

A Phase I, Multiple-Dose Study of Vedolizumab in Japanese Patients With Ulcerative Colitis

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Abstract

Although previous studies have shown that patients with ulcerative colitis may benefit from treatment with vedolizumab, a humanized monoclonal antibody targeting the $\alpha_4\beta_7$ integrin heterodimer, no data exist in Japanese populations. The aim of this phase I, open-label, multicenter study was to assess the pharmacokinetics, pharmacodynamics, efficacy, and safety of vedolizumab in Japanese patients with ulcerative colitis. Adult patients with confirmed ulcerative colitis received either 150 mg (step 1) or 300 mg (step 2) of intravenous (IV) vedolizumab on days 1, 15, and 43 of the study protocol. Pharmacokinetic, pharmacodynamic, safety, and efficacy parameters were all assessed through study end (day 239). Nine patients were enrolled in this study (150 mg, n = 3; 300 mg, n = 6). Patients who received vedolizumab IV 300 mg had approximately twice the drug exposure of those receiving vedolizumab IV 150 mg (day 1 AUC_{day14} 744 vs 408 $\mu\text{g}\cdot\text{d}/\text{mL}$) and a longer-lasting maximal saturation of $\alpha_4\beta_7$ integrin (155 vs 99 days). The number of treatment-emergent adverse events, all of which were mild or moderate in intensity, was similar between the 150-mg (15 events) and 300-mg (20 events) groups. The 2 patients (150 mg group) not in clinical remission by partial Mayo score at the start of the study met the criteria for clinical remission on days 15 and 155 of the study, respectively. In conclusion, in Japanese patients with ulcerative colitis, vedolizumab showed similar pharmacokinetic and pharmacodynamic results to those seen in non-Japanese patients. Vedolizumab was well tolerated and demonstrated clinical activity consistent with previous studies.

Keywords

inflammatory bowel disease, ulcerative colitis, vedolizumab, Japanese

Ulcerative colitis is a chronic, idiopathic, and diffuse inflammatory condition¹ with clinical symptoms including bloody diarrhea, bowel urgency, hematochezia, abdominal pain, and lack of energy.^{2,3} Inflammatory bowel diseases (IBDs) such as ulcerative colitis are thought to result from overly aggressive T-cell-mediated immune responses to commensal bacteria in the gut, resulting in injury to the digestive tract.^{2,4} Various factors may interact to cause this inappropriate T-cell response, including genetic susceptibility of patients, the population of bacteria in the intestinal lumen, and environmental triggers such as the use of nonsteroidal, anti-inflammatory drugs.⁴

In Japan the prevalence of ulcerative colitis is lower than that in Western nations; however, it has steadily increased since the 1970s.⁵ In 2012 there were approximately 166,000 patients in Japan who were receiving financial support for the management of ulcerative colitis from the government.⁶ A registry study of Japanese patients with intractable diseases showed that the age-standardized prevalence of ulcerative colitis was 63.6 patients per 100,000.⁵ For mildly to moderately active ulcerative colitis, both Japanese and international guidelines recommend preparations of aminosalicilylic acid and its derivatives as a first-line treatment and

corticosteroids as second-line treatment, depending on the severity of the symptoms.^{1,6} Corticosteroids

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are used in particular to control disease flares; however, some cases of ulcerative colitis are refractory to corticosteroid treatment, and such patients are often escalated to receive immunomodulator therapies such as 6-mercaptopurine and azathioprine.¹ Unfortunately, these therapies are associated with systemic adverse effects (AEs), and prolonged use can predispose patients to infections and venous thromboembolism (corticosteroids)⁷ and to lymphoma development, bone marrow suppression, leukopenia, and severe hair loss (immunomodulators).^{1,8}

Several biologic therapies have recently become available that target components of the immune system, including infliximab, adalimumab, certolizumab pegol, and golimumab, which act by binding the proinflammatory cytokine tumor necrosis factor α (TNF- α).⁹ However, anti-TNF- α agents are potentially associated with serious AEs such as opportunistic infections, including tuberculosis, and congestive heart failure in cardiopathic patients as well as allergic reactions. It is therefore imperative to identify novel agents, for instance, gut-selective treatments, that specifically reduce gut inflammation in patients with ulcerative colitis.

