PROTOCOL

TITLE: **A PHASE II, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF UTTR1147A COMPARED WITH PLACEBO AND COMPARED WITH VEDOLIZUMAB IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS**

PROTOCOL NUMBER: GA39925

VERSION NUMBER: 7

EUDRACT NUMBER: 2017-002350-36

IND NUMBER: 136180

NCT NUMBER: NCT03558152

TEST PRODUCT: Efmarodocokin alfa (UTTR1147A, RO7021610)

MEDICAL MONITOR: [redacted], M.D., Ph.D.

SPONSOR: Genentech, Inc.

DATE FINAL: Version 1: 6 July 2017

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
26-Jul-2021 20:25:51	Company Signatory	[redacted]

DATES AMENDED: Version 2: 16 November 2017
Version 3: 26 January 2018
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Version 4: 30 March 2018
Version 4 (VHP): 18 July 2018
Version 5: 28 February 2020
Version 6: 8 April 2021
Version 7: See electronic date stamp.

PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol GA39925 has been amended to align with the Investigator Brochure update (Version 8, April 2021) to include [redacted]

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, RANDOMIZED, PARALLEL-GROUP, DOUBLE-BLIND, DOUBLE-DUMMY, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF UTTR1147A COMPARED WITH PLACEBO AND COMPARED WITH VEDOLIZUMAB IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS**
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PHASE:	II
INDICATION:	Ulcerative colitis
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety, efficacy, and pharmacokinetics of efmarodocokin alfa compared with placebo and compared with vedolizumab in patients with moderate to severe ulcerative colitis (UC). Specific objectives and corresponding endpoints for the study are outlined below. Endoscopic scores will be based on interpretation by a central reader.

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
– To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Clinical remission at Week 8, with clinical remission defined as meeting both of the following criteria: – Modified MCS [a] of ≤ 2 – Mayo rectal bleeding subscore of 0 and other Mayo subscores of ≤ 1

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

[a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy.

Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
– To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Sustained remission, defined as clinical remission at both Week 8 and Week 30 • Clinical response at Weeks 8 and 30, with clinical response defined as achieving clinical remission or meeting both of the following criteria: – A ≥ 3-point decrease from baseline in modified MCS – A ≥ 1-point decrease from baseline in Mayo rectal bleeding subscore or a Mayo rectal bleeding subscore of 0 or 1 • Endoscopic healing at Weeks 8 and 30, with endoscopic healing defined as a Mayo endoscopic subscore of ≤ 1 • Endoscopic remission at Weeks 8 and 30, with endoscopic remission defined as a Mayo endoscopic subscore of 0 • Change from baseline in UC bowel movement signs and symptoms at Week 8 and at Week 30, as assessed by UC-PRO/SS score • Change from baseline in UC abdominal signs and symptoms at Week 8 and at Week 30, as assessed by UC-PRO/SS score • Change from baseline in patient–reported health-related QOL at Week 8 and at Week 30, as assessed by IBDQ score
Exploratory Efficacy Objective	**Corresponding Endpoints**
– To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Mucosal healing, defined as endoscopic healing and histological remission ≤ 6 as per Robarts Histological Index, at Weeks 8 and 30 • Change from baseline in UC Endoscopic Index of Severity at Week 8 and at Week 30 • Histological healing, defined as Nancy score of 0 or 1 as per Nancy Histological Index, at Weeks 8 and 30 • Change from baseline in Geboes Score at Week 8 and at Week 30 • Change from baseline in Robarts Histological Index at Week 8 and at Week 30

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

[a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy.

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE scale • Change in targeted vital signs, physical findings, and clinical laboratory test results during and following study drug administration
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of efmarodocokin alfa in patients with UC	• Serum concentration of efmarodocokin alfa at specified timepoints
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy and safety of study drug	• Relationship between serum concentration or PK parameters for study drug and efficacy endpoints • Relationship between serum concentration or PK parameters for study drug and safety endpoints
• To identify covariates that have significant impact on the exposure to efmarodocokin alfa	• Relationship between identified covariates and serum concentration or PK parameters for efmarodocokin alfa
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to efmarodocokin alfa	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers that are predictive of response to efmarodocokin alfa (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of efmarodocokin alfa activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood, stool, and colonic tissue, and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

[a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy.

Study Design

Description of Study

This is a Phase II, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of efmarodocokin alfa compared with placebo and compared with vedolizumab in the treatment of moderate to severe UC.

This study will consist of a screening period of up to 4 weeks, a 22-week treatment period, and an 8-week safety follow-up period. Part A (Weeks 0–8) will test the induction of clinical remission. The durability of clinical response and remission will be evaluated during Part B (Weeks 9–22) through the end of the safety follow-up period (Week 30). Upon approval of open-label extension (OLE) Study GA40209 by local Institutional Review Boards/Ethics Committees (IRBs/ECs) and relevant health authorities, patients enrolled in this study will have the opportunity to participate in OLE Study GA40209, if eligible.

Overall, patients will be randomly assigned in a 1:1:1:1:1:1:2:1 ratio to one of eight treatment arms as outlined below.

Treatment Regimens

Arm	Part A (Weeks 0–8)		Part B (Weeks 9–22)	
	Active Drug	Placebo	Active Drug	Placebo
1A	Efmarodocokin alfa 30 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	Efmarodocokin alfa 60 μg/kg IV at Weeks 14 and 22	VDZ placebo IV at Weeks 14 and 22
1B	Efmarodocokin alfa 30 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22
2A	Efmarodocokin alfa 60 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	Efmarodocokin alfa 60 μg/kg IV at Weeks 14 and 22	VDZ placebo IV at Weeks 14 and 22
2B	Efmarodocokin alfa 60 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22
3A	Efmarodocokin alfa 90 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	Efmarodocokin alfa 60 μg/kg IV at Weeks 14 and 22	VDZ placebo IV at Weeks 14 and 22
3B	Efmarodocokin alfa 90 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22
4	VDZ 300 mg IV at Weeks 0, 2, 6	Efmarodocokin alfa placebo IV at Weeks 0, 4, 8	VDZ 300 mg IV at Weeks 14 and 22	Efmarodocokin alfa placebo IV at Weeks 14 and 22

IV = intravenous infusion; VDZ = vedolizumab.

Treatment Regimens (cont.)

Arm	Part A (Weeks 0–8)		Part B (Weeks 9–22)	
	Active Drug	Placebo	Active Drug	Placebo
5	—	VDZ placebo IV at Weeks 0, 2, 6 Efmarodocokin alfa placebo IV at Weeks 0, 4, 8	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22

IV = intravenous infusion; VDZ = vedolizumab.

Patient disposition during the study will be based on whether patients receive rescue therapy or meet criteria for clinical remission, clinical response or disease flare, as defined below:

- Rescue therapy, defined as initiation of any treatment for UC or an increase in the dose of oral 5-aminosalicylic acid (5-ASA) or oral corticosteroids compared with baseline (randomization)

  Cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, and anti-integrin agents are not permitted as rescue therapy.
- Clinical remission, defined as meeting both of the following criteria:
  - Modified MCS of ≤ 2
  - Mayo rectal bleeding subscore of 0 and other Mayo subscores of ≤ 1
- Clinical response, defined as either achieving clinical remission or as meeting both of the following criteria:
  - A ≥ 3-point decrease from baseline in modified Mayo Clinic Score (mMCS), defined as the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy
  - A ≥ 1-point decrease from baseline in rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
- Disease flare, defined as meeting one of the following sets of criteria during Part B:
  - An increase from Week 8 in partial MCS (pMCS), defined as a composite of three MCS assessments: stool frequency, rectal bleeding, and Physician's Global Assessment, of ≥ 3 points and an absolute pMCS of ≥ 5 and an endoscopy subscore of ≥ 2
  - An absolute pMCS score of ≥ 7 and an endoscopy subscore of ≥ 2

Part A

During Part A, patients will receive IV infusions of efmarodocokin alfa, efmarodocokin alfa placebo, vedolizumab, or vedolizumab placebo. At Week 0 only, two IV infusions will be administered. At Weeks 2, 4, 6, and 8, patients will receive one IV infusion (see treatment regimens outlined above).

At Week 8 and prior to study drug administration, patients will undergo a flexible sigmoidoscopy with biopsy and a full MCS will be assessed. The mMCS and pMCS will be derived from the MCS.

Patients who receive rescue therapy and patients with persistent or worsening disease for which rescue therapy is indicated, as determined by the investigator, should return to the clinic as soon as possible for a disease evaluation visit, which will include a flexible sigmoidoscopy and MCS evaluation. The disease evaluation visit should occur no later than 1 week after initiation of rescue therapy.

Patients who receive rescue therapy will discontinue study drug and undergo all scheduled clinic assessments through Week 8, with the exception of the flexible sigmoidoscopy if already performed at a disease evaluation visit. Upon completion of the Week 8 visit, these patients may enroll in OLE Study GA40209, if eligible.

Patients who meet the criteria for clinical response at Week 8 (without use of rescue therapy) will continue into Part B. Patients who do not meet the criteria for clinical response will discontinue study drug and may enroll in OLE Study GA40209, if eligible. Study drug should not be administered at Week 8 if determination is made at the visit that patient will enroll in OLE Study GA40209.

Patients who are ineligible for or choose not to enroll in OLE Study GA40209 will enter the safety follow-up period.

Part B

During Part B, patients will receive IV infusions of efmarodocokin alfa and vedolizumab placebo (Arms 1A, 2A, and 3A), efmarodocokin alfa placebo and vedolizumab placebo (Arms 1B, 2B, 3B, and 5), or vedolizumab and efmarodocokin alfa placebo (Arm 4) at Weeks 14 and 22 as per the treatment regimens outlined above.

For patients on concomitant oral corticosteroids at baseline, the corticosteroid dose will be tapered until discontinuation, starting at Week 8.

For patients who cannot tolerate the corticosteroid taper without recurrence of UC symptoms or experience symptoms of corticosteroid withdrawal, the corticosteroid dose can be increased. If the corticosteroid dose has not been increased above the baseline level, these patients should re-initiate corticosteroid dose tapering per the above regimen within 2 weeks. Patients who are unable to tolerate a second taper should discontinue study drug and enroll in OLE Study GA40209, if eligible. Treatment with corticosteroids above the baseline dose will be considered rescue therapy.

