Inflammatory Bowel Diseases, 2021, **XX**, 1–11
https://doi.org/10.1093/ibd/izab215
Advance access publication 24 August 2021
Original Research Articles - Clinical

Long-Term Safety and Efficacy of the Anti-Mucosal Addressin Cell Adhesion Molecule-1 Monoclonal Antibody Ontamalimab (SHP647) for the Treatment of Crohn's Disease: The OPERA II Study

Geert R. D'Haens, MD, PhD,[*] Walter Reinisch, MD, PhD,[†] Scott D. Lee, MD,[‡] Dino Tarabar, MD, PhD,[§] Edouard Louis, MD, PhD,[¶] Maria Kłopocka, MD, PhD,[‖] Jochen Klaus, MD, PhD,[**] Stefan Schreiber, MD, PhD,[††] Dong Il Park, MD, PhD,[‡‡] Xavier Hébuterne, MD, PhD,[§§] Peter Nagy, MD,[¶¶] Fabio Cataldi, MD,[‖‖] Steven W. Martin, PhD,[***] Satyaprakash Nayak, PhD,[***] Anindita Banerjee, PhD,[***] Kenneth J. Gorelick, MD,[†††] and William J. Sandborn, MD[‡‡‡]

From the [*]Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands
[†]Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
[‡]Division of Gastroenterology, University of Washington, Seattle, WA, USA
[§]Clinic of Gastroenterology and Hepatology, Military Medical Academy, Belgrade, Serbia
[¶]Department of Clinical Sciences, University Hospital Centre Hospitalier Universitaire of Liège, Liège, Belgium
[‖]Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
[**]Clinic for Internal Medicine, University Hospital Ulm, Ulm, Germany
[††]Clinic for Internal Medicine I, University Hospital Schleswig-Holstein, Christian-Albrechts-University of Kiel, Kiel, Germany
[‡‡]Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, South Korea
[§§]University Côte d'Azur, Centre Hospitalier Universitaire of Nice, Nice, France
[¶¶]Shire, a Takeda company, Zug, Switzerland
[‖‖]Shire, a Takeda company, Lexington, MA, USA
[***]Pfizer, Cambridge, MA, USA
[†††]Zymo Consulting Group, Newtown Square, PA, USA
[‡‡‡]Medicine, University of California San Diego, La Jolla, CA, USA.

Address correspondence to: Peter Nagy, MD, Takeda Pharmaceuticals International AG, Thurgauerstrasse 130, 8152 Glattpark-Opfikon, Switzerland (peter.nagy@takeda.com).

Background: Patients with Crohn's disease (CD) experience intestinal inflammation. Ontamalimab (SHP647), a fully human immunoglobulin G_2 monoclonal antibody against mucosal addressin cell adhesion molecule-1, is a potential novel CD treatment. OPERA II, a multicenter, open-label, phase 2 extension study, assessed the long-term safety and efficacy of ontamalimab in patients with moderate-to-severe CD.

Methods: Patients had completed 12 weeks of blinded treatment (placebo or ontamalimab at 22.5, 75, or 225 mg subcutaneously) in OPERA (NCT01276509) or had a clinical response to ontamalimab 225 mg in TOSCA (NCT01387594). Participants received ontamalimab at 75 mg every 4 weeks (weeks 0–72), then were followed up every 4 weeks for 24 weeks. One-time dose reduction to 22.5 mg or escalation to 225 mg was permitted at the investigator's discretion. The primary end points were safety and tolerability outcomes. Secondary end points included changes in serum drug and biomarker concentrations. Efficacy end points were exploratory, and used non-responder imputation methods.

Results: Overall, 149/268 patients completed the study. The most common adverse event leading to study discontinuation was CD flare (19.8%). Two patients died; neither death was considered to be drug related. No dose reductions occurred; 157 patients had their dose escalated. Inflammatory biomarker concentrations decreased. Serum ontamalimab levels were consistent with known pharmacokinetics. Remission rates (Harvey-Bradshaw Index [HBI] ≤ 5; baseline, 48.1%; week 72, 37.3%) and response rates (baseline [decrease in Crohn's Disease Activity Index ≥ 70 points], 63.1%; week 72 [decrease in HBI ≥ 3], 42.5%) decreased gradually.

Conclusions: Ontamalimab was well tolerated; treatment responses appeared to be sustained over 72 weeks.

ClinicalTrials.gov ID: NCT01298492.

Key Words: Crohn's disease, mucosal addressin cell adhesion molecule-1, ontamalimab, clinical trial

Introduction

Crohn's disease (CD) is a chronic, progressive inflammatory bowel disease (IBD) characterized by transmural inflammation of the gastrointestinal tract.[1] Approved biologics for the treatment of CD include the anti–tumor necrosis factor (anti-TNF) antibodies infliximab, adalimumab, and certolizumab pegol (in the United States only); the anti-integrin antibody vedolizumab; and the anti-IL12/23

Received for publications: January 15, 2021. **Editorial Decision:** August 1, 2021

antibody ustekinumab. These agents have provided a significant advance in the treatment of patients with moderate-to-severe CD that does not respond to immunosuppressive therapy, who are dependent on glucocorticoids.[2,3] However, for a substantial proportion of patients, primary non-response to these agents and loss of response over time remain significant challenges.[4] Because of this, and concerns regarding the safety of anti-TNF agents and conventional therapies, there is an unmet need for novel therapies with good safety profiles and durable efficacy.

Adhesion molecules, which play a role in the migration of lymphocytes to sites of inflammation in the gut, are promising targets for the treatment of IBD.[5] The mucosal addressin cell adhesion molecule-1 (MAdCAM-1), for which integrin α4β7 is the recognized ligand, has been shown to be involved in gut immune surveillance and homing of α4β7 integrin-expressing lymphocytes to the gut mucosa.[6–8] In contrast to integrins found on circulating cells, MAdCAM-1 is expressed predominantly on the endothelium of high endothelial venules in the gut and gut-associated lymphoid tissue.[7] It is not constitutively expressed in the central nervous system (CNS)[9]

Natalizumab is an antibody that non-selectively targets the α4 integrin subunit, blocking both the α4β7 and α4β1 integrins, the latter of which interacts with the much more broadly expressed vascular cell adhesion protein-1 (VCAM-1). Natalizumab is active in CD but is characterized as having a class 1 (high) risk for progressive multifocal leukoencephalopathy (PML),[10,11] thought to be owing to rapidly reduced immune surveillance in the cerebrospinal fluid and enhanced release of John Cunningham (JC) virus–infected lymphocytes from bone marrow, both related to its effect on α4β1.[12,13] Selective targeting of the α4β7/MAdCAM-1 pathway is a promising alternative approach to the treatment of IBD, likely with a low risk for PML. The fully human immunoglobulin G2 antibody ontamalimab (previously known as SHP647 and PF-00547659) and the humanized anti-α4β7 integrin monoclonal antibody vedolizumab bind selectively and with high affinity to the 2 different components of the pathway: MAdCAM-1 and α4β7, respectively.[14,15] A study of patients with active CD indicated that high-dose induction with ontamalimab did not result in any significant decrease in the lymphocytes involved in CNS immune surveillance.[14] The low risk of PML with selective targeting of the α4β7/MAdCAM-1 pathway is also supported by positive efficacy and favorable safety results from clinical trials of both ontamalimab[14,16,17] and vedolizumab.[15] Furthermore, a recent *in vitro* study showed that ontamalimab, but not vedolizumab, induces the trafficking of specific leukocyte subpopulations, thus suggesting that ontamalimab might promote the resolution of intestinal inflammation.[18]

