age/Sex	Exposure		No. of vedolizumab infusions	Preferred term
		Days after			
		First dose ^a	Last dose ^b		
<i>Placebo-controlled studies</i>					
UC	66/M	14	14	1	Arteriosclerosis coronary artery
CD	74.9/M	N/A	N/A	8 PBO	Bronchopneumonia
CD	23.4/M	88	75	2	Myocarditis
CD	30.7/M	98	28	4	Septic shock
CD	46.9/F	97	6	5	Intentional overdose
CD	27.8/M	260	45	5	CD, sepsis
<i>Open-label studies</i>					
UC	49.2/F	332	50	4	Respiratory failure
UC	70.8/F	195	111	5	Cerebrovascular accident
UC	72.2/M	883	16	17	Pulmonary embolism
CD	32.3/M	125	125	1	Sepsis
CD	63.7/M	387	23	14	Traumatic intracranial haemorrhage
CD	38.1/M	380	98	7	Completed suicide
CD	51.1/F	1193	58	42	Hepatic neoplasm malignant

Abbreviations: CD, Crohn's disease; N/A, not applicable; PBO, placebo; UC, ulcerative colitis.

^aTime from the first dose of vedolizumab (in any study) to the date of death.

^bTime from the last dose of vedolizumab to the date of death.

Figure S1

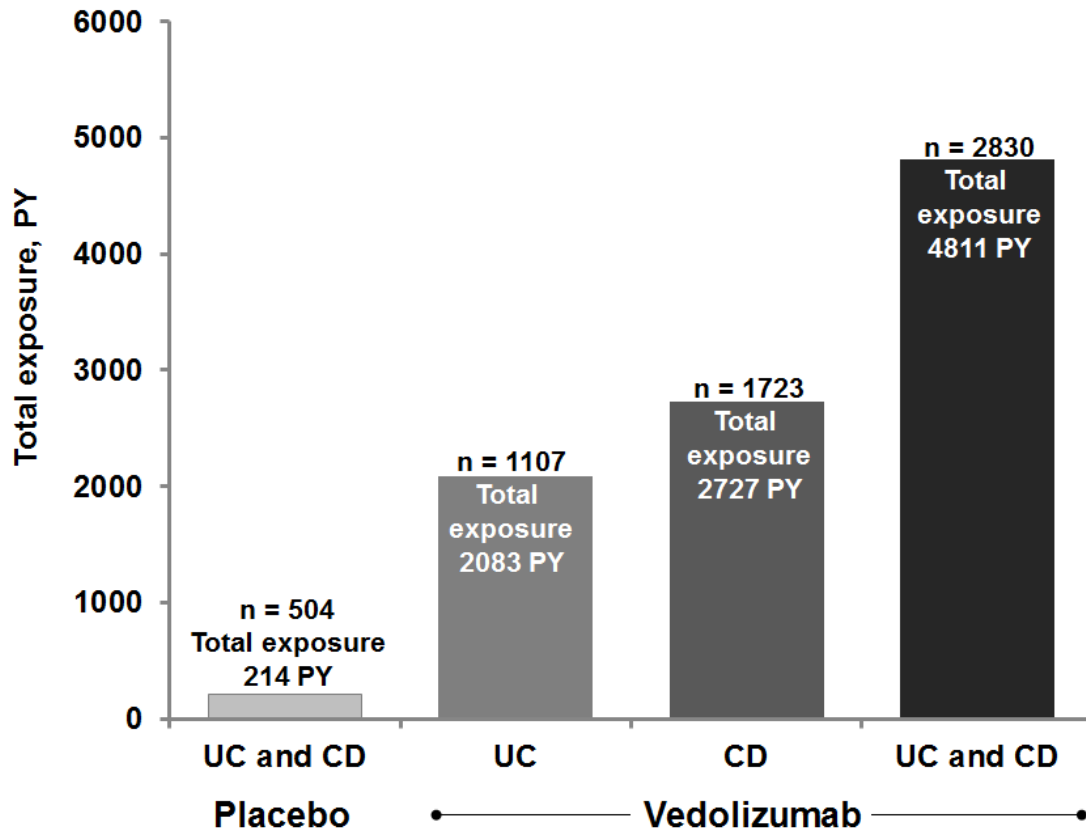


Figure S1. Exposure to vedolizumab and placebo in the overall safety population.

Patients who were randomised to placebo in GEMINI 1, GEMINI 2, or GEMINI 3 and then enrolled into an open-label study could contribute to PYs in either the placebo or vedolizumab group. Placebo patients include those from GEMINI 1, GEMINI 2, and GEMINI 3. UC patients include those from studies C13002, C13004, GEMINI 1, and GEMINI LTS. CD patients include those from studies C13004, GEMINI 2, GEMINI 3, and GEMINI LTS. Abbreviations: CD, Crohn's disease; LTS, long-term safety; PY, person-year; UC, ulcerative colitis.