Patients who receive rescue therapy and patients with worsening disease for which rescue therapy is indicated, as determined by the investigator, should return to the clinic as soon as possible for a disease evaluation visit, which will include a flexible sigmoidoscopy and MCS evaluation. The disease evaluation visit should occur no later than 1 week after initiation of rescue therapy.

Patients who receive rescue therapy or experience disease flare will discontinue study drug and may enroll in OLE Study GA40209, if eligible. Study drug should not be administered at Weeks 14 or 22 if determination is made at the visit that patient will enroll in OLE Study GA40209. Patients who are ineligible for or choose not to enroll in OLE Study GA40209 will enter the safety follow-up period.

Patients who complete Part B (i.e., through Week 22) will enter the safety follow-up period.

Safety Follow-Up Period and Early Termination Visit

Patients who complete the treatment period (Parts A and B) and patients who discontinue study drug without entering OLE Study GA40209 will enter the safety follow-up period and undergo assessments at 4 and 8 weeks after their last dose of study drug. Patients who discontinue study drug prematurely should return to the clinic for an early termination visit within 1 week of the event and will then enter the safety follow-up period. Patients who are unwilling to complete the safety follow-up period should return to the clinic for an early termination visit as soon as possible and no later than 30 days after their final dose.

A flexible sigmoidoscopy and MCS evaluation will be performed at second visit of safety follow-up, approximately 8 weeks after the last dose of study drug, if patient has completed the treatment period (Parts A and B) and 8-week safety follow-up, i.e., second visit of safety follow-up corresponds to Week 30 for that patient.

Patients who complete the treatment period (Parts A and B) and the safety follow-up period may enroll in OLE Study GA40209, if eligible.

Open-Label Extension Study GA40209

Upon approval of OLE Study GA40209 by local IRBs/ECs and relevant health authorities, patients who enter OLE Study GA40209 at Week 8 or during Part B (i.e., do not complete maintenance treatment will receive treatment with open-label efmarodocokin alfa during OLE Study GA40209.

Patients who enter OLE Study GA40209 after completing the treatment period (Parts A and B) and the safety follow-up period will receive treatment with open-label efmarodocokin alfa, if protocol-defined criteria are met.

Number of Patients

Approximately 270 patients will be enrolled across global investigational sites.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with requirements of the study, in the investigator's judgment
- Age 18–80 years, inclusive, at time of signing Informed Consent Form
- Diagnosis of UC established and confirmed by clinical and endoscopic evidence at least 3 months prior to randomization

  The diagnosis of UC should be corroborated by histopathology and documented by a histopathology report. A histopathologic examination should be performed at screening if no prior report is readily available.
- Confirmation of moderate to severe UC, defined as an mMCS of 4–9 with an endoscopic subscore of ≥ 2 as determined by the central reading procedure, a rectal bleeding subscore of ≥ 1, and a stool frequency subscore of ≥ 1 during the screening period (i.e., prior to Day 1)
- Evidence of UC a minimum of 20 cm from the anal verge as determined by baseline endoscopy (flexible sigmoidoscopy or colonoscopy)
- Colonoscopy within 1 year prior to randomization that confirms left-sided colitis (inflammation up to the splenic flexure), extensive colitis (inflammation beyond the splenic flexure but not involving the entire colon), or pancolitis (inflammation of the entire colon) and includes both of the following:
  - Removal of any adenomatous polyps
  - Performance of multiple random mucosal biopsies to evaluate for dysplasia in all patients with left-sided colitis of >12 years' duration or extensive colitis or pancolitis of >8 years' duration
- Inadequate response, loss of response, or intolerance to prior immunosuppressant treatment (i.e., AZA, 6-MP, MTX, or TNF inhibitors [maximum of two prior TNF inhibitors]) and/or corticosteroid treatment

  Inadequate response, loss of response, or intolerance to prior AZA, 6-MP, or MTX treatment is defined as one or more of the following:
  - Persistent signs or symptoms of active disease despite treatment with at least one 12-week regimen of AZA (≥ 2 mg/kg/day), 6-MP (≥ 1 mg/kg/day), and/or MTX (≥ 25 mg/week) within the previous 5 years
  - Persistent signs or symptoms of active disease despite a 6-TG level of ≥ 230 pmol/8×10^8 RBCs (as measured by quantitative high-performance liquid chromatography or liquid chromatography/tandem mass spectrometry) during at least one 12-week regimen of AZA or 6-MP within the previous 5 years
  - History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, TPMT genetic mutation, or infection) within the previous 5 years

  Inadequate response, loss of response, or intolerance to prior TNF inhibitor treatment is defined as one or more of the following:
  - Persistent signs or symptoms of active disease despite treatment with at least two induction doses of infliximab (≥ 5 mg/kg), adalimumab (160 mg for first two doses and 80 mg for subsequent doses, or 80 mg for first two doses and 40 mg for subsequent doses), or golimumab (200 mg for first two doses and 100 mg for subsequent doses)
  - Recurrence of signs or symptoms of active disease during maintenance after initial response to induction therapy with infliximab (≥ 5 mg/kg), adalimumab (≥ 40 mg), or golimumab (≥ 100 mg)

- Intolerance to TNF inhibitor (including, but not limited to, injection-site reaction, demyelination, congestive heart failure, or infection)

Inadequate response, loss of response, or intolerance to prior corticosteroid treatment is defined as one or more of the following:

- Persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included ≥ 30 mg/day of oral prednisone (or equivalent) for at least 2 weeks or ≥ 30 mg/day of IV prednisone (or equivalent) for at least 1 week within the previous 5 years (corticosteroid refractory)
- Two failed attempts to taper corticosteroids below 10 mg/day of oral prednisone (or equivalent) (corticosteroid dependent)
- History of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection) within the previous 5 years (corticosteroid intolerant)

- For patients receiving ongoing UC therapy with oral 5-ASA, oral corticosteroids, or oral probiotics: stable dose as outlined below.
  - Oral 5-ASA at a dose that has been stable for at least 4 weeks at the time of randomization
  - Oral corticosteroid therapy at a dose of ≤ 20 mg/day of prednisone (or equivalent) that has been stable for at least 2 weeks at the time of randomization

  Oral probiotic (e.g., Culturelle, or *Saccharomyces boulardii*) at a dose that has been stable for at least 2 weeks at the time of randomization
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 18 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (recommendations related to contraception and pregnancy testing in clinical trials, CTFG Final version – 2014-09-15, Section 4.1).

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 18 weeks after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Immunizations current according to local standards as described in the vedolizumab prescribing information and/or based on the investigator's clinical judgment
- Agreement to refrain from donating blood for 6 months after receiving the last dose of study drug

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of psoriasis or psoriatic arthritis
- History of any other inflammatory skin disorders requiring oral corticosteroids, immunosuppressants, or biological therapy within the previous year
- History of cancer within the previous 5 years
- History of non-melanoma skin cancer, gastrointestinal (GI) cancer, or colon cancer, or known family history of GI cancer or colon cancer (defined as one first-degree relative or two second-degree relatives)
- History of a cervical intraepithelial neoplasia of Grade >1, cervical smear indicating the presence of adenocarcinoma in situ, or high-grade squamous intraepithelial lesions (HSILs)
- Conditions other than UC (e.g., asthma) that could require treatment with >20 mg/day of prednisone (or equivalent) during the course of the study
- Poorly controlled diabetes, defined as glycosylated hemoglobin (HbA_{1c}) $>8.0\%$
- History of primary sclerosing cholangitis
- Requirement for hospitalization during the study due to severity of UC
- Hospitalized (other than for elective reasons) within 4 weeks prior to screening
- Any acute or chronic condition that, in the opinion of the investigator, would limit the patient's ability to complete or participate in this clinical study
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 18 weeks after the last dose of study drug
- Lack of peripheral venous access
- Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure [New York Heart Association Class III or IV]), pulmonary, renal, hepatic, endocrine, or GI disorders (excluding UC)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- Family history of sudden unexplained death or long QT syndrome
- QT interval corrected through use of Fridericia's formula >450 ms (men) or >470 ms (women) demonstrated by at least two ECGs
- History of alcoholism or drug abuse as judged by the investigator within 1 year of screening
- If stipulated by local or national laws: employed by the site, the Sponsor, or Sponsor representatives or financially dependent on, or related to, an employee of the site, the Sponsor, or Sponsor representatives
- If stipulated by local or national laws: institutionalization or detention by way of official or judicial order
- Prior extensive colonic resection, subtotal or total colectomy, or proctocolectomy, or planned surgery for UC
- Diagnosis of indeterminate colitis or granulomatous (Crohn's) colitis
- Suspicion of ischemic colitis, radiation colitis, or microscopic colitis
- Diagnosis of toxic megacolon within 12 months prior to screening
- Current fistula or history of fistula
- Current pericolonic abscess
- History or current evidence of unresectable colonic mucosal dysplasia
- History of high-grade colonic mucosal dysplasia
- Stricture (stenosis) of the colon
- Prior treatment with efmarodocokin alfa or participation in Study GA29469

- Prior treatment with vedolizumab, etrolizumab, natalizumab, efalizumab, or any other anti-integrin agents
- Use of IV corticosteroids within 30 days prior to randomization with the exception of a single administration of IV corticosteroids
- Treatment with corticosteroid enemas or suppositories or topical (rectal) 5-ASA preparations within 2 weeks prior to randomization
- Treatment with AZA, 6-MP, or MTX within 2 weeks prior to randomization
- Treatment with a TNF inhibitor within 8 weeks prior to randomization
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 4 weeks prior to randomization
- Prior treatment with rituximab
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to randomization, with the exception of AZA and 6-MP
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use

  Occasional use of NSAIDs or acetaminophen (e.g., for headache, arthritis, myalgias, or menstrual cramps) and aspirin up to 325 mg/day is permitted.
- Use of anticoagulants, including, but not limited to, warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban

  Use of antiplatelet agents, such as aspirin up to 325 mg/day or clopidogrel, is permitted.
- Apheresis (e.g., Adacolumn® apheresis) within 2 weeks prior to randomization
- Participation in an investigational study involving non-biologic therapy within 30 days or 5 half-lives of the investigational product (whichever is greater) prior to randomization
- Participation in an investigational study involving biologic therapy (including vaccines) within 90 days or 5 half-lives of the investigational product (whichever is greater) prior to randomization
- History of moderate or severe allergic, anaphylactic, or anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins or hypersensitivity to efmarodocokin alfa (active drug substance) or any of the excipients (sucrose, methionine, sodium phosphate, or polysorbate 20)
- Tube feeding, defined formula diets, or parenteral alimentation within 3 weeks prior to randomization
- Congenital or acquired immune deficiency
- Evidence of, or treatment for, *Clostridium difficile* (as assessed by *C. difficile* toxin testing) within 60 days prior to randomization or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to randomization
- History of invasive fungal infections such as *Candida* or *Aspergillus* (excluding thrush or other superficial fungal infections) within 6 months prior to randomization
- History of severe herpes (simplex type 1, simplex type 2, or zoster) infection or reactivation within 12 weeks prior to randomization, or frequent recurrence of herpes (more than two times per year)
- History of any other opportunistic infections within 12 weeks prior to randomization
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 8 weeks prior to screening or oral antibiotics within 4 weeks prior to screening
- History of organ transplant
- Colonic biopsy positive for cytomegalovirus at screening, as determined by histologic examination or immunohistochemistry per local standards
- Positive HIV antibody test at screening

- Positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a negative HBsAg test and a positive total hepatitis B core antibody test at screening will not be excluded if they have a negative hepatitis B virus DNA test.
- Positive hepatitis C virus (HCV) antibody test at screening, except in patients who meet either of the following sets of criteria:
  - Patient has undetectable HCV RNA levels for >6 months after completion of HCV anti-viral treatment and a negative HCV RNA test at screening
  - Patient has a history of HCV antibody positivity, a history of undetectable HCV RNA levels for >6 months, and a negative HCV RNA test at screening
- Positive for tuberculosis during screening or within 3 months prior to screening, defined as a positive QuantiFERON®-TB Gold test (QFT) or (if QFT is not available) a positive purified protein derivative (PPD) skin test according to Centers for Disease Control and Prevention guidelines, with the following exceptions:
  - Patients with a history of Bacillus Calmette-Guérin (BCG) vaccination who have a positive PPD skin test will not be excluded if they have a negative QFT at screening
  - Patients who have a positive or indeterminate QFT and patients with no history of BCG vaccination who have a positive PPD skin test will not be excluded if they meet all of the following criteria:
    a) No symptoms consistent with TB
    b) Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB) per local standard of care prior to screening
    c) No known exposure to a case of active TB after most recent prophylaxis
    d) No evidence of active TB on chest X-ray performed during screening or within 3 months prior to screening
- Glomerular filtration rate <60 mL/min as calculated through use of the Modification of Diet in Renal Disease (MDRD) study equation or creatinine clearance rate <60 mL/min as calculated by the Cockcroft-Gault formula
- ALT, AST, or alkaline phosphatase $>2.5\times$ ULN, total bilirubin $>1.5\times$ ULN, or presence of abnormalities in synthetic function tests judged to be clinically significant by the investigator

  Patients with known Gilbert syndrome who have unconjugated hyperbilirubinemia will not be excluded.
- Platelet count $<100\times10^9$/L (100,000/μL)
- Hemoglobin <90 g/L (9 g/dL)
- ANC $<1.5\times10^9$/L (1500/μL)
- Absolute lymphocyte count $<0.5\times10^9$/L (500/μL)

End of Study

The end of this study is defined as the date when the last patient completes his or her final study visit. The end of the study is expected to occur approximately 30 weeks after the last patient initiates treatment.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 40 months.

Investigational Medicinal Products

The investigational medicinal products for this study are efmarodocokin alfa and vedolizumab (active comparator).

Test Product (Investigational Drug)

Efmarodocokin alfa or efmarodocokin alfa placebo will be administered by IV infusion.

During Part A, patients will receive an infusion of efmarodocokin alfa or efmarodocokin alfa placebo according to the following dosing regimen.

- Arms 1A and 1B: Efmarodocokin alfa 30 μg/kg at Weeks 0, 4, and 8
- Arms 2A and 2B: Efmarodocokin alfa 60 μg/kg at Weeks 0, 4, and 8
- Arms 3A and 3B: Efmarodocokin alfa 90 μg/kg at Weeks 0, 4, and 8
- Arm 4: Efmarodocokin alfa placebo at Weeks 0, 4, and 8
- Arm 5: Efmarodocokin alfa placebo at Weeks 0, 4, and 8

During Part B, patients will receive an infusion of efmarodocokin alfa or efmarodocokin alfa placebo according to the following dosing regimen.

- Arms 1A, 2A, and 3A: Efmarodocokin alfa 60 μg/kg at Weeks 14 and 22
- Arms 1B, 2B, and 3B, 4 and 5: Efmarodocokin alfa placebo at Weeks 14 and 22

Comparator

Vedolizumab 300 mg or vedolizumab placebo will be administered by IV infusion.

During Parts A and B, patients in Arms 1−3 and Arm 5 will receive an infusion of vedolizumab placebo at Weeks 0, 2, 6, 14 and 22.

During Parts A and B, patients in Arm 4 will receive an infusion of 300 mg vedolizumab at Weeks 0, 2, 6, 14 and 22.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is clinical remission at Week 8. The primary analysis will be conducted by first comparing the efmarodocokin alfa arms versus the placebo arm. A comparison between the efmarodocokin alfa arms and the vedolizumab arm will be carried out secondarily. The difference between pooled Arm 1, pooled Arm 2, and pooled Arm 3, versus Arm 4 and versus Arm 5 in the proportion of patients with clinical remission at Week 8 will be evaluated by the Mantel-Haenszel test statistic, stratified by prior treatment with TNF inhibitors (yes/no). Additional stratification variables may be used if appropriate (e.g., if a large number of very small strata are not generated), such as concomitant treatment with corticosteroids (yes/no) or prior treatment with immunomodulators (AZA, 6-MP, or MTX) (yes/no). An 80% two-sided confidence interval of the differences in the proportion of patients with clinical remission at Week 8 will be provided to aid in the interpretation of the study results.

Determination of Sample Size

A target of approximately 270 patients will be enrolled and randomly assigned in a 1:1:1:1:1:1:2:1 ratio to Arms 1A, 1B, 2A, 2B, 3A, 3B, 4, and 5. The A and B arms for each efmarodocokin alfa dose will be pooled (i.e., 1A + 1B; 2A + 2B; 3A + 3B) for analyses of endpoints at or before Week 8. Thus, the primary efficacy analysis of clinical remission at Week 8 will compare data for pooled Arm 1 (1A + 1B), pooled Arm 2 (2A + 2B), and pooled Arm 3 (3A + 3B), versus Arm 4 and versus Arm 5. The sample size of 60 patients per pooled efmarodocokin alfa arm provides approximately 80% power to detect an improvement of 16 percentage points over the vedolizumab arm (Arm 4; $n = 60$) and approximately 80% power to detect an improvement of 26 percentage points over the placebo arm (Arm 5; $n = 30$) in the proportion of patients with clinical remission at Week 8, assuming a clinical remission rate of approximately 15%−20% in a vedolizumab-treated population and approximately 5%−10% in a placebo-treated population with both populations consisting of 25% TNF-α naive patients and 75% TNF-IR patients and a two-sided type I error rate of 0.2.

Interim Analyses

An interim analysis will be performed when approximately 50% of patients have completed Part A (through Week 8). The interim results will be evaluated on the basis of descriptive summaries of the primary and key secondary outcomes for Part A, including estimated rates, between-group differences in rates, 80% CIs, and exploratory p-values with no type I error

adjustments or formal stopping criteria. Results of the interim analysis may inform potential early stopping of enrollment if the benefit-risk profile for the efmarodocokin alfa arms is considerably unfavorable. The interim analysis will be conducted by the Internal Monitoring Committee. Recruitment of patients will continue during the period of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ADA	anti-drug antibody, also known as anti-therapeutic antibody
AESI	adverse event of special interest
AIS	adenocarcinoma in situ
AZA	azathioprine
BCG	bacillus Calmette-Guérin
C_{max}	maximum concentration
C_{min}	minimum concentration
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DE	disease evaluation (visit)
DMBT1	Deleted in Malignant Brain Tumors 1 (protein)
DSS	dextran sulfate sodium
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	Food and Drug Administration
GI	gastrointestinal
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HSIL	high-grade squamous intraepithelial lesion
HV	healthy volunteer
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council for Harmonisation
IL-22	interleukin-22
IL-22R	interleukin-22 receptor
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous

Abbreviation	Definition
IxRS	interactive voice or web-based response system
MCS	Mayo Clinic Score
mMCS	modified Mayo Clinic Score
MMF	mycophenolate mofetil
MTD	maximum tolerated dose
MTX	methotrexate
NCI	National Cancer Institute
PD	pharmacodynamic
PGA	Physician's Global Assessment
PK	pharmacokinetic
pMCS	partial Mayo Clinic Score
PRO	patient-reported outcome
Q2W	every 2 weeks
Q4W	every 4 weeks
Q6W	every 6 weeks
QTcF	QT interval corrected using Fridericia's formula
RBR	Research Biosample Repository
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SC	subcutaneous
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
TNF-IR	inadequate response to anti-tumor necrosis factor
UC	ulcerative colitis
UC-PRO/SS	Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms
ULN	upper limit of normal
VHP	Voluntary Harmonisation Procedure

1. BACKGROUND

1.1 BACKGROUND ON ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic inflammatory condition that affects the colon but has the potential for extra-intestinal complications. Although there are many risk factors associated with the development of UC, the disease fundamentally represents dysregulation of the mucosal immune system in a genetically susceptible individual in response to commensal microbiota and other environmental triggers. UC is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain and may be complicated by severe bloody diarrhea and toxic megacolon, requiring major and sometimes urgent surgery. The overall incidence of UC ranges from 6.3 to 24.3 cases per 100,000 persons per year, and prevalence ranges from 4.9 to 505.0 cases per 100,000 persons, with the highest estimates in European and Northern American populations (Molodecky et al. 2012). Although the incidence and prevalence vary between regions of the world, both have been increasing in some regions. This rise may be due in part to better detection and diagnosis as well as environmental factors such as improved hygiene and Western diet. The disease can affect any age group, but occurrence peaks between the ages of 15 and 35 years.