To date, results of 4 phase 1 and phase 2 clinical trials investigating ontamalimab in IBD have been published: 2 in patients with CD[14,16] and 2 in patients with ulcerative colitis.[19,20] In TOSCA, a 12-week open-label study, ontamalimab was given to 39 patients with active CD who had previously received immunosuppressants.[14] In that study, 80% of patients treated with ontamalimab at 225 mg had a clinical response, and 77% were in clinical remission at week 12. In OPERA, a phase 2, double-blind, placebo-controlled trial, 3 doses of ontamalimab (22.5, 75, and 225 mg) were investigated in 265 patients with CD.[16] Clinical response and remission were observed in greater proportions of patients in all the ontamalimab groups than in the placebo group, although differences between the placebo group and each of the ontamalimab groups were not statistically significant, possibly owing to higher-than-expected placebo response rates. Furthermore, *post hoc* analyses of data from patients with evidence of inflammation (shown by elevated baseline high-sensitivity C-reactive protein [hsCRP] levels or Simple Endoscopic Scores for CD) suggested that the drug might have improved remission rates.[16] The aims of OPERA II, a phase 2, open-label extension study of the TOSCA and OPERA trials, were to evaluate the long-term safety, pharmacokinetics (PK), and efficacy of ontamalimab after induction therapy in patients with moderate-to-severe CD with a history of failed immunosuppressant therapy.

Methods

Study Design

OPERA II was a 72-week, multicenter, open-label, phase 2 extension (ClinicalTrials.gov ID: NCT01298492) to 2 feeder studies: OPERA (NCT01276509)[16] and TOSCA (NCT01387594).[14] The trial was conducted from July 22, 2011, to July 27, 2016, and involved 81 centers in 15 countries (Austria, Belgium, Canada, France, Germany, Japan, the Netherlands, Norway, Poland, Republic of Korea, Serbia, Slovakia, South Africa, Spain, and the United States), of which 76 were active (ie, enrolled patients) and not terminated. The end of the study was the last visit of the last patient. The protocol and its amendments were approved by the Institutional Review Board or Ethics Committee at each center. This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines, and all patients gave written informed consent.

Eligible patients included patients with CD who had completed blinded induction treatment (placebo or ontamalimab at 22.5, 75, or 225 mg) in the 12-week, double-blind trial OPERA, regardless of response, and those who had completed 12 weeks of treatment in the open-label study TOSCA and had demonstrated a clinical response, defined as a decrease in Harvey-Bradshaw Index (HBI) score of 3 points or more. Supplementary Table 1 shows more information on the patient populations and response criteria in OPERA and TOSCA. Patients were excluded if they were taking azathioprine, 6-mercaptopurine, or methotrexate at OPERA II baseline (see Supplementary Table 2 for exclusion criteria). It was estimated that approximately 210 patients (~180 patients from OPERA and ~30 patients from TOSCA) would enroll in this extension study.

Intervention

Patients received ontamalimab at 75 mg subcutaneously (s.c.) at baseline and every 4 weeks up to and including week 72 (Figure 1). After the active treatment period, patients entered a 24-week follow-up period consisting of visits every 4 weeks. The 75-mg dose was selected based on phase 1 and 2 data, which showed 99% binding of free soluble MAdCAM-1 with ontamalimab at 75 mg.[21] The dose could be decreased to 22.5 mg s.c. every 4 weeks in the event of intolerance or adverse events (AEs), or increased to 225 mg s.c. every

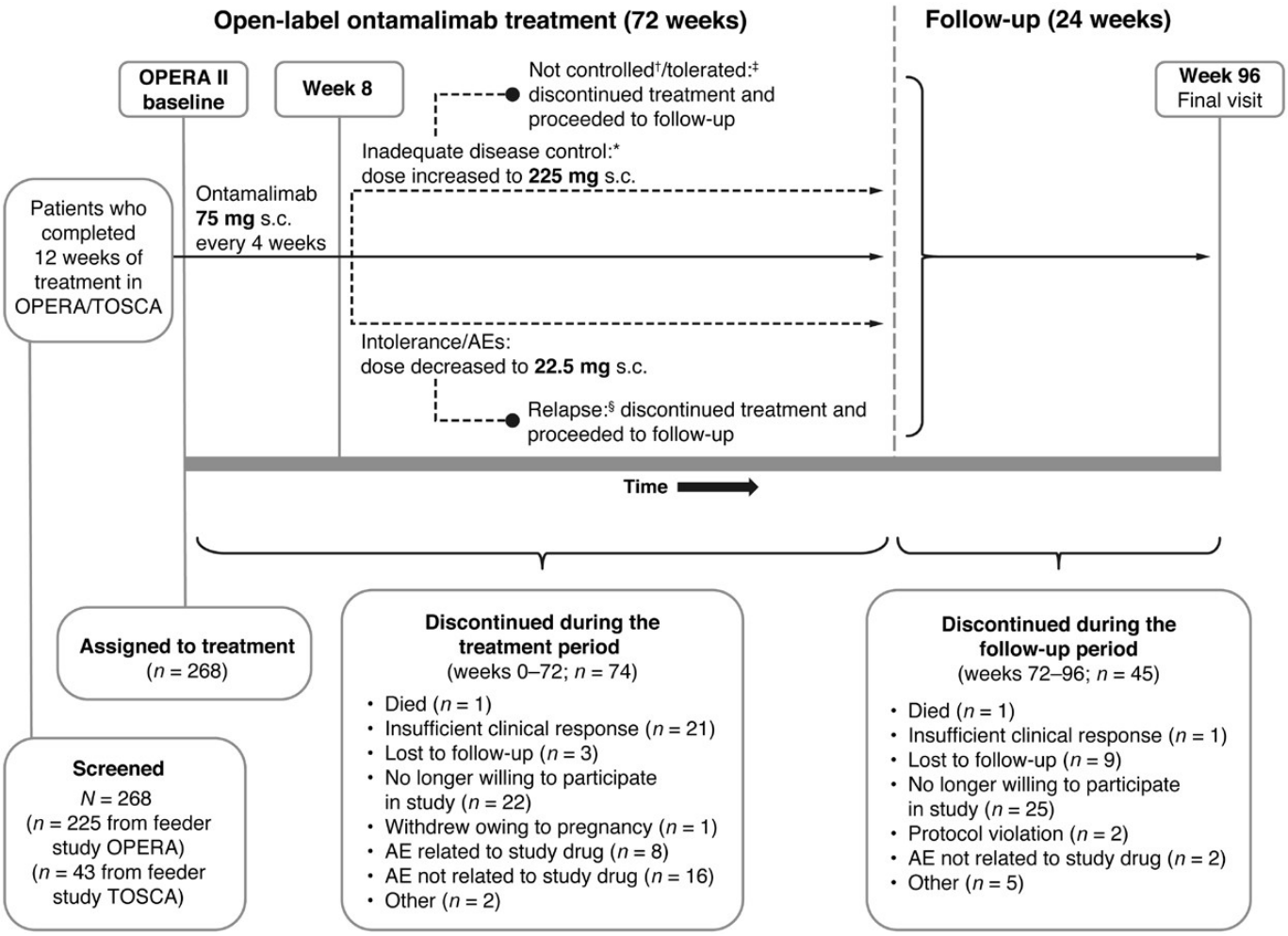

Figure 1. Ontamalimab treatment schedule and patient disposition during OPERA II. A single ontamalimab dose change (increase or decrease) was permitted at any study visit from week 8 onwards. *Usually characterized by an HBI score increase of ≥3 to a value of ≥8 in those with acceptable disease control at baseline (after ruling out other potential causes: eg, infection) or continued inadequate disease control (usually an HBI score ≥8) in those not controlled at baseline. †Usually characterized by an HBI score reduction of <3 or an HBI score ≥8 after at least 8 weeks at the higher dose. ‡Dose could not be reduced in these patients. §HBI score increased by ≥3 from the lowest value following a response, to a value of ≥8. Abbreviations: AE, adverse event; HBI, Harvey-Bradshaw Index; s.c., subcutaneously.