Vedolizumab is a humanized monoclonal antibody that recognizes the $\alpha_4\beta_7$ integrin heterodimer expressed on leukocytes, preventing its adhesion to the mucosal addressin cell adhesion molecule-1 receptor found on mucosal vasculature.¹⁰ Vedolizumab demonstrates gut selectivity and high specificity for the $\alpha_4\beta_7$ integrin, preventing infiltration of the intestinal mucosa by leukocytes and avoiding AEs caused by nonspecific binding. Other therapies that target the α_4 component can have adverse effects on other tissues by interfering with the activity of other integrin heterodimers; for example, treatment with the monoclonal antibody natalizumab can predispose patients to progressive multifocal leukoencephalopathy (PML) by reducing immune surveillance of the central nervous system,^{11,12} which is governed by the $\alpha_4\beta_1$ integrin heterodimer.¹³

The GEMINI 1 trial demonstrated that vedolizumab was efficacious in predominantly white patients with ulcerative colitis, with an increased likelihood of clinical remission and mucosal healing compared with placebo following 6 weeks of induction treatment.¹⁴ However, studies of vedolizumab in Japanese patients with ulcerative colitis are lacking despite the strong possibility of clinical benefit in this population. Here we report the results of a phase 1 study investigating multiple doses of vedolizumab in Japanese patients with ulcerative colitis.

Methods

Study Design and End Points

This study was conducted in compliance with the Institutional Review Board regulations of each site and in

accordance with the ethical principles proposed in the Declaration of Helsinki. All patients provided written informed consent.

This phase 1, open-label, multiple-dose study of vedolizumab in Japanese patients with ulcerative colitis consisted of 2 6-week treatment periods: step 1, vedolizumab 150 mg; step 2, dose escalation to 300 mg vedolizumab. The primary objectives were to investigate the pharmacokinetics (PK), safety, and tolerability of the 2 intravenous (IV) dose levels of vedolizumab in Japanese patients with ulcerative colitis. Secondary objectives were to analyze pharmacodynamics (PD) and efficacy in the same population.

Patient Population

Eligible patients were adults aged between 18 and 70 years old at the time of consent with a confirmed diagnosis of ulcerative colitis (in accordance with the Revised Diagnostic Criteria for ulcerative colitis, 1998).¹⁵ Use of adequate contraception from the time of screening to 28 weeks following the final administration of the study drug was a requirement, as were negative test results for hepatitis B surface antigens, hepatitis C virus antibody, human immunodeficiency virus, and serologic reactions for syphilis. Patients also had to weigh at least 40 kg at screening and before study drug administration. Patients were excluded if they were scheduled to receive a surgical procedure for ulcerative colitis between screening and study end; had hemoglobin <10 g/dL at screening; started to receive or increased the dosage of an oral mesalamine or salazosulfapyridine within 2 weeks before screening; started to receive ≤ 30 mg/d of oral prednisolone or other oral corticosteroid at equivalent dose or increased its dosage within 4 weeks before screening; received a >30 mg/d of oral prednisolone or other oral corticosteroid at an equivalent dose within 4 weeks of screening; received a corticosteroid injection within 6 weeks of screening; received any immunomodulator 12 weeks before screening (ongoing, stable-dose therapy with azathioprine or 6-mercaptopurine was acceptable if it had not started or had the dosage increased within 8 weeks of screening); or received any monoclonal antibody agents within 24 weeks of screening. Patients with any other bowel disease except ulcerative colitis were ineligible to participate in the study, as were those with ulcerative colitis-associated dysplasia or cancer in the rectum or colon, gastrointestinal infection, or any other serious disease (eg, liver or renal disorders).

Dosing and Regimen

Vedolizumab 2, 6, or 10 mg/kg was demonstrated as well tolerated and effective compared with placebo in a previous phase 2 study. However, antivedolizumab antibody and neutralizing antivedolizumab antibody

were detected in a dose-dependent manner (25% in the 2 mg/kg cohort, 7% in the 6 mg/kg cohort, and 0% in the 10 mg/kg cohort).¹⁶ A dose-dependent reduction in immunogenicity with vedolizumab was also reported in another phase 1 study with healthy volunteers, indicating that a 300-mg dose was more effective than 150 mg.¹⁷ As a result, the clinical dose was subsequently determined as 300 mg.¹⁴ As the first evaluation in Japanese patients and the potential risk of PML, 150 mg was deemed appropriate for initial evaluation. However, for ethical reasons related to the lower efficacy of this dose, only 3 patients were allocated to the 150-mg group.

Following screening and enrollment into step 1 of the study, eligible patients received vedolizumab 150 mg by IV infusion over 30-60 minutes on days 1, 15, and 43. In step 2, additional patients were to be enrolled to receive vedolizumab 300 mg IV on days 1, 15, and 43. Dose modification was not permitted. Follow-up began on day 44 (the day after the final dose of study drug was administered) until day 238.