Pharmacologic management of UC currently includes anti-inflammatory drugs (corticosteroids and aminosalicylates such as 5-aminosalicylic acid [5-ASA]), immunosuppressants (such as azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]), tumor necrosis factor (TNF) inhibitors, and anti-$\alpha 4\beta 7$ integrin agents (such as vedolizumab). Newer therapies aim to modify the disease by inducing mucosal healing, to decrease dependence on corticosteroids, and to reduce the probability of progression to surgery, without significantly compromising immune competence.

1.2 BACKGROUND ON EFMARODOCOKIN ALFA

Efmarodocokin alfa *(also known as UTTR1147A)* is a human interleukin-22 (IL-22) fusion protein in which the cytokine IL-22 is linked with the Fc portion of IgG4 to improve the cytokine's pharmacokinetic (PK) characteristics. The Fc portion of the fusion protein incorporates a mutation that minimizes the potential for Fc effector function.

IL-22 belongs to the IL-10 cytokine family (Ouyang et al. 2011) and binds specifically to the IL-22 receptor (IL-22R) heterodimer, which is expressed on a variety of epithelial tissues including the gastrointestinal (GI) tract epithelium, epidermal keratinocytes, liver hepatocytes, pancreatic acinar epithelium, and renal tubular epithelium (Gurney 2004). IL-22 modulates innate immunity in epithelial tissues (Wolk et al. 2004), including the GI tract mucosal epithelium, by upregulating antimicrobial peptides, increasing mucin production, and stimulating epithelial barrier repair (Sugimoto et al. 2008; Zheng et al. 2008). In murine models of UC, IL-22 has demonstrated efficacy through these epithelial protective mechanisms (Sugimoto et al. 2008). Therefore,

efmarodocokin alfa is being developed as a therapeutic for inflammatory bowel diseases (IBDs) such as Crohn's disease and UC on the basis of IL-22's demonstrated biology.

1.2.1 Summary of Nonclinical Studies

Extensive in vitro and in vivo nonclinical studies have been conducted to characterize the pharmacologic activity, safety, PK, and pharmacodynamic (PD) profiles of efmarodocokin alfa. These studies define the pharmacologic activities and PK/PD relationships and provide a safety profile supporting IV dosing in humans.

In an in vivo model of dextran sulfate sodium (DSS)-induced mouse colitis, muIL-22 Fc, a mouse surrogate for efmarodocokin alfa with full-length mouse IL-22 and the Fc portion of mouse IgG2a, was efficacious in a dose-dependent manner. At the lowest efficacious dose of 1.25 μg (efficacy assessed by colon histologic score), the corresponding minimum serum concentration of muIL-22 Fc was approximately 10 ng/mL. These results are consistent with the conclusions reported by other investigators (Sugimoto et al. 2008; Pickert et al. 2009; Neufert et al. 2010).

REG3A was evaluated as a PD biomarker in cynomolgus monkeys (Studies 12-2623, 13-2601, and 15-0279). Results from these studies demonstrated that elevations in REG3A correlate with efmarodocokin alfa drug levels. REG3A levels returned to baseline levels despite variability in individual responses by the end of these studies, with the exception of animals given 1,500 μg/kg in Study 12-2623, where REG3A levels remained elevated throughout the duration of the study. Taken together, these in vivo biomarker data demonstrate that REG3A is a relevant biomarker for pharmacological activity of efmarodocokin alfa and suggest that IL-22R engagement was achieved.

Toxicology studies of up to 6 months duration have been conducted in rats, cynomolgus monkeys, and Yucatan minipigs. These studies have identified a transient acute phase inflammatory response and epidermal hyperplasia with skin reddening as clinical safety risks. These risks are considered predictable, manageable, monitorable, and reversible in the clinic.

Refer to the Efmarodocokin Alfa Investigator's Brochure for details on nonclinical studies.

1.2.2 Summary of Clinical Studies

Results from Study GA29468, a Phase Ia, placebo-controlled, single-dose, dose-escalation study in healthy volunteers (HVs), showed that efmarodocokin alfa had acceptable tolerability at single IV doses of up to 90 μg/kg and SC doses of up to 60 μg/kg. Starting at 30 μg/kg IV, dose-dependent reversible increases in the number and intensity of skin events (e.g., dry skin, patchy erythema, and subjective skin-related complaints such as skin discomfort) were reported (see Section 5.1.1.1 for additional details). At the highest IV dose (120 μg/kg), 3 of 4 HVs experienced protocol-defined dermatologic dose-limiting toxicities.

Dose-dependent increases in serum levels of PD biomarkers SAA, REG3A, and C–reactive protein (CRP), indicative of IL-22R engagement by efmarodocokin alfa, were observed following treatment with efmarodocokin alfa compared to placebo. Transient increases in CRP were consistent with data from nonclinical studies and importantly occurred in the absence of symptoms of inflammation (e.g., fever, leukocytosis, vital sign changes).

All abnormal clinical laboratory results reported as treatment-emergent adverse events were assessed by the investigator as mild or moderate in intensity and not related to treatment with efmarodocokin alfa, except for mild to moderate dose-dependent elevations in CRP, as noted above. No clinically significant changes for individuals or dose-related trends by cohort were noted for laboratory tests (except for CRP and fibrinogen), vital signs measurements, 12-lead ECGs, or body weight measurements for this study.

Anti-drug antibodies (ADAs) occurred in 1 of 44 (2.3%) subjects. This subject was in the low-dose (3 μg/kg) SC treatment group. A positive ADA result for this subject was first observed at Day 57 (study completion); ADAs were not detected at earlier timepoints. The safety and tolerability profile for this subject was similar to that for other subjects in the cohort.

In *the* Phase Ib, placebo-controlled, multiple-dose, dose-escalation study in HVs*, patients with UC,* and patients with *CD* (Study GA29469), *efmarodocokin alfa was adequately tolerated at IV doses up to 60 μg/kg IV Q2W in HVs and patients in the only CD cohort evaluated, and up to 90 μg/kg IV Q2W in patients with UC.* In HVs, a dose regimen of 90 μg/kg Q2W was not tolerated, as two HVs experienced dermatologic dose-limiting adverse events at this dose (severe skin discomfort and severe dry skin) that occurred after the second dose of blinded efmarodocokin alfa or placebo. Topical emollients and topical corticosteroids provided minimal relief. Skin effects were fully reversible. *PK exposures were approximately dose proportional within HVs and within patients with UC. Patients with UC or CD had relatively low drug exposures as compared to HVs when dosed at the same level. Two participants had ADAs at baseline, and no participants were found to have treatment-emergent ADAs. The observed increases trending upwards with increasing efmarodocokin alfa dose levels returned to baseline levels for CRP and SAA, whereas REG3A levels returned to near baseline level by study completion suggestive of sustained pathway activation though considerable variability was observed in the different cohorts.*

Refer to the Efmarodocokin Alfa Investigator's Brochure for details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

While effective therapeutic options, including anti-integrin agents and TNF inhibitors, are available to reduce the acute symptomatic flares in disease activity in patients with moderate to severe UC, no currently available therapy achieves sustained remission in

more than 10%–30% of patients with chronic IBD (Hanauer et al. 2002; Sandborn et al. 2005; Feagan et al. 2013). Furthermore, anti-integrin agents and TNF inhibitors are associated with severe adverse events including hypersensitivity reactions and increased risk of infections (including serious infections such as tuberculosis [TB]). Consequently, patients and physicians must carefully weigh the benefit-risk ratio both before starting and while managing long-term treatment with anti-integrin agents or TNF inhibitors.

Vedolizumab, an $\alpha 4\beta 7$ integrin receptor antagonist, is the only biological therapy indicated for treating both patients who are TNF inhibitor naïve, as well as patients for whom treatment with TNF inhibitors, immunomodulators, and/or corticosteroids has failed. However, vedolizumab has a slow onset of action (6 weeks) and reduced efficacy during induction for patients with inadequate response to anti-TNF therapy (TNF-IR). At Week 6, the rate of response to vedolizumab and placebo were 39.0% and 20.6%, respectively, in TNF-IR patients (Feagen et al. 2017).

As described above, IL-22 stimulates mucin and anti-microbial peptide production in the intestine, which can modulate bacterial growth and protect the intestinal epithelium. Changes in bacterial flora have been associated with a variety of immunologically-mediated diseases and, along with altered epithelial barrier function, are thought to be key drivers in the inflammatory process of IBD (Sugimoto et al. 2008; Zheng et al. 2008; Eidenschenk et al. 2014). Efmarodocokin alfa, an IL-22 fusion protein, is a novel therapeutic agent being developed to promote mucosal healing and achieve sustained clinical remission while potentially allowing reduction or elimination of the immunosuppression associated with current therapies for UC.

The safety profile of efmarodocokin alfa, as demonstrated in the Phase I studies, supports further investigation to compare efmarodocokin alfa with placebo and with vedolizumab in the induction and maintenance of clinical remission for patients who have failed conventional therapy.

The present double-blind, double-dummy, comparator study employs a robust design and utilizes an independent and centrally read endoscopy to confirm patient eligibility and endpoint determination. Patients will receive an active therapy (vedolizumab or efmarodocokin alfa) or placebo during Part A (through Week 8). Patients who respond to efmarodocokin alfa therapy through Week 8 of Part A will continue active treatment or switch to placebo during Part B (through Week 22), followed by an 8-week safety follow-up period. Patients who respond to vedolizumab or placebo through Week 8 of Part A will continue with vedolizumab or placebo, respectively, in Part B (through Week 22), followed by an 8-week safety follow-up period. Patients enrolled in this study will have the opportunity to participate in open-label extension (OLE) Study GA40209, if eligible (see Section 3.1.5). See Section 3 for additional information regarding study design.

As efmarodocokin alfa is an investigational medicinal product (IMP), the full safety profile will be further characterized as clinical development progresses. A safety plan is outlined in Section 5.1.

Refer to the Efmarodocokin Alfa Investigator's Brochure for details on nonclinical and clinical studies and additional safety information.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, efficacy, and pharmacokinetics of efmarodocokin alfa compared with placebo and compared with vedolizumab in patients with moderate to severe UC. Specific objectives and corresponding endpoints for the study are outlined below. Endoscopic scores will be based on interpretation by a central reader.

In this protocol, "study drug" refers to blinded drug (i.e., efmarodocokin alfa, vedolizumab, or placebo).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Clinical remission at Week 8, with clinical remission defined as meeting both of the following criteria: – Modified MCS [a] of ≤ 2 – Mayo rectal bleeding subscore of 0 and other Mayo subscores of ≤ 1

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

[a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 3).