4 weeks in patients with an inadequate response (Figure 1). A single ontamalimab dose change (escalation or reduction) was permitted at any study visit from week 8 onwards. All dose changes were conducted at the discretion of the investigator, based on typically defined HBI score criteria and the investigator's clinical judgment. An inadequate response was defined as disease exacerbation (typically an HBI score increase of 3 points or more, to a value of 8 or more) in patients with acceptable disease control at baseline (after ruling out other potential causes: eg, infection) or continued inadequate disease control (typically an HBI score of 8 or more) in patients not controlled at baseline.

Patients whose dose was reduced owing to tolerability issues could discontinue treatment and enter into the follow-up period if they experienced a relapse; this was characterized by an HBI score increase of 3 or more points from the lowest value following a response, to a value of 8 or more. Patients whose dose was increased to 225 mg could discontinue treatment and enter into the follow-up period if their clinical condition did not improve after 8 or more weeks on the higher dose; lack of improvement was characterized by an HBI score reduction of less than 3 or by an HBI score of 8 or more.

Patients were to discontinue immunosuppressants before entering the study. Patients receiving glucocorticoids at entry to OPERA II tapered them during the study, in accordance with local guidelines. In patients with clinical remission or response in the feeder studies, tapering was initiated at the start of OPERA II. In patients without a response at the start of OPERA II, tapering began once patients achieved a clinically significant response or remission and was completed, if possible, by week 40.

Oral glucocorticoids (up to 1 mg/kg prednisone equivalent) and budesonide (up to 9 mg) were permitted as rescue medications but were to be tapered off within 12 weeks of their initiation. A second and final course of rescue treatment was permitted 8 weeks after the first rescue treatment.

Objectives and Outcome Measures

The primary objective of this study was to monitor the safety and tolerability of ontamalimab. The end points used to assess safety throughout included the numbers and types of AEs and serious AEs (SAEs; as defined by the Medical Dictionary for Regulatory Activities [MedDRA]). Clinical laboratory assessments, as well as vital signs and cardiac and neurological assessments, were completed every 4 weeks from baseline to week 96.

The secondary objectives were to assess the PK and immunogenicity of ontamalimab. The end points analyzed were serum concentrations of ontamalimab and anti-ontamalimab antibody and neutralizing antibody (NAb) statuses (positive or negative).

Pharmacodynamic (PD) end points were also analyzed; these were concentrations of serum hsCRP, serum MAdCAM-1, and fecal calprotectin (FC). Blood samples were collected at baseline and every 4 weeks for analyses of ontamalimab and hsCRP concentrations, and at baseline and week 24 for analyses of free soluble MAdCAM-1 concentrations. Detection of MAdCAM-1 was performed using a qualified assay.[22] Samples were tested for anti-drug antibodies (ADAs) using a qualified semi-quantitative electrochemiluminescence immunoassay (which permitted the detection of ADAs with serum ontamalimab concentrations <100 µg/mL), and positive samples were further tested for the presence of NAbs using a validated enzyme-linked immunosorbent assay (ELISA).[23] Stool samples were collected at baseline, every 4 weeks until week 24, and then at week 32 and week 72. Stool samples were stored at –80°C, and FC was analyzed using a validated and specific enzymatic immunoassay (ELISA).

Exploratory efficacy end points included: clinical remission and response rates at weeks 24 and 72; rate of clinical relapse at any point during the study and time to relapse; proportion of patients whose dose was escalated or reduced; and proportion of patients who discontinued from the study by week 16, which was the first point at which patients who escalated or reduced their dose at week 8 could be withdrawn owing to a lack of clinical improvement. Clinical remission was defined as an HBI score of less than 5, clinical response was defined as a decrease of 3 or more in HBI score from the baseline value in the feeder study,[24] and relapse was defined as an increase of 3 or more from the lowest HBI score measured following a response, with a total HBI score of 8 or more.

Statistical Analyses

All safety and efficacy end points were analyzed using the modified intent-to-treat population, which included all patients who received at least 1 dose of ontamalimab during OPERA II. PK and PD end points (FC and serum levels of hsCRP, ontamalimab, and soluble MAdCAM-1) were analyzed for all patients who received at least 1 dose of the study drug and had data on at least 1 PK and/or PD end point.

For continuous measurements, descriptive statistics were provided; for categorical measurements, frequencies and percentages were used to summarize data. Data processing, data set constructions, and *ad hoc* regression analyses of safety and efficacy end points were performed in SAS (version 9.1.3 or later; SAS Institute Inc., Cary, NC), and those for PK, PD, and biomarker end points were performed in R (version 3.4.1 or later; The R Foundation, Vienna, Austria)[25] with the assistance of RStudio (version 1.0.153 or later; RStudio Inc., Boston, MA).[26] Statistical modeling for the analyses in R was implemented using the ggplot2 package with the "glm" and "lm" commands used for logistic and linear regressions, respectively.

Clinical response and remission rates were summarized using both non-responder imputation (in which missing data are considered treatment failures) and observed case approaches in the modified intent-to-treat population. Time to relapse was analyzed using a Kaplan-Meier approach.

PK and PD samples were excluded from analyses if dosing or timing information was missing. Unplanned samples and those collected upon early termination were also excluded. To evaluate relationships between PK, PD, and efficacy end points, correlation analyses were performed. For categorical end points, the proportion of binary events was assessed by PK concentration quartile. Continuous end points (eg, FC and hsCRP concentrations) were plotted as a function of serum concentrations of ontamalimab. If the graphical analysis indicated a relationship between 2 end points, regression analyses were performed.

Results

In total, 268 patients were included in the study and started on treatment (Figure 1). The mean age of patients was 36.5 years (standard deviation, 11.7 years); 151 patients (56.3%) were women (Table 1). During the treatment period, 74 patients discontinued the study, and another 45 discontinued during the follow-up period; 149 patients completed the study. The most common reasons for discontinuation during the treatment period were AEs (24/268; 9.0%), withdrawal of consent (22/268; 8.2%), and an insufficient clinical response (21/268; 7.8%); during follow-up, the most common reasons were withdrawal of consent (25/268; 9.3%) and loss to follow-up (9/268; 3.4%).

A total of 157 patients had their dose escalated (median time to dose escalation, 28.0 weeks; 95% confidence interval [CI], 19.6–36.1 weeks). No patient had their dose reduced to 22.5 mg. Week 16 was the first time point at which patients with unsatisfactory improvement despite dose escalation could be withdrawn; of the 68 patients whose dose was escalated by week 8, 13 (19.1%) subsequently discontinued the study by week 16. Reasons for discontinuation in this group were: AEs not related to the study drug (n = 5; 38.5%); an insufficient clinical response (n = 4; 30.8%); AEs related to the study drug (n = 2; 15.4%); and withdrawal of consent (n = 2; 15.4%). Overall, 104 patients (38.8%) were receiving glucocorticoids at the start of the study; all patients who completed the 72-week active treatment period discontinued glucocorticoids during this time.

Safety and Tolerability

During the treatment period, 249 (92.9%) patients reported a total of 1550 AEs, 385 of which were considered by the investigator to be treatment related (Table 2). During the follow-up period, 133/194 patients (68.6%) experienced a total of 461 AEs, 42 of which were considered to be treatment related. The most frequently reported AE was CD flare. Supplementary Table 3 shows the incidence of AEs that occurred in more than 5% of patients during the treatment period. During the treatment period, 10 patients experienced SAEs that were considered treatment related (Table 2): these were headache, vul-

Table 1. Patient demographics and characteristics at the start of the treatment period.