Study Assessments

Pharmacokinetics. Venous blood samples for vedolizumab serum concentration were collected at the following time points for both the 150-mg and 300-mg dose groups: on day 1 (first dose) at predose, 2, 6, and 12 hours; on days 2, 3 (applicable only to first 3 patients in step 1), and 8; on day 15 (second dose) at predose, 2, and 6 hours; on days 16 and 29; on day 43 (third dose) at predose, 2, and 6 hours; and during follow-up (day 44 and weeks 8, 10, 14, 18, 22, 26, 30, and 34). Serum concentrations of vedolizumab were measured by enzyme-linked immunosorbent assay by QPS Holdings, LLC (Newark, Delaware).

The following main PK parameters were estimated from the serum concentration-time profile of vedolizumab by noncompartmental analysis (WinNonlin version 5.3; Pharsight Corporation, Cary, North Carolina): after the initial dose (day 1), area under the serum concentration-time curve (AUC) from week 0 to week 2 (AUC_{day14}), maximum observed serum concentration (C_{max}), time of first occurrence of C_{max} , apparent terminal elimination half-life ($t_{1/2z}$), apparent total body clearance, and volume of distribution during the terminal disposition phase; after the third dose (day 43), AUC from week 0 to week 8 (AUC_{day56}), C_{max} , time to C_{max} , and $t_{1/2z}$.

Safety Assessments. The safety results for each enrolled subject were analyzed following each administered dose before the subsequent dose of the study drug was administered. Following the conclusion of step 1, all safety data obtained were evaluated before step 2 (dose escalation). AEs were assessed and graded

according to the *Medical Dictionary for Regulatory Activities* version 13.1 and summarized using preferred terms and system organ classes. Additional safety end points of key interest included incidence of PML, development of antivedolizumab antibody, and neutralizing antibody titers, assessed pretreatment, at weeks 4 and 6 (treatment), and at weeks 8, 10, 14, 18, 22, 26, 30, and 34 (follow-up).

PD Evaluations. Percentage mucosal addressin cell adhesion molecule-1 represents a suitable proxy for assessment of $\alpha_4\beta_7$ integrin saturation¹⁸ and was measured by flow cytometry and analyzed at the same time points as for PK assessments by Mitsubishi Chemical Medience Corporation (Tokyo, Japan).

Efficacy Evaluations. The partial Mayo score¹⁹ was used to monitor changes in ulcerative colitis disease activity during the course of the study by the treating physician. Clinical remission was defined as a partial Mayo score of ≤ 2 with no individual subscore > 1 . Clinical response was defined as a decrease in total score of at least 2 points and at least 25% from baseline, with a decrease of rectal bleeding subscore of at least 1 point from baseline or accompanying rectal bleeding subscore ≤ 1 . Observations were made pretreatment on days 1, 15, and 43 as well as during follow-up on days 71, 155, and 239.

Statistical Analysis. All data were to be reviewed before database lock to assess accuracy and completeness of the study database, patient evaluability, and appropriateness of the planned statistical methods. Four analysis sets were used in this study, namely a PK analysis set, a safety analysis set, a PD analysis set, and an efficacy analysis set; each of these consisted of 3 patients in the vedolizumab 150-mg group and 6 patients in the vedolizumab 300-mg group. Neither patients nor data were excluded from any analysis set. Results were summarized using descriptive statistics. All data analysis was performed using SAS release version 9.2 (SAS Institute, Cary, North Carolina).

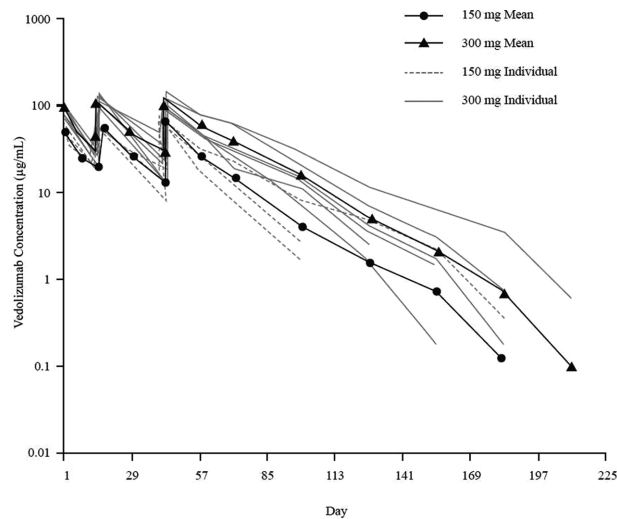
Results

Patient Disposition and Baseline Characteristics

Of 12 patients screened from 3 centers in Japan, 9 were enrolled in the study. Three patients received vedolizumab 150 mg (step 1), and 6 patients were treated with vedolizumab 300 mg (step 2). One patient in the 150-mg group discontinued the study due to an AE following completion of study drug administrations. Patient baseline characteristics are listed in Table 1. Overall there were more male than female subjects in the study (77.8% were male), and mean patient age was 44.7 years. Body mass index and body