Table 1 Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Sustained remission, defined as clinical remission at both Week 8 and Week 30 • Clinical response at Weeks 8 and 30, with clinical response defined as achieving clinical remission or meeting both of the following criteria: – A ≥3-point decrease from baseline in modified MCS – A ≥1-point decrease from baseline in Mayo rectal bleeding subscore or a Mayo rectal bleeding subscore of 0 or 1 • Endoscopic healing at Weeks 8 and 30, with endoscopic healing defined as a Mayo endoscopic subscore of ≤1 • Endoscopic remission at Weeks 8 and 30, with endoscopic remission defined as a Mayo endoscopic subscore of 0
• To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab (cont.)	• Change from baseline in UC bowel movement signs and symptoms at Week 8 and at Week 30, as assessed by UC-PRO/SS score • Change from baseline in UC abdominal signs and symptoms at Week 8 and at Week 30, as assessed by UC-PRO/SS score • Change from baseline in patient–reported health-related QOL at Week 8 and at Week 30, as assessed by IBDQ score
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Mucosal healing, defined as endoscopic healing and histological remission ≤ 6 as per Robarts Histological Index, at Weeks 8 and 30 • Change from baseline in UC Endoscopic Index of Severity at Week 8 and at Week 30 • Histological healing, defined as Nancy score of 0 or 1 as per Nancy Histological Index, at Weeks 8 and 30 • Change from baseline in Geboes Score at Week 8 and at Week 30 • Change from baseline in Robarts Histological Index at Week 8 and at Week 30

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

[a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 3).

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of efmarodocokin alfa compared with placebo and compared with vedolizumab	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE scale • Change in targeted vital signs, physical findings, and clinical laboratory test results during and following study drug administration
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of efmarodocokin alfa in patients with UC	• Serum concentration of efmarodocokin alfa at specified timepoints
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy and safety of study drug	• Relationship between serum concentration or PK parameters for study drug and efficacy endpoints • Relationship between serum concentration or PK parameters for study drug and safety endpoints
• To identify covariates that have significant impact on the exposure to efmarodocokin alfa	• Relationship between identified covariates and serum concentration or PK parameters for efmarodocokin alfa
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to efmarodocokin alfa	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

- [a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 3).

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To identify biomarkers that are predictive of response to efmarodocokin alfa (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events (i.e., safety biomarkers), can provide evidence of efmarodocokin alfa activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood, stool, and colonic tissue, (listed in Section 4.5.8) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA = anti-drug antibody; IBDQ = Inflammatory Bowel Disease Questionnaire; MCS = Mayo Clinic Score; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PD = pharmacodynamic; PK = pharmacokinetic; UC-PRO/SS = Ulcerative Colitis–Patient-Reported Outcome Signs and Symptoms.

Note: Endoscopic scores will be based on interpretation by a central reader.

[a] Modified MCS is the composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 3).

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

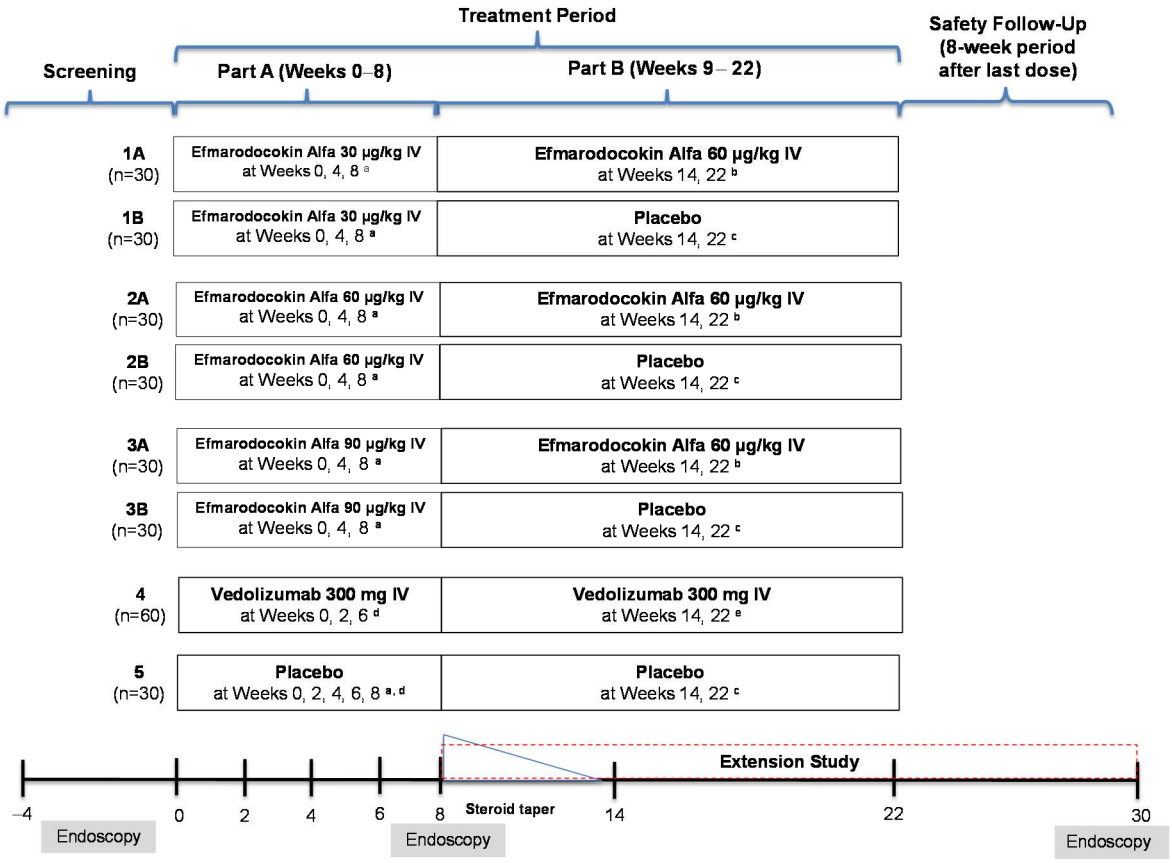
This is a Phase II, randomized, parallel-group, double-blind, double-dummy, placebo-controlled, multicenter study to evaluate the efficacy, safety, and pharmacokinetics of efmarodocokin alfa compared with placebo and compared with vedolizumab in the treatment of moderate to severe UC.

This study will consist of a screening period of up to 4 weeks, a 22-week treatment period, and an 8-week safety follow-up period. Part A (Weeks 0–8) will test the induction of clinical remission. The durability of clinical response and remission will be evaluated during Part B (Weeks 9–22) through the end of the safety follow-up period (Week 30). Upon approval of OLE Study GA40209 by local Institutional Review Boards/Ethics Committees (IRBs/ECs) and relevant health authorities, patients enrolled in this study will have the opportunity to participate in OLE Study GA40209, if eligible (see Section 3.1.5).

Approximately 270 patients will be enrolled across global investigational sites. Overall, patients will be randomly assigned in a 1:1:1:1:1:1:2:1 ratio to one of eight treatment arms (see Figure 1). The treatment regimens for Part A and Part B are outlined for each

treatment arm in Table 2. The first dose of study drug will be administered on Day 1 of Week 0. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



[a] Vedolizumab placebo will be administered at Weeks 0, 2, and 6.

[b] Vedolizumab placebo will be administered at Weeks 14 and 22.

[c] Efmarodocokin alfa placebo and vedolizumab placebo will be administered at Weeks 14 and 22.

[d] Efmarodocokin alfa placebo will be administered at Weeks 0, 4, and 8.

[e] Efmarodocokin alfa placebo will be administered at Weeks 14 and 22.

Table 2 Treatment Regimens

Arm	Part A (Weeks 0–8)		Part B (Weeks 9–22)	
	Active Drug	Placebo	Active Drug	Placebo
1A	Efmarodocokin alfa 30 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	Efmarodocokin alfa 60 μg/kg IV at Weeks 14 and 22	VDZ placebo IV at Weeks 14 and 22
1B	Efmarodocokin alfa 30 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22
2A	Efmarodocokin alfa 60 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	Efmarodocokin alfa 60 μg/kg IV at Weeks 14 and 22	VDZ placebo IV at Weeks 14 and 22
2B	Efmarodocokin alfa 60 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22
3A	Efmarodocokin alfa 90 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	Efmarodocokin alfa 60 μg/kg IV at Weeks 14 and 22	VDZ placebo IV at Weeks 14 and 22
3B	Efmarodocokin alfa 90 μg/kg IV at Weeks 0, 4, 8	VDZ placebo IV at Weeks 0, 2, 6	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22
4	VDZ 300 mg IV at Weeks 0, 2, 6	Efmarodocokin alfa placebo IV at Weeks 0, 4, 8	VDZ 300 mg IV at Weeks 14 and 22	Efmarodocokin alfa placebo IV at Weeks 14 and 22
5	—	VDZ placebo IV at Weeks 0, 2, 6 Efmarodocokin alfa placebo IV at Weeks 0, 4, 8	—	VDZ placebo IV + Efmarodocokin alfa placebo IV at Weeks 14 and 22

IV = intravenous infusion; VDZ = vedolizumab.

Patient disposition during the study will be based on whether patients receive rescue therapy or meet criteria for clinical remission, clinical response or disease flare, as defined below:

- Rescue therapy, defined as initiation of any treatment for UC or an increase in the dose of oral 5-ASA or oral corticosteroids compared with baseline (randomization)

  Cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil (MMF), and anti-integrin agents are not permitted as rescue therapy (see Section 4.4.1 for details).

- Clinical remission, defined as meeting both of the following criteria:
  - Modified MCS of ≤ 2

    mMCS is a composite of three MCS assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 3).
  - Mayo rectal bleeding subscore of 0 and other Mayo subscores of ≤ 1
- Clinical response, defined as achieving clinical remission or as meeting both of the following criteria:
  - A ≥ 3-point decrease from baseline in modified Mayo Clinic Score (mMCS)
  - A ≥ 1-point decrease from baseline in rectal bleeding subscore or a rectal bleeding subscore of 0 or 1
- Disease flare, defined as meeting one of the following sets of criteria during Part B:
  - A ≥ 3 increase from Week 8 in partial MCS (pMCS) and an absolute pMCS of ≥ 5 and an endoscopy subscore of ≥ 2

    pMCS is a composite of three MCS assessments: stool frequency, rectal bleeding, and Physician's Global Assessment (PGA) (see Appendix 4)
  - An absolute pMCS score of ≥ 7 and an endoscopy subscore of ≥ 2

3.1.2 Part A

During Part A, patients will receive IV infusions of efmarodocokin alfa, efmarodocokin alfa placebo, vedolizumab, or vedolizumab placebo. At Week 0 only, two IV infusions will be administered. At Weeks 2, 4, 6, and 8, patients will receive one IV infusion (see treatment regimens outlined in Table 2).