	Patients from Feeder Study, OPERA, *n* = 225	Patients from Feeder Study, TOSCA, *n* = 43	Total, *N* = 268
Women, *n* (%)	128 (56.9)	23 (53.5)	151 (56.3)
Mean (SD) age, years	36.1 (11.5)	38.8 (12.3)	36.5 (11.7)
Race, n (%)[a]			
White	190 (84.4)	41 (95.3)	231 (86.2)
Black	6 (2.7)	0	6 (2.2)
Asian	24 (10.7)	1 (2.3)	25 (9.3)
Other	5 (2.2)	1 (2.3)	6 (2.2)
Mean (SD) weight, kg	71.4 (19.9)	71.2 (16.2)	71.3 (19.3)
Mean (SD) BMI, kg/m^2	24.6 (6.3)	23.7 (3.9)	24.4 (6.0)
Was the patient a non-responder at baseline?[b] *n* (%)			
Yes	89 (39.6)	0	89 (33.2)
No	126 (56.0)	43 (100.0)	169 (63.1)
Unknown	10 (4.4)	0	10 (3.7)
Mean (SD) baseline HBI score	5.2 (3.1)	2.7 (1.5)	4.9 (3.0)
Received placebo in feeder study, *n* (%)	58 (25.8)	0 (0)	58 (21.6)

Abbreviations: BMI, body mass index; CDAI, Crohn's Disease Activity Index; HBI, Harvey-Bradshaw Index; SD, standard deviation.
[a]Not all percentages add up to 100 owing to rounding.
[b]Non-responders were those who did not have a decrease in CDAI ≥ 70 points from baseline to week 8 or week 12 in OPERA, and those who did not have a decrease in HBI score of ≥3 in TOSCA; only responders were included from TOSCA.

Table 2. All-cause and treatment-related AEs experienced during the treatment and follow-up periods.

	Treatment period,[a] *n* = 268		Follow-up period, *n* = 194	
	All-cause	Treatment-related	All-cause	Treatment-related
Number of AEs	1550	385	461	42
Number (%) of patients with AEs	249 (92.9)	124 (46.3)	133 (68.6)	31 (16.0)
Number (%) of patients with SAEs	80 (29.9)	10 (3.7)	57 (29.4)	1 (0.5)
Number (%) of patients with severe AEs	59 (22.0)	15 (5.6)	45 (23.2)	2 (1.0)
Number (%) of patients who discontinued the study owing to AEs	53 (19.8)	15 (5.6)	1 (0.5)	0

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a]The total number of patient-months of treatment for the 268 patients who were enrolled and treated was 4088.6.

var abscess, worsening of CD, *Clostridium difficile* infection, cerebral venous thrombosis, anal abscess, abdominal hernia, liver abscess, increased blood creatine phosphokinase concentration, and pelvic abscess rupture (*n* = 1 each). During the follow-up period, an event of colon cancer in a 43-year-old man who received ontamalimab at 75 mg and escalated to 225 mg was reported as treatment related by the investigator, but not by the sponsor. Approximately one-fifth of patients experienced severe AEs (22.0%) or AEs leading to discontinuation (19.8%; Table 2). The most common AE or SAE leading to discontinuation was CD flare.

Two patients in this study died: 1 during the treatment period and 1 during the follow-up period. The first patient, a 30-year-old woman who received ontamalimab at 75 mg, died of multiple organ failure after postoperative aspiration following a resection of the terminal ileum; her death was not considered drug related by the investigator or sponsor. The second patient, a 36-year-old man who received ontamalimab at 75 mg and escalated to 225 mg at day 147 owing to worsening of CD, died of metastatic neoplasm of an unknown primary origin shortly after a missed visit at week 84, with adenocarcinoma identified on cytology. In accordance with the wishes of the patient's family, no autopsy was performed. The investigator considered that the worsening of CD was related to the malignancy, but that there was no reasonable possibility that the malignancy was drug related. In the opinion of the sponsor, the malignancy was possibly an intercurrent illness and was not related to the study drug.

Overall, 264 patients were evaluable for laboratory abnormalities. During the treatment period, the most commonly reported laboratory abnormalities (without regard to abnormalities at baseline) were the presence of leukocyte esterase in the urine (*n* = 128; 48.5%), N-terminal prohormone of brain natriuretic peptide (NT-proBNP) more than 1.0× the upper limit of normal (*n* = 118; 44.7%), and the presence of hemoglobin in the urine (*n* = 103; 39.0%). None of these findings were considered clinically significant. Of 14 patients with echocardiogram evaluations prompted by elevated NT-proBNP, 2 had abnormal results; neither was considered clinically significant. The proportions of patients (*n* = 268) with clinically significant changes in neurological assessments were 6.0% for the 9-hole peg test; 0.8% for the symbol digits modality test; 0.4% for the category verbal fluency test; 17.2% for the 25-foot walk test;

and 19.4% for the multiple sclerosis neuropsychological questionnaire. No cases of PML were observed.

PK, PD, Biomarkers, and Immunogenicity

After exclusion of samples with missing information, unplanned samples, and those collected on early termination, 1748 hsCRP, 1504 FC, 277 free soluble MAdCAM-1, and 2940 ontamalimab PK samples were included for analysis and plotting. Missing dose information was the most common reason for exclusion across all PK or PD end points.

In patients receiving ontamalimab at 75 mg, the mean serum trough concentration of ontamalimab was 7.33 µg/mL at week 4 and remained at approximately this level over time, with a mean steady-state concentration of 7.57 µg/mL at week 72 (Supplementary Figure 1). Patients who escalated to 225 mg reached a mean steady-state serum ontamalimab level of 20.25 µg/mL at 16 weeks after dose escalation.

Patients' serum concentrations of free soluble MAdCAM-1, an indicator of ontamalimab target engagement, decreased over time (Supplementary Figure 2). In patients who continued to receive ontamalimab at 75 mg, the mean ± 95% CI concentrations of free soluble MAdCAM-1 were 124.9 ± 65.0 ng/mL (n = 49) at baseline, 13.2 ± 5.7 ng/mL (n = 28) at week 12, and 15.7 ± 5.2 ng/mL (n = 46) at week 24. In patients who escalated to 225 mg, mean ± 95% CI concentrations of free soluble MAdCAM-1 were 6.4 ± 1.4 ng/mL (n = 38) 4 weeks after escalation and 5.8 ± 1.3 ng/mL (n = 21) 16 weeks after escalation.

Concentrations of hsCRP decreased over time, both in patients who continued to receive ontamalimab at 75 mg and those who escalated to 225 mg, but patients who escalated had slightly higher hsCRP concentrations at baseline (Figure 2A), reflecting greater levels of inflammation and therefore worse disease. Concentrations of FC also decreased over time in both patient subgroups, but the decrease was slower than that observed for hsCRP. FC levels were also slightly higher at baseline in patients who escalated than in those who continued to receive ontamalimab at 75 mg (Figure 2B). While the concentration of hsCRP showed an overlap of the CIs for patients with and without dose escalation at all time points analyzed (Figure 2A), the analysis of FC concentrations showed an overlap only starting from week 20 (Figure 2B).

Higher serum concentrations of ontamalimab appeared to be associated with slightly decreased concentrations of hsCRP and FC (Supplementary Figures 3 and 4). No consistent or clinically meaningful associations were observed between serum ontamalimab concentration and HBI score, clinical remission, or clinical response to treatment with ontamalimab (Supplementary Figures 5–7).