Table 1. Summary of Demographic and Baseline Characteristics for All Treatment Groups, All Analysis Sets

	150 mg (n = 3)	300 mg (n = 6)	Total (n = 9)
Mean age (y)	45.3	44.3	44.7
Range	27.0–70.0	21.0–62.0	21.0–70.0
Male, n (%)	2 (66.7)	5 (83.3)	7 (77.8)
Mean height (cm)	160.0	170.7	167.1
Range	157.0–165.0	157.0–181.0	157.0–181.0
Mean body weight (kg)	58.97	74.05	69.02
Range	43.70–78.30	50.5–93.1	43.7–93.1
Median body mass index (kg/m ²)	22.00	24.90	24.70
Range	17.70–28.80	20.5–31.8	17.7–31.8
Current smoker, n (%)	1 (33.3)	0	1 (11.1)
Acute exacerbation within 12 months, n (%)	2 (66.7)	1 (16.7)	3 (33.3)
Hospitalization at or within 12 months, n (%)	1 (33.3)	0	1 (11.1)
Colonoscopy and proctoscopy within 6 months, n (%)	2 (66.7)	2 (33.3)	4 (44.4)

**Figure 1.** Changes in arithmetic mean serum concentrations of vedolizumab following multiple intravenous infusions of vedolizumab at 150 mg and 300 mg in Japanese patients with ulcerative colitis.

weight were higher in the vedolizumab 300-mg group compared with the 150-mg group. All patients received concomitant treatment with 5-aminosalicylic acid, and 2 patients in the 150-mg group additionally received corticosteroids (started from 2 to 12 months before screening for the present study), and 1 patient in each group received azathioprine.

Pharmacokinetics

Semilogarithmic graphs of the mean serum concentration-time curves of vedolizumab following multiple IV infusions at 150 mg and 300 mg are shown in Figure 1. Following IV dosing, serum concentrations of vedolizumab increased with increasing dose.

Table 2. Summary of Pharmacokinetic Parameters of Vedolizumab After Intravenous Infusions of Vedolizumab on Day 1 in Japanese Patients With Ulcerative Colitis

Variable	150 mg (n = 3)			300 mg (n = 6)		
	Mean	SD	Median	Mean	SD	Median
Day 1						
AUC _{day14} (µg·d/mL)	408	48	388	744	92	744
AUC _{last} (µg·d/mL)	413	43	388	744	92	756
MRT _{last} (d)	5.7	0.1	5.8	5.3	0.1	5.3
C _{max} (µg/mL)	52.9	10.5	50.2	99.6	23.4	101.5
t _{max} (d)	0.43	0.53	0.13	0.24	0.16	0.20
AUC _∞ (µg·d/mL)	704	103	742	1176	199	1165
λ _z (1/d)	0.0691	0.0144	0.0756	0.0740	0.0068	0.0762
t _{1/2z} (d)	10.4	2.5	9.2	9.5	1.0	9.1
CL (L/d)	0.22	0.03	0.20	0.26	0.04	0.26
V _z (L)	3.20	0.665	3.22	3.52	0.431	3.51
MRT _∞ (d)	15.5	3.0	14.5	13.5	1.6	12.8
Day 43						
AUC _{day14} (µg·d/mL)	582	55	595	1176	261	1075
AUC _{day28} (µg·d/mL)	865	146	904	1863	502	1625
AUC _{day56} (µg·d/mL)	1154	297	1179	2621	868	2196
C _{max} (µg/mL)	68.7	7.8	66.2	126.5	26.7	121.0
t _{max} (d)	0.24	0.10	0.29	0.15	0.06	0.12
λ _z (1/d)	0.0467	0.0125	0.0514	0.0414	0.0086	0.0414
t _{1/2z} (d)	15.7	4.9	13.5	17.4	3.9	16.7

λ_z indicates terminal disposition phase rate constant; AUC, area under the serum concentration-time curve; AUC_{day14}, AUC from week 0 to week 2; AUC_{day28}, AUC from week 0 to week 4; AUC_{day56}, AUC from week 0 to week 8; AUC_{last}, AUC to time of last quantifiable concentration; AUC_∞, AUC to infinity, calculated using the observed value of the last quantifiable concentration; CL, total clearance after intravenous administration, calculated using the observed value of the last quantifiable concentration; C_{max}, maximum observed concentration; MRT, mean residence time; t_{max}, time of first occurrence of C_{max}; t_{1/2z}, terminal disposition phase half-life; V_z, volume of distribution during the terminal disposition phase.