Restrictions regarding treatment with concomitant therapy during Part A are outlined in Section 4.4.

At Week 8 and prior to study drug administration, patients will undergo a flexible sigmoidoscopy with biopsy and a full MCS will be assessed. The mMCS and pMCS will be derived from the MCS (see Section 4.5.7.1).

Patients who receive rescue therapy (see Section 4.4.1) and patients with persistent or worsening disease for which rescue therapy is indicated, as determined by the investigator, should return to the clinic as soon as possible for a disease evaluation visit,

which will include a flexible sigmoidoscopy and MCS evaluation (see Appendix 1). The disease evaluation visit should occur no later than 1 week after initiation of rescue therapy.

Patients who receive rescue therapy will discontinue study drug and undergo all scheduled clinic assessments through Week 8, with the exception of the flexible sigmoidoscopy if already performed at a disease evaluation visit. Upon completion of the Week 8 visit, these patients may enroll in OLE Study GA40209, if eligible.

Patients who meet the criteria for clinical response (see Section 3.1.1) at Week 8 (without use of rescue therapy) will continue into Part B. Patients who do not meet the criteria for clinical response will discontinue study drug and may enroll in OLE Study GA40209, if eligible. Study drug should not be administered at Week 8 if determination is made at the visit that patient will enroll in OLE Study GA40209. Details on Week 8 visit are provided in Appendix 1.

Patients who are ineligible for or choose not to enroll in OLE Study GA40209 will enter the safety follow-up period (see Section 3.1.4).

3.1.3 Part B

During Part B, patients will receive IV infusions of efmarodocokin alfa and vedolizumab placebo (Arms 1A, 2A, and 3A), efmarodocokin alfa placebo and vedolizumab placebo (Arms 1B, 2B, 3B, and 5), or vedolizumab and efmarodocokin alfa placebo (Arm 4) at Weeks 14 and 22 as per the treatment regimens outlined in Table 2.

Restrictions regarding treatment with concomitant therapy during Part B are outlined in Section 4.4.

For patients on concomitant oral corticosteroids at baseline, the corticosteroid dose will be tapered until discontinuation, starting at Week 8. The tapering schedule will be as follows:

- For patients on >10 mg/day of oral prednisone (or equivalent), the dose should be reduced at a rate of 5 mg/week until a dose of 10 mg/day dose is reached. Thereafter, the dose should be reduced at a rate of 2.5 mg/week until discontinuation.
- For patients on ≤ 10 mg/day of oral prednisone (or equivalent), the dose should be reduced at a rate of 2.5 mg/week until discontinuation.

For patients who cannot tolerate the corticosteroid taper without recurrence of UC symptoms or experience symptoms of corticosteroid withdrawal, the corticosteroid dose can be increased. If the corticosteroid dose has not been increased above the baseline level, these patients should re-initiate corticosteroid dose tapering per the above regimen within 2 weeks. Patients who are unable to tolerate a second taper should discontinue study drug and enroll in OLE Study GA40209, if eligible. Treatment with corticosteroids above the baseline dose will be considered rescue therapy.

Patients who receive rescue therapy (see Section 4.4.1) and patients with worsening disease for which rescue therapy is indicated, as determined by the investigator, should return to the clinic as soon as possible for a disease evaluation visit, which will include a flexible sigmoidoscopy and MCS evaluation (see Appendix 1). The disease evaluation visit should occur no later than 1 week after initiation of rescue therapy.

Patients who receive rescue therapy or experience disease flare (see Section 3.1.1) will discontinue study drug and may enroll in OLE Study GA40209, if eligible. Study drug should not be administered at Weeks 14 or 22 if determination is made at the visit that patient will enroll in OLE Study GA40209. Patients who are ineligible for or choose not to enroll in OLE Study GA40209 will enter the safety follow-up period (see Section 3.1.4).

Patients who complete Part B (i.e., through Week 22) will enter the safety follow-up period (see Section 3.1.4).

3.1.4 Safety Follow-Up Period and Early Termination Visit

Patients who complete the treatment period (Parts A and B) and patients who discontinue study drug without entering OLE Study GA40209 will enter the safety follow-up period and undergo assessments at 4 and 8 weeks after their last dose of study drug. Patients who discontinue study drug prematurely for the reasons listed in Section 4.6.1 should return to the clinic for an early termination visit within 1 week of the event and will then enter the safety follow-up period. Patients who are unwilling to complete the safety follow-up period should return to the clinic for an early termination visit as soon as possible and no later than 30 days after their final dose (see Appendix 1 for additional details).

A flexible sigmoidoscopy and MCS evaluation will be performed at second visit of safety follow-up, approximately 8 weeks after the last dose of study drug, if patient has completed the treatment period (Parts A and B) and 8-week safety follow-up, i.e., second visit of safety follow-up corresponds to Week 30 for that patient.

Patients who complete the treatment period (Parts A and B) and the safety follow-up period may enroll in OLE Study GA40209, if eligible.

3.1.5 Open-Label Extension Study GA40209

Upon approval of OLE Study GA40209 by local IRBs/ECs and relevant health authorities, patients who enter OLE Study GA40209 at Week 8 or during Part B (i.e., do not complete maintenance treatment) as outlined in Sections 3.1.2 and 3.1.3 will receive treatment with open-label efmarodocokin alfa during OLE Study GA40209.

Patients who enter OLE Study GA40209 after completing the treatment period (Parts A and B) and the safety follow-up period will receive treatment with open-label efmarodocokin alfa, if protocol-defined criteria are met.

3.1.6 Internal Monitoring Committee

An Internal Monitoring Committee (IMC) will monitor data on safety, efficacy, and study conduct on an ongoing basis. The IMC consists of Sponsor representatives from Clinical Science, Drug Safety, and Biostatistics, and may invite representatives from other functional areas (e.g., Clinical Pharmacology, Research) or external experts on an ad hoc basis when additional expertise is required. Sponsor representatives will not be involved in the conduct of the study or have any contact with study investigators or site staff.

The IMC will review cumulative unblinded data on a periodic basis as defined in the IMC charter. In addition, ad hoc reviews may be requested by the IMC or the Sponsor at any time to address potential safety concerns. The data will include, but will not be limited to, demographic data, adverse events data (including serious adverse events and adverse events of special interest), ECG data, and relevant laboratory data. An interim efficacy analysis will be performed by the IMC (see Section 6.9).

After reviewing the data, the IMC may make recommendations such as the following:

- The trial will continue as planned
- The trial will continue with a reduction in dose level or frequency within a treatment arm
- The trial will continue with discontinuation of enrollment in a treatment arm, including placebo
- The trial will stop for safety reasons
- Additional analyses will need to be performed
- Enrollment will be held pending further safety evaluation

The IMC may also provide recommendations for amending the protocol after consideration of all available data. Final decisions will rest with the Sponsor's study team.

Any outcomes of these reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective IRBs/ECs. Biannual summaries of the conclusions and recommendations of the IMC will be sent to the IRBs/ECs.

A detailed description of the procedures, data flow, and meeting schedule of the IMC will be provided in the IMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes his or her final study visit. The end of the study is expected to occur approximately 30 weeks after the last patient initiates treatment.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 40 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Efmarodocokin Alfa Dose and Schedule

Three dose regimens, 30 μg/kg Q4W, 60 μg/kg Q4W, and 90 μg/kg Q4W, have been selected for Part A of the study primarily on the basis of available safety data from the completed Phase Ia study (GA29468) in HVs and safety data from the multiple-ascending dose Phase Ib study (GA29469) in HVs and patients with UC. In the Phase Ia study, efmarodocokin alfa demonstrated an adequate safety and tolerability profile in HVs treated with single IV doses of up to 90 μg/kg, the maximum tolerated dose (MTD) for that study per the protocol-specified criteria.

Results of the Phase Ib study show that efmarodocokin alfa was adequately tolerated at IV doses up to 60 μg/kg IV Q2W in HVs (MTD per protocol-specific criteria) and patients with CD, and up to 90 μg/kg IV Q2W in patients with UC.

Half-life of *efmarodocokin alfa ranged from 15.7-17.7* days in HVs and *12.4 to 13.8* days in patients with UC based on Phase Ib data, so it is expected to have minimal drug accumulation with Q4W dosing. The observation was in line with data from studies with anti-TNF and other biologic agents that patients with UC had lower systemic drug exposure than HVs at the same dose level (Hua et al. 2015), possibly due to increased drug clearance in patients with UC than HVs (Fausel et al. 2015; Rosen et al. 2015).

The 90 μg/kg Q4W dose regimen is the highest dose regimen tested within the tolerable exposure range to evaluate whether efmarodocokin alfa at this dose level is safe and efficacious in patients with UC. Given the minimal drug accumulation with Q4W dosing, as well as faster drug clearance observed in patients with UC, the C_{max} with 90 μg/kg Q4W in patients with UC at Week 8 is estimated to be similar to the C_{max} seen in Phase Ia single IV dose of 90 μg/kg in HVs. In addition, the predicted $AUC_{tau,4wks}$ would be well

covered by the exposure seen in Phase Ib adequately-tolerated 60 μg/kg Q2W cohort in HVs.

The 60 μg/kg Q4W dose regimen has been adequately tolerated both in HVs and in patients with UC in the Phase Ib study. Early signs of clinical activity were seen in Phase Ib so this dose regimen will be tested in larger cohort of patients with UC.

The 30 μg/kg Q4W dose regimen will provide 3-fold exposure separation from the high dose cohort, and allows for a wider dose-ranging evaluation to define the therapeutic window for efmarodocokin alfa.