In total, 2039 serum samples were analyzed by ADA assay, and 63 patients were positive for ADAs at 1 or more time points. Of those patients, 14 developed NAbs. All increases in ADA titer over time were less than 2-fold, with most ADA titers only slightly above the cutoff value of 4.64.

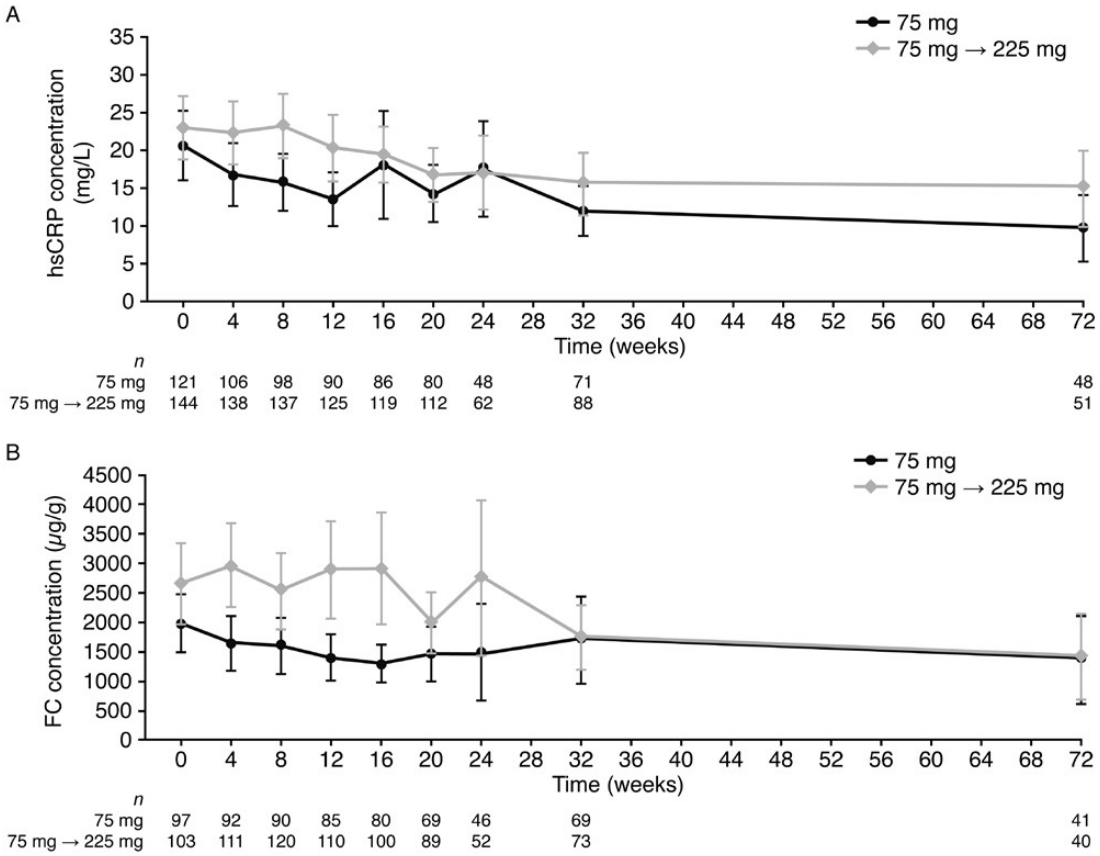

Figure 2. Concentrations of (A) hsCRP and (B) FC over time in patients who continued to receive ontamalimab at 75 mg versus those who escalated to 225 mg, grouped by the final dose received. Data show means ± 95% CIs. Abbreviations: CI, confidence interval; FC, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein.

Efficacy

The mean HBI score–defined clinical remission rate (HBI score of less than 5) was 48.1% at baseline in OPERA II and was almost the same at week 24 (47.8%); rates remained relatively stable over time until week 72 (37.3%) using a non-responder imputation approach (Figure 3A) and, as expected, they increased over time when considering observed cases only (Supplementary Figure 8A). Of the 128 patients who were not in clinical remission at baseline (including patients who continued to receive ontamalimab at 75 mg and those who escalated), 84 (65.6%) achieved remission during the study; in this subgroup, the median time to achieving remission was 16.9 weeks (Figure 4A).

HBI score–defined response rates (a decrease of 3 or more in HBI score from baseline in the feeder study) decreased over time when using a non-responder imputation approach (Figure 3B), changing from baseline (63.1%) to week 24 (54.5%) and week 72 (42.5%). Again, as expected, response rates increased over time in the observed case analysis (Supplementary Figure 8B). Of the 99 patients without a clinical response at baseline, 68 (68.7%) achieved a clinical response during the study, with a median time to response of 13.9 weeks (Figure 4B).

The mean change in HBI score over time appeared similar in patients who dose-escalated and those who continued to receive ontamalimab at 75 mg (Supplementary Figure 9). In patients who escalated, the proportion of those in remission remained relatively stable from week 12 (n = 21; 31.8%) to week 72 (n = 48; 32.2%) when using a non-responder imputation approach (Supplementary Figure 10A). Remission rates were higher, but also remained relatively stable, in patients who continued to receive 75 mg (week 12, n = 107 [56.0%]; week 72, n = 52 [48.1%]; Supplementary Figure 10A). A similar pattern was observed for response rates (Supplementary Figure 10B).

Of the 226 patients who had a response at any time during the study, 119 (52.7%) experienced relapse. The median time to relapse was 67.4 weeks.

Discussion

This is the first long-term study (of more than 12 weeks' duration) to assess the safety and efficacy of an anti-MAdCAM-1 antibody in patients with moderate-to-severe CD. During 72 weeks of treatment, ontamalimab was well tolerated, with a safety profile similar to that observed in previous shorter trials. Furthermore, PK, PD, ADA, and efficacy analyses demonstrated the durability of treatment response in the long term and the absence of a clinically meaningful antibody response.

At both doses, ontamalimab was well tolerated, with the most common AEs and AEs leading to treatment discontinuation relating to the underlying disease itself. No cases of PML were seen over the 2-year study period. This is consistent with results from the open-label TOSCA study, which