Notably, vedolizumab did not accumulate substantially between doses, although the predose serum concentrations between the second and third doses were slightly higher than 0. After C_{max} was reached following the third dose of the study drug on day 43, the serum concentration of vedolizumab decreased in a mostly monoexponential fashion until concentrations reached approximately 1–10 µg/mL. At concentrations below 1 µg/mL the elimination profile was nonlinear, indicating that vedolizumab exhibited target-mediated drug disposition. Importantly, the terminal disposition phase of vedolizumab was similar between the 150-mg and 300-mg groups.

Descriptive statistics of PK parameters are shown in Table 2. The mean C_{max} was greater for the 300-mg dose of the study drug than for the 150-mg dose (99.6 vs 52.9 µg/mL, respectively) on day 1 of the analysis. The mean t_{1/2z} following the first dose of vedolizumab was similar for both treatment groups (10.4 vs 9.46 days for the 150-mg vs 300-mg groups, respectively). The mean AUC_{day14} of the 300-mg group was almost double that of the 150-mg group (1176 vs 582 µg·d/mL),

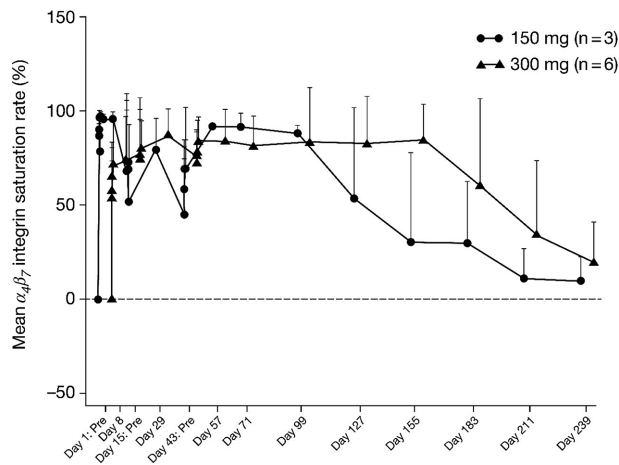


Figure 2. Changes in mean $\alpha_4\beta_7$ integrin saturation rates following multiple intravenous infusions of vedolizumab 150 mg and 300 mg in Japanese patients with ulcerative colitis.

indicating a higher exposure in patients in the 300-mg group compared with the 150-mg group. The mean $t_{1/2z}$ following the last dose of vedolizumab was also similar between treatment groups, at 15.7 days for the 150-mg group versus 17.4 days for the 300-mg group.

Pharmacodynamics

PD analysis of $\alpha_4\beta_7$ integrin saturation is shown in Figure 2 and Supplementary Figure S1. Both 150 mg and 300 mg of vedolizumab resulted in rapid $\alpha_4\beta_7$ receptor saturation, and this was maintained well beyond the end of the treatment period. Following the last dose, the saturation lasted up to days 99 and 155 in the 150-mg and 300-mg groups, respectively, before gradually decreasing. These data indicate that near-maximal $\alpha_4\beta_7$ integrin saturation was achieved after the first dose in both treatment groups and was maintained throughout the treatment period in the 300-mg group.

The geometric mean area under the drug effect-time curve by percentage integrin saturation after 14 days was similar between the 150-mg and 300-mg groups after dosing on day 1 (1230.6 vs 990.7%·day; $n = 3$ and $n = 5$ [PD parameters were not estimated on day 1 for 1 patient due to protocol deviation with the sampling time], respectively) and after dosing on day 43 (1098.6 vs 1167.4%·day; $n = 3$ and $n = 6$, respectively). The geometric mean maximum effect (E_{max}) of vedolizumab by percent integrin saturation was similar between 150 mg and 300 mg treatment groups on days 1 (99.1% vs 95.3%, $n = 3$ and $n = 5$, respectively), 43 (95.4% vs 98.1%, $n = 2$ [One patient in the 150-mg group was discontinued due to AEs and was not evaluated on day 183] and $n = 6$, respectively) and over the course of the study (99.7% vs 98.8%, $n = 2$ [One patient in the 150-mg group was discontinued due to AEs and was not evaluated on day 183] and $n = 5$ [PD parameters were

not estimated on day 1 for 1 patient due to protocol deviation with the sampling time], respectively).