Figure S2

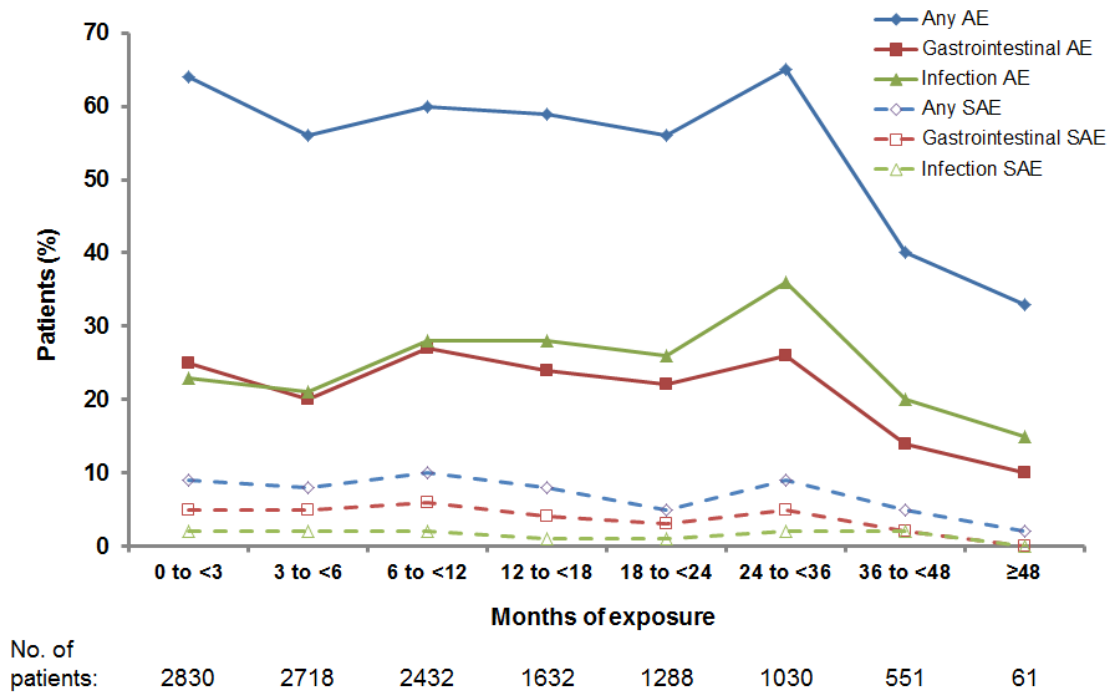


Figure S2. Adverse events (solid lines) and serious adverse events (dotted lines) by months of vedolizumab exposure. Gastrointestinal AEs and SAEs (red lines) and infection AEs and SAEs (green lines) include all events listed under the gastrointestinal disorders and infections and infestations system organ classes of the MedDRA version 14.0. Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

Figure S3

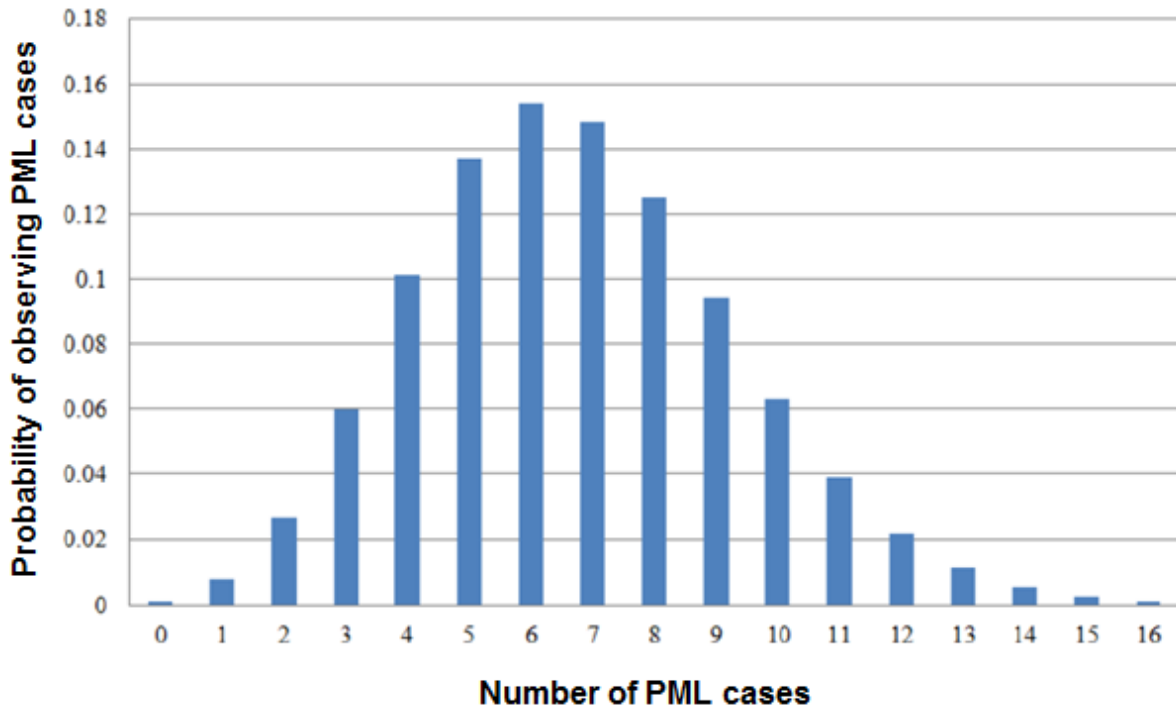


Figure S3. Poisson probability distribution of the likelihood of observing cases of PML with vedolizumab if the risk were similar to that of natalizumab.

Abbreviations: PML, progressive multifocal leukoencephalopathy

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