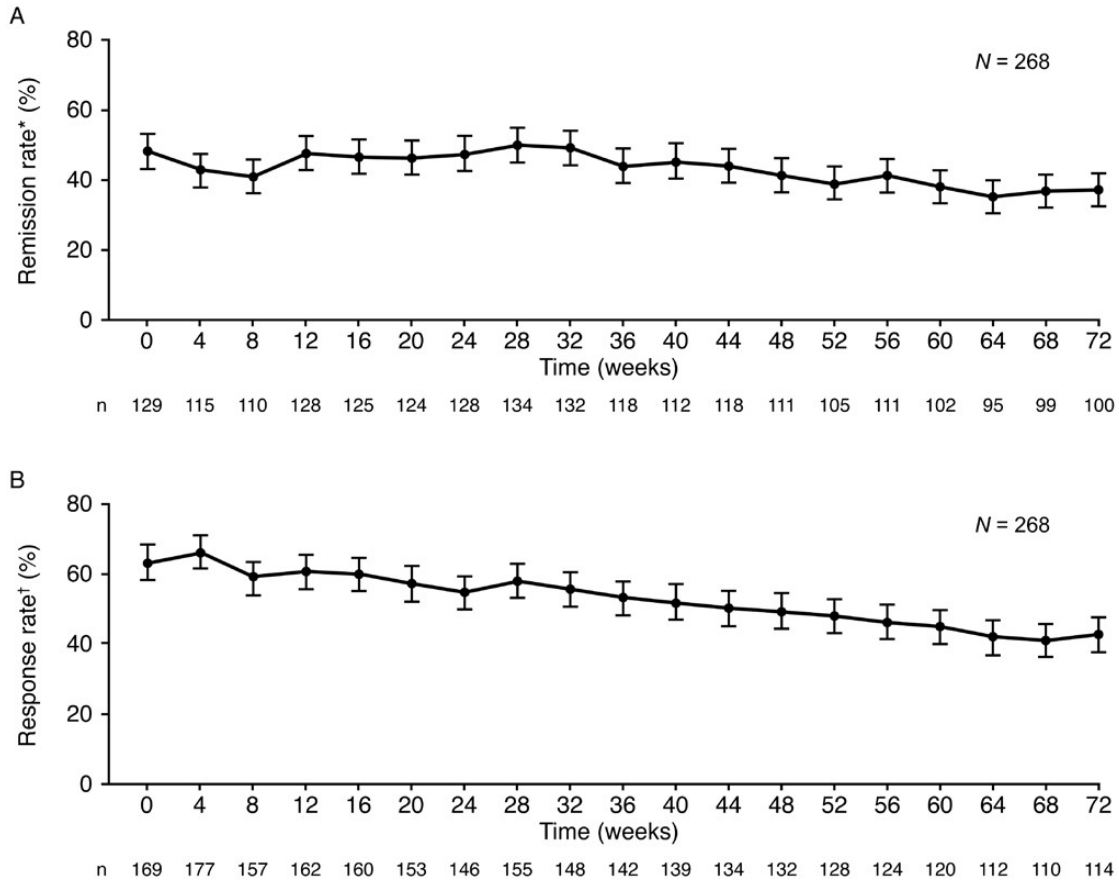

Figure 3. Overall proportions of patients in HBI score–defined (A) clinical remission* and (B) clinical response† from baseline to week 72, calculated using a non-responder imputation approach. Data show means ± 90% CIs. Numbers on figures show numbers of patients in (A) remission* and (B) response† at each time point. *Clinical remission was defined as an HBI score <5. †Clinical response was defined as an HBI score that decreased by ≥3 from the baseline value in the feeder study. Abbreviations: CI, confidence interval; HBI, Harvey-Bradshaw Index.

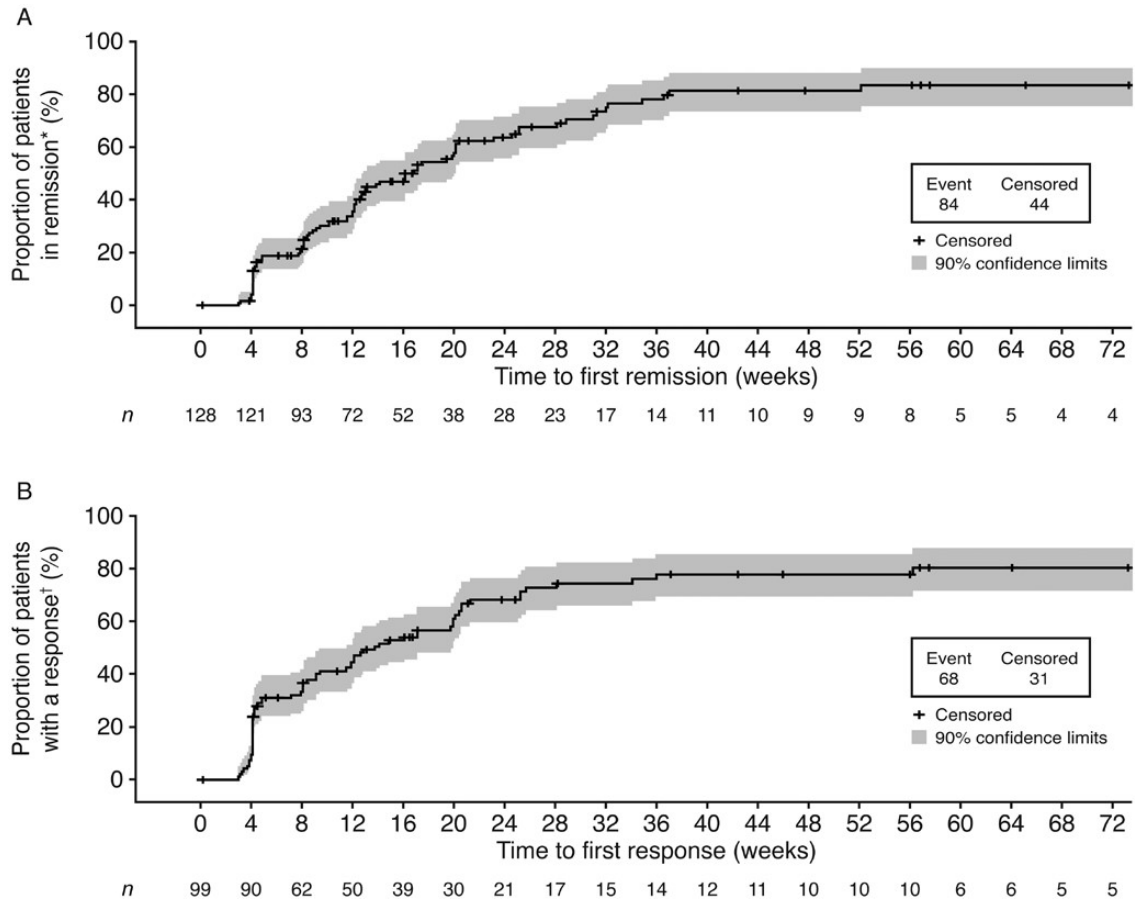

Figure 4. Kaplan-Meier graph showing (A) time to remission* in the subgroup of patients not in remission at baseline and (B) time to response† in the subgroup of patients with no response at baseline. *Clinical remission was defined as an HBI score <5. †Clinical response was defined as an HBI score that decreased by ≥3 from the baseline value in the feeder study. Abbreviation: HBI, Harvey-Bradshaw Index.

demonstrated that induction therapy with ontamalimab was not associated with reductions in lymphocytes or T-cell subsets in the cerebrospinal fluid.[14] This is noteworthy given the established risk of PML with natalizumab, a non-selective anti-α4 integrin antibody, which is thought to be mediated by the inhibition of α-integrin–VCAM-1 interactions in the CNS and bone marrow.[10,27–29] One patient was diagnosed with a malignancy of unknown primary origin and died during the follow-up period, but both the investigator and sponsor considered that this death was unrelated to the study drug.

Clinical remission and response rates demonstrated the durability of the initial treatment response observed with ontamalimab in the TOSCA study and shown in *post hoc* analyses from the phase 2 OPERA study. Moreover, high proportions of patients who received ontamalimab in OPERA/TOSCA but who were not in clinical remission or did not have a clinical response at the OPERA II baseline had achieved remission or response by the study's end (65.6% and 68.7%, respectively). This suggests that remission and response rates may increase with longer duration of treatment with ontamalimab.

In general, patients with an inadequate response to ontamalimab who dose-escalated did not experience substantially improved clinical remission or response rates, although levels of biomarkers indicative of disease activity improved in this subgroup. Patients who dose-escalated had higher concentrations of hsCRP and FC at baseline than those who continued to receive 75 mg, which suggests that these patients had more active disease that was more refractory to treatment. Following dose escalation, concentrations of these inflammatory biomarkers decreased in both groups, but hsCRP levels at the end of treatment remained slightly higher in those who dose-escalated. Further research to characterize the relationship between hsCRP levels and clinical remission might help to identify those patients who are most likely to experience a response or remission with ontamalimab therapy.