Safety

As shown in Table 3, 35 treatment-emergent AEs (TEAEs), all of which were mild or moderate in intensity, were reported across both dose groups (15 events in the vedolizumab 150-mg group and 20 events in the vedolizumab 300-mg group). A total of 12 events (9 in the 150-mg group and 3 in the 300-mg group) were considered to be study-drug related by the investigator. One patient in each group had a serious TEAE, and both of these events were considered related to the study drug (colon dysplasia with vedolizumab 150-mg group, revealed by colonoscopy 3 months after the last dose of study drug, and ileus in the 300-mg group). Analysis of all TEAEs by system organ class showed that GI disorders (eg, abdominal discomfort, lower abdominal pain) were the most prevalent in both treatment groups (Table 4). Nasopharyngitis was most commonly reported by patients ($n = 4$) in the vedolizumab 300-mg group, although this was considered to be unrelated to study-drug administration. One of the 3 patients receiving vedolizumab 150 mg discontinued the study due to a serious TEAE (colon dysplasia) following completion of study-drug administration. The patient required total colectomy as a result, and although he was considered to have been at high risk of dysplasia due to colonoscopy results obtained before the start of the study drug, this serious TEAE was considered to be study-drug related because the event was noted about 6 months after the start of the study. No deaths were reported in the study. No patients developed PML or experienced signs and symptoms consistent with PML during the study period.

One patient in the 150-mg group (patient 2) tested positive for antivedolizumab antibody and for neutralizing antivedolizumab antibodies on day 155 but not on day 239. This patient had a relapse from day 155 to day 239, with his partial Mayo score increasing from 2 to 6 (Supplementary Figure S2 and Supplementary Table S1). However, on day 155 the serum concentration of vedolizumab in patient 2 was below the limit for quantification ($<0.125 \mu\text{g/mL}$); therefore, it was not possible to determine whether the decrease in efficacy was due to the presence of neutralizing antivedolizumab antibodies or to the low concentration of vedolizumab in serum. In addition, PD analysis showed that $\alpha_4\beta_7$ integrin saturation in patient 2 rapidly decreased after day 99 to almost 0% on day 127 (Supplementary Figure S1).

One patient in the 300-mg group (patient 9) also tested positive for antivedolizumab antibody on days 155, 183, 211, and 239 and for neutralizing antivedolizumab antibody on days 183 and 239. Efficacy of vedolizumab in this patient was not assessable

Table 3. Overview of Adverse Events and Serious Adverse Events

	Number (%)					
	150 mg (n = 3)		300 mg (n = 6)		Total (n = 9)	
	Events	Patients	Events	Patients	Events	Patients
TEAEs	15	3 (100.0)	20	6 (100.0)	35	9 (100.0)
Related ^a	9		3		12	
Not related	6		17		23	
Severity of TEAEs						
Mild	10		18		28	
Moderate	5		2		7	
Severe	0		0		0	
Leading to study drug discontinuation	0		0		0	
Serious TEAEs	1	1 (33.3)	1	1 (16.7)	2	2 (22.2)
Related ^a	1		1		2	
Not related	0		0		0	
Leading to study drug discontinuation	0		0		0	
Deaths		0		0		0

TEAEs, treatment-emergent adverse events.

^aEvents attributed by investigator as definitely, probably, or possibly related to study drug.

Table 4. Incidence of All TEAEs by System Organ Class

System Organ Class	Number of Patients (%)	
	150 mg (n = 3)	300 mg (n = 6)
Subjects with any TEAEs	3 (100.0)	6 (100.0)
Gastrointestinal disorders	3 (100.0)	3 (50.0)
Infections and infestations	0	4 (66.7)
Nervous system disorders	2 (66.7)	1 (16.7)
Musculoskeletal and connective tissue disorders	0	2 (33.3)
Respiratory, thoracic, and mediastinal disorders	2 (66.7)	0
Skin and subcutaneous tissue disorders	1 (33.3)	1 (16.7)
Cardiac disorders	1 (33.3)	0
Eye disorders	1 (33.3)	0
General disorders and administration site conditions	1 (33.3)	0
Hepatobiliary disorders	0	1 (16.7)
Injury, poisoning, and procedural complications	0	1 (16.7)
Investigations	0	1 (16.7)

A subject who reported 2 or more AEs within the same SOC was counted only once for that SOC. AEs indicates adverse events; SOC, system organ class; TEAEs, treatment-emergent AEs.

because his partial Mayo score was ≤ 1 throughout the study (Supplementary Figure S2 and Supplementary Table S1). Patient 9's PD profile was similar to those of patients without neutralizing antivedolizumab antibodies (Supplementary Figure S1).