The dose regimen for Part B has been selected to determine whether further dosing with efmarodocokin alfa is necessary to sustain clinical benefit. Arms 1A, 2A, and 3A will receive 60 μg/kg efmarodocokin alfa on Weeks 14 and 22. An 8-week dosing interval corresponds to the maximum duration for sustained PD effects observed after a single dose of efmarodocokin alfa. Arms 1B, 2B, and 3B will receive placebo during Part B as a short-term treatment control. Data from efmarodocokin alfa-treated arms in Part B will be compared with data from placebo-treated Arms 1B, 2B, and 3B to evaluate the benefit-risk balance when continuing treatment with efmarodocokin alfa after clinical response is achieved during Part A.

The safety follow-up period of 8 weeks is close to 5 times the efmarodocokin alfa half-life to allow complete drug washout and to provide sufficient safety monitoring.

3.3.2 Rationale for Patient Population

There is a high unmet medical need in the treatment of patients with moderate to severe UC. These patients typically require use of immunosuppressive agents to achieve mucosal healing and clinical remission. The current standard-of-care biologic therapies for this patient population are vedolizumab and TNF inhibitors. However, the immunosuppressive nature of conventional and biologic therapies increases the overall risk of serious infections. Furthermore, no currently available therapy achieves sustained remission in more than 10%–30% of patients with chronic IBD (Hanauer et al. 2002; Sandborn et al. 2005; Feagan et al. 2013). Vedolizumab is able to induce clinical remission in only about 10% of TNF-IR patients (Feagan et al. 2017).

Because of the limitations in the currently available therapies, a need exists for new treatments to achieve sustained corticosteroid-free remission and mucosal healing without increasing immune suppression. Moreover, there is a need to develop therapies for patients for whom both conventional and biologic therapies have failed. Efmarodocokin alfa is being developed as a novel therapeutic agent to promote mucosal healing and achieve sustained clinical remission in patients with UC while potentially allowing reduction or elimination of immunosuppression.

The eligibility criteria for this study define patients with moderate to severe UC who may benefit from the anticipated effects of efmarodocokin alfa. All patients considered for participation will have a diagnosis of moderate to severe UC established and confirmed by clinical and endoscopic evidence at least 3 months prior to randomization. Patients must have demonstrated an inadequate response, loss of response, or intolerance to prior immunosuppressant treatment (i.e., AZA, 6-MP, MTX, or TNF inhibitors) and/or corticosteroid treatment (as defined in Section 4.1.1). Patients who have had prior exposure to vedolizumab and other anti-integrin agents will be excluded. Patients who may be at increased risk and those who require intervention other than the standard-of-care therapies as defined in this protocol are excluded.

3.3.3 Rationale for Placebo Control Group

In accordance with the International Council for Harmonisation (ICH) E10 guideline and the European Medicines Agency draft "Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis" (EMA 2016), a placebo-treated control group will be used in this study to provide optimal evaluation of the efficacy and safety of efmarodocokin alfa.

The placebo group is utilized in UC trials to control for the variability in outcome measures associated with subjective assessments such as patient reported outcomes and disease factors such as spontaneous remission and the inherent variability in disease flares. Furthermore, use of an active comparator alone in this study may underestimate the safety and efficacy profile of efmarodocokin alfa and would require a larger patient population to evaluate its benefit-risk profile.

Use of a placebo control group (Arm 5) in Part A of the study will provide optimal evaluation of the efficacy and safety of efmarodocokin alfa, including the identification and evaluation of specific safety signals that may be unique to treatment with efmarodocokin alfa as compared with vedolizumab or compared with signals related to the underlying disease. Patients in the placebo-treated arm who meet the criteria for clinical response (see Section 3.1.1) at Week 8 will continue treatment with placebo in Part B of the study to maintain study blind.

Use of placebo in Part B in efmarodocokin alfa Arms 1B, 2B, and 3B will allow for evaluation of the safety and efficacy of continued dosing after patients respond to efmarodocokin alfa. Data from the Phase Ib study indicate that patients who received efmarodocokin alfa and achieved clinical remission maintained remission for up to 3 months after discontinuation of study drug. Therefore, use of placebo in Part B will serve as a short-term treatment control and allow for evaluation of the benefit-risk profile of continuing treatment with efmarodocokin alfa and potentially minimize unnecessary exposure to efmarodocokin alfa after clinical response is achieved in Part A. Any patient in Part B who cannot tolerate a second corticosteroid taper, receives rescue therapy (see Section 4.4.1), or experiences disease flare will have the opportunity to enter OLE Study GA40209, if eligible.

3.3.4 Rationale for Active Comparator

Vedolizumab, an $\alpha 4\beta 7$ integrin receptor antagonist, is the only biological therapy indicated for treating both patients who are TNF inhibitor naive and patients for whom treatment with TNF inhibitors, immunomodulators, and/or corticosteroids has failed.

Because vedolizumab is a gut-selective antibody and works mechanistically on a different target than UTTR1174A, the adverse event profiles between the two drugs are different. The adverse events documented for treatment with vedolizumab are well characterized. The most common adverse events, affecting at least 5% of patients receiving at least one dose of vedolizumab (Feagan et al. 2013), do not overlap with the most common adverse events observed for efmarodocokin alfa in the Phase Ia study (GA29468). As a result, having vedolizumab as the active comparator will further contribute to the safety profile assessment of efmarodocokin alfa.

As vedolizumab is one of the standard of care treatments for moderate to severe UC, it is an appropriate comparator when evaluating the efficacy of efmarodocokin alfa. Moreover, because a high drop-out rate is expected in the placebo arm after Week 8, it is critical to have an active arm so control data are available for long-term assessment of the efficacy and safety of efmarodocokin alfa.

3.3.5 Rationale for Pharmacokinetic Sample Collection

The PK sampling schedule for this study is designed to capture data at specific timepoints to characterize several key PK parameters of efmarodocokin alfa, such as C_{max} at postdose and C_{min} at predose. Exploratory vedolizumab PK analyses may also be performed.

3.3.6 Rationale for Biomarker Assessments

Biomarkers will be assessed in serum, plasma, stool, and colonic tissue to demonstrate evidence of biologic activity of efmarodocokin alfa in patients with UC, to characterize PK/PD relationships, and to support dose and dose regimen selection for future studies. Plasma 4β-hydroxycholesterol levels will be measured to assess the potential effect of efmarodocokin alfa on hepatic CYP3A activity. The relationship between blood, stool, and colonic tissue biomarkers and safety, immunogenicity, and other biomarker endpoints may also be explored. The assessment of PD biomarkers including, but not limited to, DMBT1 may be measured in colonic tissue biopsies to help understand concentrations of efmarodocokin alfa required to achieve a pharmacologic and therapeutic effect in diseased tissue.

There is significant variability in response to current treatment and disease progression that likely reflects significant heterogeneity in UC pathobiology (Ananthakrishnan 2013; Loftus et al. 2014). Treatment with efmarodocokin alfa is predicted to benefit patients with UC by enhancing barrier function through direct effects on the intestinal epithelium, including increased mucus and antimicrobial peptide production, and direct effects on

epithelial proliferation and tight junctions. Efmarodocokin alfa may also have an effect on the microbiome and may address the gut dysbiosis associated with IBD. Predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with an increased likelihood of responding to efmarodocokin alfa, thus potentially providing guidance for treatment decisions.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 270 patients with moderate to severe UC will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with requirements of the study, in the investigator's judgment
- Age 18–80 years, inclusive, at time of signing Informed Consent Form
- Diagnosis of UC established and confirmed by clinical and endoscopic evidence at least 3 months prior to randomization

  The diagnosis of UC should be corroborated by histopathology and documented by a histopathology report. A histopathologic examination should be performed at screening if no prior report is readily available.
- Confirmation of moderate to severe UC, defined as an mMCS of 4–9 with an endoscopic subscore of ≥2 as determined by the central reading procedure described in Section 4.5.7, a rectal bleeding subscore of ≥1, and a stool frequency subscore of ≥1 during the screening period (i.e., prior to Day 1)
- Evidence of UC a minimum of 20 cm from the anal verge as determined by baseline endoscopy (flexible sigmoidoscopy or colonoscopy)
- Colonoscopy within 1 year prior to randomization that confirms left-sided colitis (inflammation up to the splenic flexure), extensive colitis (inflammation beyond the splenic flexure but not involving the entire colon), or pancolitis (inflammation of the entire colon) and includes both of the following:
  - Removal of any adenomatous polyps
  - Performance of multiple random mucosal biopsies to evaluate for dysplasia in all patients with left-sided colitis of >12 years' duration or extensive colitis or pancolitis of >8 years' duration
- Inadequate response, loss of response, or intolerance to prior immunosuppressant treatment (i.e., AZA, 6-MP, MTX, or TNF inhibitors [maximum of two prior TNF inhibitors]) and/or corticosteroid treatment

Inadequate response, loss of response, or intolerance to prior AZA, 6-MP, or MTX treatment is defined as one or more of the following:

- Persistent signs or symptoms of active disease despite treatment with at least one 12-week regimen of AZA (≥2 mg/kg/day), 6-MP (≥1 mg/kg/day), and/or MTX (≥25 mg/week) within the previous 5 years
- Persistent signs or symptoms of active disease despite a 6-TG level of ≥230 pmol/8×10^8 RBCs (as measured by quantitative high-performance liquid chromatography or liquid chromatography/tandem mass spectrometry) during at least one 12-week regimen of AZA or 6-MP within the previous 5 years
- History of intolerance to AZA, 6-MP, or MTX (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, TPMT genetic mutation, or infection) within the previous 5 years

Inadequate response, loss of response, or intolerance to prior TNF inhibitor treatment is defined as one or more of the following:

- Persistent signs or symptoms of active disease despite treatment with at least two induction doses of infliximab (≥5 mg/kg), adalimumab (160 mg for first two doses and 80 mg for subsequent doses, or 80 mg for first two doses and 40 mg for subsequent doses), or golimumab (200 mg for first two doses and 100 mg for subsequent doses)
- Recurrence of signs or symptoms of active disease during maintenance after initial response to induction therapy with infliximab (≥5 mg/kg), adalimumab (≥40 mg), or golimumab (≥100 mg)
- Intolerance to TNF inhibitor (including, but not limited to, injection-site reaction, demyelination, congestive heart failure, or infection)

Inadequate response, loss of response, or intolerance to prior corticosteroid treatment is defined as one or more of the following:

- Persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included ≥30 mg/day of oral prednisone (or equivalent) for at least 2 weeks or ≥30 mg/day of IV prednisone (or equivalent) for at least 1 week within the previous 5 years (corticosteroid refractory)
- Two failed attempts to taper corticosteroids below 10 mg/day of oral prednisone (or equivalent) (corticosteroid dependent)
- History of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection) within the previous 5 years (corticosteroid intolerant)

- For patients receiving ongoing UC therapy with oral 5-ASA, oral corticosteroids, or oral probiotics: stable dose as outlined below.
  - Oral 5-ASA at a dose that has been stable for at least 4 weeks at the time of randomization
  - Oral corticosteroid therapy at a dose of $\leq$ 20 mg/day of prednisone (or equivalent) that has been stable for at least 2 weeks at the time of randomization
  - Oral probiotic (e.g., Culturelle, or *Saccharomyces boulardii*) at a dose that has been stable for at least 2 weeks at the time of randomization
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $<$ 1% per year during the treatment period and for 18 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (recommendations related to contraception and pregnancy testing in clinical trials, CTFG Final version – 2014-09-15, Section 4.1).