Serum trough ontamalimab concentrations were consistent with predictions based on the half-life of ontamalimab and concentrations observed in the OPERA study.[16] The associations between serum trough ontamalimab and inflammatory biomarker concentrations and treatment outcomes were less clear. Across all patients, serum concentrations of hsCRP and FC were generally lower in patients with higher serum ontamalimab concentrations. However, neither clinical remission nor response to treatment appeared to be associated with ontamalimab concentrations.

Ontamalimab is the only anti-MAdCAM-1 monoclonal antibody to enter clinical trials. While comparisons have been drawn to anti-integrin monoclonal antibodies, such as natalizumab and vedolizumab, that target the same system of leukocyte trafficking, ontamalimab is unique in that it does not interact with circulating white blood cells but rather with the fixed MAdCAM-1-bearing endothelial cells. Since the

long-term efficacy and safety of vedolizumab was evaluated only in patients who responded to induction treatment,[15] the data cannot be compared directly.

A key strength of this study is the duration of exposure to ontamalimab, which permitted novel observations of sustained response and remission over an extended period, and an increase in the number of patients achieving response or remission despite an absence of response at baseline. However, the absence of a placebo or comparator group limits the interpretation of these results. Furthermore, the high dropout rate (44%; 119/268 over 72 weeks) may limit the generalizability of the results, while the lack of blinding in this open-label study might have increased the likelihood of bias in HBI scoring. It should be noted that response and remission were measured differently in this study (which used HBI scores) than in OPERA (which used Crohn's Disease Activity Index scores). Measures of symptomatic severity, such as HBI scores, and endoscopic severity are poorly correlated,[30] and no endoscopic end points were included in this study.

In the present long-term extension study in patients with moderate-to-severe CD, the anti-MAdCAM-1 antibody ontamalimab was well tolerated and had a good safety profile, with no observed cases of PML. Response and remission rates induced by ontamalimab were sustained over 72 weeks and increased in patients with no response or remission at baseline, indicating that some patients require a longer duration of treatment to respond.

Supplementary Data

Supplementary data are available at *Inflammatory Bowel Diseases* online.

Acknowledgments

The authors thank Yuemei Wang, of Shire (a Takeda company), for her help with the statistical analysis; and Katie Pillidge, PhD, and Emma Saxon, PhD, of PharmaGenesis London, for medical writing support funded by Shire, a member of the Takeda group of companies.

Author Contributions

F.C. and K.J.G. designed the study. G.R.D., S.D.L., D.T., E.L., M.K., J.K., S.S., D.I.P., X.H., and W.J.S. were principal investigators and contributed to data acquisition. S.W.M., S.N., A.B., and P.N. contributed to the analysis of the data. All authors contributed to the critical revision of this manuscript for important intellectual content.

Funding

The OPERA II trial (NCT01298492) was sponsored by Pfizer. These analyses were funded by Pfizer and Shire, a member of the Takeda group of companies. Medical writing support was funded by Shire, a member of the Takeda group of companies.

Conflicts of Interest

G.R.D. has served as a consultant for Ablynx, Allergan PLC, Alphabiomics, AM Pharma, Amakem, Amgen, Arena Pharmaceuticals, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celltrion, Dr Falk Pharma, Echo Pharmaceuticals, Engene, Ferring Pharmaceuticals, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Hospira, Immunic Therapeutics, Johnson & Johnson, Kintai Therapeutics, Lilly, Medtronic, Merck Sharp & Dohme, Millennium Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, Mundipharma, Nestlé, Nextbiotics, Novo Nordisk, Otsuka Pharmaceutical, Pfizer, PhotoPill Medical, ProDigest, Progenity, Prometheus, Protagonist Therapeutics, Receptos, RedHill BioPharma, Robarts Clinical Trials, Samsung Bioepis, Sandoz, Seres Therapeutics, Setpoint Medical, Shire (a member of the Takeda group of companies), Takeda, Teva Pharmaceutical Industries, TiGenix, Tillotts Pharma, TopiVert, Versant Ventures, and Vifor. W.R. has served on advisory boards for 4SC, Abbott Laboratories, AbbVie, AESCA, Astellas, AstraZeneca, Avaxia, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cellerix, Celltrion, Centocor, ChemoCentryx, Danone Austria, Elan, Ferring, Galapagos NV, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin, Lipid Therapeutics, MedImmune, Merck Sharp & Dohme, Millennium Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, Nestlé, Novartis, Ocera Therapeutics, Otsuka, PDL BioPharma, Pfizer, Pharmacosmos, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, SetPoint Medical, Takeda, Therakos, TiGenix, UCB Pharma, Zealand, and Zyngenia; has received grants and research support from Abbott Laboratories, AbbVie, AESCA, Centocor, Dr Falk Pharma GmbH, Immundiagnostik, and Merck Sharp & Dohme; has been a speaker for Abbott Laboratories, AbbVie, AESCA, Aptalis, Celltrion, Centocor, Danone Austria, Dr Falk Pharma GmbH, Elan, Ferring, Immundiagnostik, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Otsuka, PDL BioPharma, Pharmacosmos, PLS Education, Schering-Plough, Shire International GmbH (a member of the Takeda group of companies), Takeda, Therakos, Yakult, and Vifor; and has been a consultant for 4SC, Abbott Laboratories, AbbVie, AESCA, Amgen, AM-Pharma, AOP Orphan, AstraZeneca, Avaxia, BioClinica, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cellerix, Celltrion, Centocor, ChemoCentryx, Covance, Danone Austria, Dr Falk Pharma GmbH, Elan, Ernst & Young, Ferring, Galapagos NV, Genentech, Gilead Sciences, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin, LivaNova, Mallinckrodt, MedImmune, Merck Sharp & Dohme, Millennium Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, Nestlé, Novartis, Ocera Therapeutics, Otsuka, Parexel, PDL BioPharma, Pfizer, Pharmacosmos, Philip Morris Institute, Procter & Gamble, Prometheus, Provention Bio, Robarts Clinical Trials, Roland Berger GmBH, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, SetPoint Medical, Sigmoid, Takeda, Therakos, TiGenix, UCB Pharma, Vifor, Zealand, and Zyngenia. S.D.L. has received grants and research support from AbbVie, Arena, Atlantic Pharmaceuticals, Celgene, Gilead Sciences, Janssen, Pfizer, Salix, Shield Therapeutics PLC/Consultancy, Takeda, Tetherex, and UCB Pharma; and has served as a consultant for Arena, Celgene, Celltrion, Cornerstones, Janssen, Lilly, Mesoblast Inc., Pfizer, Takeda, and UCB Pharma. D.T. has received lecture fees from AbbVie, Ferring, Merck Sharp & Dohme, Pfizer, Roche, Sandoz,