Efficacy

Results of the partial Mayo score evaluation are shown in Supplementary Figure S2 and Supplementary Table S1. Two patients (both receiving vedolizumab 150 mg) did not meet the criteria for clinical remission on day 1 of the study (scores of 3 and 7). Patient 2 experienced a clinical remission on day 15 of the study. Patient 3 experienced a clinical response to therapy on the day of the last study drug administration, day 43, and a clinical remission on day 155, 16 weeks after last dose of study drug. However, on day 239, some 28 weeks after last dose of study drug, both patients exhibited partial Mayo scores of 6 and 3, respectively. Therefore, both patients had relapsed at the end of the study. These results were in line with the decrease in saturation of $\alpha_4\beta_7$ integrin observed in the PD analysis: in both patients, the study drug saturated $\alpha_4\beta_7$ integrin receptors during and after the treatment, but saturation was lost concomitantly to the observed increase in partial Mayo score.

Discussion

This study is the first examination of vedolizumab in Japanese patients with ulcerative colitis and provides important information regarding its PK, PD, safety, and efficacy profile in this population. Although the precise etiology of IBD still remains unclear, it is believed that both the patient's genetics and environmental factors contribute to the disease etiology.²⁰ The genetic background of patients with ulcerative colitis, which is a complex immunologically mediated disease, seems to be similar between Asian and white populations; however, some East Asia-specific ulcerative colitis susceptibility loci indicate that differences exist within the ethnicities.^{21,22} Also, inflammation-related genetic polymorphisms that are associated with ulcerative colitis in Asians differ from those associated with white populations.²³ Consequently, a difference in genetic background among ethnicities may affect treatment responses for ulcerative colitis. In fact, distinct treatment outcomes for ulcerative colitis have been previously reported in Japanese patients for treatments including adalimumab,²⁴⁻²⁶ leukocytapheresis,^{27,28} and tacrolimus.^{29,30} Therefore, it is important to investigate both the PK and PD for ulcerative colitis drugs in this population in separate clinical trials.

Vedolizumab exhibited target-mediated drug disposition, and at concentrations below 1 $\mu\text{g/mL}$, the elimination was nonlinear, similar to that observed in non-Japanese patients,¹⁶ which suggests similar expression levels of the $\alpha_4\beta_7$ integrin target across different populations. Vedolizumab exposure in the present study indicates that doubling the dose of vedolizumab from 150 mg to 300 mg results in a concomitant

increase in AUC_{day14} and C_{max} on day 1 (1.82- and 1.86-fold, respectively). Despite these differences, $\alpha_4\beta_7$ integrin saturation was rapidly induced in both treatment groups; however, the duration of this effect was longer in the 300-mg group. This PK and PD profile of vedolizumab is similar to that seen in a US dose-ranging study of patients with ulcerative colitis treated with vedolizumab (2, 6, and 10 mg/kg).¹⁶ Patients in this study also exhibited proportional increases in C_{max} (day 1: 54, 154, and 279 $\mu\text{g/mL}$ for vedolizumab 2, 6, and 10 mg/kg, respectively) and AUC (day 14: 375, 1058, and 1765 $\mu\text{g}\cdot\text{d/mL}$, respectively) with increasing doses of vedolizumab, and complete saturation of $\alpha_4\beta_7$ integrin at every dose of the study drug.¹⁶ These data suggest that both doses of vedolizumab inhibit $\alpha_4\beta_7$ activity to a similar extent.

All patients (100%) in the present study experienced a TEAE, which is a higher ratio than that observed in the phase 2 study in Western patients (75% and 64% of patients receiving 2 mg/kg and 6 mg/kg, respectively).¹⁶ However, vedolizumab delivered intravenously up to 300 mg was generally well tolerated in Japanese patients with ulcerative colitis because all TEAEs were mild or moderate in intensity. The numbers of TEAEs were comparable for the dose groups, with GI disorders by system organ class and nasopharyngitis by preferred term being the most commonly reported. In the Western phase 2 study, the most reported TEAE by preferred term was headache, occurring in 19% of patients; nasopharyngitis was the fourth most common TEAE, reported by 8% of patients.¹⁶ In the present study, 1 serious TEAE was reported for each of the vedolizumab 150-mg and 300-mg groups, both of which were deemed to be related to the study drug. PML is a known toxicity with nonspecific α_4 integrin inhibition.^{11,12} No evidence of PML was observed with vedolizumab, which is likely due to its specific binding profile. The phase 3 study of vedolizumab in mainly white populations (GEMINI 1) demonstrated a similar frequency of AEs between placebo and vedolizumab 300-mg treatment groups.¹⁴ Although there was no placebo group in the present study, our data suggest that Japanese patients can tolerate the standard 300-mg dose used to treat IBD in other countries.^{14,31}

Analysis of the efficacy of 150 mg vedolizumab showed that there was a tendency of the partial Mayo score to decrease on treatment with vedolizumab. The 2 patients who did not meet the definition of clinical remission at the start of the study experienced a clinical remission on days 15 and 155 of the study period, respectively. These data, albeit extremely limited, suggest that vedolizumab is effective at reducing the symptoms of ulcerative colitis in Japanese patients and can induce a clinical remission. These findings should be confirmed in future trials but echo the results the phase 3 GEMINI

1 study in which 47.1% of patients exhibited a clinical response when treated with vedolizumab as induction therapy, compared with 25.5% in the placebo group, along with greater rates of remission and mucosal healing.¹⁴

Because the focus of this phase 1 study was to examine the PK and safety of vedolizumab, there were limitations with respect to the small number of patients and noninclusion of patients with moderately to severely active ulcerative colitis. Furthermore, due to the single-arm design of the study, determination of efficacy by the full Mayo score with full endoscopic findings was not feasible. In addition, PK analyses would have benefited from a serum collection time point immediately after the intravenous infusion for a more accurate determination of the C_{max} .

We could not investigate the effect of human antivedolizumab antibody on the PK of vedolizumab in the present study because only 1 patient in each dosing group tested positive for antivedolizumab antibody. Nevertheless, this has been previously evaluated using population modeling with data from the GEMINI trials. The presence of antivedolizumab antibodies was estimated to increase the linear clearance of vedolizumab by only 12%.¹⁷ However, similarly to the present study, inferences regarding this impact are limited by the low incidence of antivedolizumab antibodies observed in these trials.

In conclusion, these data demonstrate that Japanese patients with ulcerative colitis exhibit a similar PK profile and response to treatment with vedolizumab as seen for patients in overseas studies, with a similar safety profile and clinical efficacy observed in patients receiving the 150-mg dose. As a result, vedolizumab could form an important component of the treatment armamentarium for Japanese patients with ulcerative colitis, adding to the array of currently recommended therapies for IBD in Japan.¹ Importantly, vedolizumab specifically acts on the intestinal mucosa, resulting in decreased inflammation by inhibiting $\alpha_4\beta_7$ -mediated recruitment of leukocytes to the GI tract.³² This targeted approach is novel in the Japanese context, as the therapies recommended in guidelines for IBD treatment (mesalamine, sulfasalazine, corticosteroids, and immunomodulators) may need to be applied topically via an enema to achieve optimal results.^{1,33} In addition, immunomodulators such as 6-mercaptopurine and cyclosporine may be associated with some serious side effects, such as bone marrow suppression, development of nonmelanomatous skin cancers, and hepatosplenic T-cell lymphoma.^{1,8} Because vedolizumab has been shown to be effective in patients with moderately to severely active ulcerative colitis previously treated with corticosteroids, purine antimetabolites, and/or TNF- α inhibitors,¹⁴ this humanized monoclonal antibody

has the potential to provide a new line of therapy for patients with ulcerative colitis that is resistant to treatments currently available in Japan.

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Declaration of Conflicting Interests

K.W. has received payment for advisory services to Takeda Pharmaceutical Company Ltd, including board membership, consultancy, expert testimony, giving lectures including service on speakers' bureaus, and development of educational presentations. K.W. or his institution have received consulting fees or honoraria and fees for participation in review activities such as data-monitoring boards, statistical analyses, end-point committees, and the like.

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K.O., A.N., and H.O. are employees of Takeda Pharmaceutical Company Ltd.

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Contributions

Kiyonori Kobayashi, Kazunori Oda, and Akira Nishimura were responsible for the study design. Data collection was done by Kiyonori Kobayashi, Yasuo Suzuki, Kenji Watanabe, Miyuki Mukae, Akihiro Yamada, and Hirokazu Yamagami. Hiroyuki Okamoto was responsible for data analysis. Kiyonori Kobayashi and Kazunori Oda were responsible for the interpretation of data. Kiyonori Kobayashi was responsible for preparation of the manuscript. All authors provided critical revision of the article as well as final approval of the version to be published.

Data-Sharing Statement

Takeda makes patient-level, deidentified data sets, and associated documents available after applicable marketing approvals and commercial availability have been received, an opportunity for the primary publication of the research

has been allowed, and other criteria have been met as set forth in Takeda's Data-Sharing Policy (see <https://www.takedaclinicaltrials.com> for details). To obtain access, researchers must submit a legitimate academic research proposal for adjudication by an independent review panel, who will review the scientific merit of the research and the requestor's qualifications and conflict(s) of interest that can result in potential bias. Once approved, qualified researchers who sign a data-sharing agreement are provided access to these data in a secure research environment.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.