and Takeda; has received grants and research support from Amicus and Roche; and has been a consultant for Pfizer. E.L. has served as a speaker for Abbott Laboratories, AbbVie, AstraZeneca, Chiesi, Dr Falk Pharma, Ferring, Hospira, Janssen, Merck Sharp & Dohme, Pfizer, and Takeda; has served as an advisory board member for Abbott Laboratories, AbbVie, Celgene, Celltrion, Ferring, Hospira, Janssen, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, and Takeda; has received educational grants from Merck Sharp & Dohme and Takeda; has received grants and research support from Pfizer and Takeda; and has been a consultant for AbbVie and Lilly. M.K. has received speaker fees from AbbVie, Egis, Ferring, Sanofi, and Takeda; has received support to attend congresses from AbbVie, Egis, and Ferring; and has received grants and research support from Egis. J.K. has received travel assistance fees and has served as a speaker and an advisory board member for AbbVie, Celltrion, Dr Falk Pharma, Hospira, Janssen, Merck Sharp & Dohme, Pfizer, Shield Therapeutics, and Takeda. S.S. has served as an advisory board member for Pfizer, Roche, Shire (a member of the Takeda group of companies), and Takeda. D.I.P. has served as an advisory board member for AbbVie, Celltrion, Ferring, and Shire (a member of the Takeda group of companies). X.H. has served on advisory boards for AbbVie, Fresenius Kabi, Janssen, LivaNova, Nutricia, and Takeda; and has received funds for educational activities from AbbVie, ARARD, Ferring, Fresenius Kabi, Mayoly Spindler, Merck Sharp & Dohme, Nestlé, Nutricia, and Takeda. P.N. is an employee of Shire (a member of the Takeda group of companies). F.C. is a previous employee of Pfizer. S.W.M., S.N., and A.B. are employees of Pfizer. K.J.G. has served as a consultant for Pfizer and Shire (a member of the Takeda group of companies). W.J.S. has received research grants from Abbvie, Atlantic Healthcare, Amgen, Eli Lilly, Genentech, Gilead Sciences, Janssen Pharmaceuticals, Receptos, Pfizer, Prometheus, and Takeda; has received consulting fees from Abbvie, Allergan PLC, Amgen, Arena Pharmaceuticals, Avexegen Therapeutics, BeiGene, Boehringer Ingelheim, Celgene, Celltrion, Conatus Pharmaceuticals, Cosmo Pharmaceuticals, Escalier Biosciences, Eli Lilly, Ferring Pharmaceuticals, Forbion, Genentech, Gilead Sciences, Gossamer Bio, Incyte, Janssen Pharmaceuticals, Kyowa Hakko Kirin, Landos Biopharma, Oppilan Pharma, Otsuka Pharmaceutical, Pfizer, Precision IBD, Progenity, Prometheus, Reistone Biopharma, Ritter Pharmaceuticals, Robarts Clinical Trials, Series Therapeutics, Shire (a member of the Takeda group of companies), Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Takeda, Theravance Biopharma, TiGenix, Tillotts Pharma, UCB, Ventyx, Vimalan Biosciences, and Vivelix Pharmaceuticals; and has received stock or stock options from BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals, Ventyx Biosciences, and Vimalan Biosciences.

Data Availability

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article, will be made available within 12 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet.* 2012;380:1590–1605.
2. Peyrin-Biroulet L, Deltenre P, de Suray N, et al. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol.* 2008;6:644–653.
3. Barré A, Colombel JF, Ungaro R. Review article: predictors of response to vedolizumab and ustekinumab in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2018;47:896–905.
4. Lopetuso LR, Gerardi V, Papa V, et al. Can we predict the efficacy of anti-TNF-alpha agents? *Int J Mol Sci.* 2017;18(9): 1973.
5. Ghosh S, Panaccione R. Anti-adhesion molecule therapy for inflammatory bowel disease. *Therap Adv Gastroenterol.* 2010;3:239–258.
6. Nakache M, Berg EL, Streeter PR, Butcher EC. The mucosal vascular addressin is a tissue-specific endothelial cell adhesion molecule for circulating lymphocytes. *Nature.* 1989;337:179–181.
7. Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol.* 1997;151:97–110.
8. Streeter PR, Berg EL, Rouse BT, et al. A tissue-specific endothelial cell molecule involved in lymphocyte homing. *Nature.* 1988;331:41–46.
9. Allavena R, Noy S, Andrews M, Pullen N. CNS elevation of vascular and not mucosal addressin cell adhesion molecules in patients with multiple sclerosis. *Am J Pathol.* 2010;176:556–562.
10. Nelson SM, Nguyen TM, McDonald JW, MacDonald JK. Natalizumab for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2018;8:CD006097.
11. Chahin S, Berger JR. A risk classification for immunosuppressive treatment-associated progressive multifocal leukoencephalopathy. *j Neurovirol.* 2015;21:623–631.
12. Stüve O, Marra CM, Jerome KR, et al. Immune surveillance in multiple sclerosis patients treated with natalizumab. *Ann Neurol.* 2006;59:743–747.
13. Major EO, Yousry TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. *Lancet Neurol.* 2018;17:467–480.
14. D'Haens G, Vermeire S, Vogelsang H, et al. Effect of PF-00547659 on central nervous system immune surveillance and circulating β7+ T cells in Crohn's disease: report of the TOSCA study. *J Crohns Colitis.* 2018;12:188–196.
15. Vermeire S, Loftus EV Jr, Colombel JF, et al. Long-term efficacy of vedolizumab for Crohn's disease. *J Crohns Colitis.* 2017;11:412–424.
16. Sandborn WJ, Lee SD, Tarabar D, et al. Phase II evaluation of anti-MAdCAM antibody PF-00547659 in the treatment of Crohn's disease: report of the OPERA study. *Gut.* 2018;67:1824–1835.
17. Pullen N, Molloy E, Carter D, et al. Pharmacological characterization of PF-00547659, an anti-human MAdCAM monoclonal antibody. *Br J Pharmacol.* 2009;157:281–293.
18. D'Alessio S, Spanò S, Palliser D, et al. MAdCAM-1 antagonism with ontamalimab promotes drainage of leukocytes in vitro through the intestinal lymphatic endothelium from patients with inflammatory bowel disease. *United Europ Gastr J.* 2020;8(S8):453.
19. Vermeire S, Ghosh S, Panes J, et al. The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study. *Gut.* 2011;60:1068–1075.
20. Vermeire S, Sandborn WJ, Danese S, et al. Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase

2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390:135–144.
21. Martin SW, Magnusson MO, Matthews IT, et al. Mechanistic population pharmacokinetics (PK) model of PF-00547659, a fully human IgG2 anti-MAdCAM antibody, in ulcerative colitis patients: results of a first in human (Fih) study. *Gastroenterology*. 2009;136:A641.
22. Fernandez Ocana M, Zhang J, Jones B, et al. Validation of assay for detection of free soluble mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in human serum and cerebrospinal fluid. *J Crohn's Colitis*. 2019;13(Suppl 1):S119.
23. Wang Q, Goetsch M. An electrochemiluminescence (ECL) immunoassay for the detection of anti-drug antibodies against the anti-mucosal addressin cell adhesion molecule (MAdCAM) monoclonal antibody ontamalimab (SHP647). *J Crohn's Colitis*. 2019;13(Suppl 1):S096.
24. Vermeire S, Schreiber S, Sandborn WJ, et al. Correlation between the Crohn's disease activity and Harvey-Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol*. 2010;8:357–363.
25. R Foundation for Statistical Computing. *R: A Language and Environment for Statistical Computing [computer program]. Version 3.4.1 or later.* Vienna, Austria: R Foundation for Statistical Computing; 2017.
26. RStudio, Inc. *RStudio: Integrated Development for R [computer program]. Version 1.0.153 or later.* Boston, MA: RStudio, Inc; 2015.
27. Stüve O, Marra CM, Bar-Or A, et al. Altered CD4+/CD8+ T-cell ratios in cerebrospinal fluid of natalizumab-treated patients with multiple sclerosis. *Arch Neurol*. 2006;63:1383–1387.
28. Frohman EM, Monaco MC, Remington G, et al. JC virus in CD34+ and CD19+ cells in patients with multiple sclerosis treated with natalizumab. *JAMA Neurol*. 2014;71:596–602.
29. Zohren F, Toutzaris D, Klärner V, et al. The monoclonal anti-VLA-4 antibody natalizumab mobilizes CD34+ hematopoietic progenitor cells in humans. *Blood*. 2008;111:3893–3895.
30. Cellier C, Sahmoud T, Froguel E, et al. Correlations between clinical activity, endoscopic severity, and biological parameters in colonic or ileocolonic Crohn's disease. A prospective multicentre study of 121 cases. The Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives. *Gut*. 1994;35:231–235.