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 18 weeks after the last dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Immunizations current according to local standards as described in the vedolizumab prescribing information and/or based on the investigator's clinical judgment
- Agreement to refrain from donating blood for 6 months after receiving the last dose of study drug

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of psoriasis or psoriatic arthritis
- History of any other inflammatory skin disorders requiring oral corticosteroids, immunosuppressants, or biological therapy within the previous year
- History of cancer within the previous 5 years
- History of non-melanoma skin cancer, GI cancer, or colon cancer, or known family history of GI cancer or colon cancer (defined as one first-degree relative or two second-degree relatives)
- History of a cervical intraepithelial neoplasia (CIN) of Grade >1, cervical smear indicating the presence of adenocarcinoma in situ (AIS), or high-grade squamous intraepithelial lesions (HSILs)
- Conditions other than UC (e.g., asthma) that could require treatment with >20 mg/day of prednisone (or equivalent) during the course of the study
- Poorly controlled diabetes, defined as glycosylated hemoglobin (HbA_{1c}) $>8.0\%$
- History of primary sclerosing cholangitis
- Requirement for hospitalization during the study due to severity of UC
- Hospitalized (other than for elective reasons) within 4 weeks prior to screening
- Any acute or chronic condition that, in the opinion of the investigator, would limit the patient's ability to complete or participate in this clinical study
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 18 weeks after the last dose of study drug
- Lack of peripheral venous access
- Significant uncontrolled comorbidity, such as cardiac (e.g., moderate to severe heart failure [New York Heart Association Class III or IV]), pulmonary, renal, hepatic, endocrine, or GI disorders (excluding UC)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- Family history of sudden unexplained death or long QT syndrome
- QT interval corrected through use of Fridericia's formula (QTcF) >450 ms (men) or >470 ms (women) demonstrated by at least two ECGs
- History of alcoholism or drug abuse as judged by the investigator within 1 year of screening
- If stipulated by local or national laws: employed by the site, the Sponsor, or Sponsor representatives or financially dependent on, or related to, an employee of the site, the Sponsor, or Sponsor representatives
- If stipulated by local or national laws: institutionalization or detention by way of official or judicial order

Exclusion Criteria Related to Inflammatory Bowel Disease

- Prior extensive colonic resection, subtotal or total colectomy, or proctocolectomy, or planned surgery for UC
- Diagnosis of indeterminate colitis or granulomatous (Crohn's) colitis
- Suspicion of ischemic colitis, radiation colitis, or microscopic colitis
- Diagnosis of toxic megacolon within 12 months prior to screening
- Current fistula or history of fistula
- Current pericolonic abscess
- History or current evidence of unresectable colonic mucosal dysplasia
- History of high-grade colonic mucosal dysplasia
- Stricture (stenosis) of the colon

Exclusion Criteria Related to Prior or Concomitant Therapy

- Prior treatment with efmarodocokin alfa or participation in Study GA29469
- Prior treatment with vedolizumab, etrolizumab, natalizumab, efalizumab, or any other anti-integrin agents
- Use of IV corticosteroids within 30 days prior to randomization with the exception of a single administration of IV corticosteroids
- Treatment with corticosteroid enemas or suppositories or topical (rectal) 5-ASA preparations within 2 weeks prior to randomization
- Treatment with AZA, 6-MP, or MTX within 2 weeks prior to randomization
- Treatment with a TNF inhibitor within 8 weeks prior to randomization
- Use of cyclosporine, tacrolimus, sirolimus, or MMF within 4 weeks prior to randomization
- Prior treatment with rituximab
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab) within 12 months prior to randomization, with the exception of AZA and 6-MP
- Chronic nonsteroidal anti-inflammatory drug (NSAID) use

    Occasional use of NSAIDs or acetaminophen (e.g., for headache, arthritis, myalgias, or menstrual cramps) and aspirin up to 325 mg/day is permitted.
- Use of anticoagulants, including, but not limited to, warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban

    Use of antiplatelet agents, such as aspirin up to 325 mg/day or clopidogrel, is permitted.
- Apheresis (e.g., Adacolumn® apheresis) within 2 weeks prior to randomization
- Participation in an investigational study involving non-biologic therapy within 30 days or 5 half-lives of the investigational product (whichever is greater) prior to randomization

- Participation in an investigational study involving biologic therapy (including vaccines) within 90 days or 5 half-lives of the investigational product (whichever is greater) prior to randomization
- History of moderate or severe allergic, anaphylactic, or anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins or hypersensitivity to efmarodocokin alfa (active drug substance) or any of the excipients (sucrose, methionine, sodium phosphate, or polysorbate 20)
- Tube feeding, defined formula diets, or parenteral alimentation within 3 weeks prior to randomization

Exclusion Criteria Related to Infection Risk

- Congenital or acquired immune deficiency
- Evidence of, or treatment for, *Clostridium difficile* (as assessed by *C. difficile* toxin testing) within 60 days prior to randomization or other intestinal pathogens (as assessed by stool culture and ova and parasite evaluation) within 30 days prior to randomization
- History of invasive fungal infections such as *Candida* or *Aspergillus* (excluding thrush or other superficial fungal infections) within 6 months prior to randomization
- History of severe herpes (simplex type 1, simplex type 2, or zoster) infection or reactivation within 12 weeks prior to randomization, or frequent recurrence of herpes (more than two times per year)
- History of any other opportunistic infections within 12 weeks prior to randomization
- Any major episode of infection requiring hospitalization or treatment with IV antibiotics within 8 weeks prior to screening or oral antibiotics within 4 weeks prior to screening
- History of organ transplant
- Colonic biopsy positive for cytomegalovirus (CMV) at screening, as determined by histologic examination or immunohistochemistry per local standards

Exclusion Criteria Related to Screening Laboratory Values

- Positive HIV antibody test at screening
- Positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening will <u>not</u> be excluded if they have a negative hepatitis B virus (HBV) DNA test.
- Positive hepatitis C virus (HCV) antibody test at screening, except in patients who meet <u>either</u> of the following sets of criteria:
  - Patient has undetectable HCV RNA levels for >6 months after completion of HCV anti-viral treatment and a negative HCV RNA test at screening
  - Patient has a history of HCV antibody positivity, a history of undetectable HCV RNA levels for >6 months, and a negative HCV RNA test at screening

- Positive for TB during screening or within 3 months prior to screening, defined as a positive QuantiFERON®-TB Gold test (QFT) or (if QFT is not available) a positive purified protein derivative (PPD) skin test according to Centers for Disease Control and Prevention guidelines, with the following exceptions:
  - Patients with a history of Bacillus Calmette-Guérin (BCG) vaccination who have a positive PPD skin test will not be excluded if they have a negative QFT at screening
  - Patients who have a positive or indeterminate QFT and patients with no history of BCG vaccination who have a positive PPD skin test will not be excluded if they meet all of the following criteria:
    a) No symptoms consistent with TB
    b) Documented history of a completed course of adequate prophylaxis (completed treatment for latent TB) per local standard of care prior to screening
    c) No known exposure to a case of active TB after most recent prophylaxis
    d) No evidence of active TB on chest X-ray performed during screening or within 3 months prior to screening
- Glomerular filtration rate <60 mL/min as calculated through use of the Modification of Diet in Renal Disease (MDRD) study equation or creatinine clearance rate <60 mL/min as calculated by the Cockcroft-Gault formula
- ALT, AST, or alkaline phosphatase $>2.5\times$ ULN, total bilirubin $>1.5\times$ ULN, or presence of abnormalities in synthetic function tests judged to be clinically significant by the investigator

  Patients with known Gilbert syndrome who have unconjugated hyperbilirubinemia will not be excluded.
- Platelet count $<100\times10^9$/L (100,000/μL)
- Hemoglobin <90 g/L (9 g/dL)
- ANC $<1.5\times10^9$/L (1500/μL)
- Absolute lymphocyte count $<0.5\times10^9$/L (500/μL)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Overall, patients will be assigned in a 1:1:1:1:1:1:2:1 ratio to one of eight treatment arms (see Figure 1). Following completion of the screening period and after all patient eligibility requirements are confirmed, patients will be assigned a subject number and will be randomly assigned to a treatment arm through an interactive voice or web-based response system (IxRS).

Patients will be randomized on the same day that treatment is to be initiated (Day 1). Randomization will be performed using a permuted blocks randomization method with stratification by prior treatment with TNF inhibitors (yes/no).

Study site personnel (with the exception of the unblinded pharmacist) and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

While PK and ADA samples must be collected from all patients to maintain the blinding of treatment assignment, PK and ADA assay results for patients receiving placebo or vedolizumab are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. See Section 4.5.8 regarding serum sample analyses.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. The investigator will be able to break the treatment code by contacting the IxRS.

If deemed necessary, the Medical Monitor may be unblinded to individual patient assignment after approval is obtained from the IMC Chair.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMPs for this study are efmarodocokin alfa and vedolizumab (active comparator).

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Efmarodocokin Alfa and Efmarodocokin Alfa Placebo

Efmarodocokin alfa and efmarodocokin alfa placebo will be supplied by the Sponsor as a sterile solution in single-use 2-mL vials. Diluent will also be supplied by the Sponsor. For information on the formulation and handling of efmarodocokin alfa, see the pharmacy manual and the efmarodocokin alfa Investigator's Brochure.

4.3.1.2 Vedolizumab and Vedolizumab Placebo

Vedolizumab and vedolizumab placebo will be supplied by the investigative site or the Sponsor in selected countries as lyophilized powder in single-use vials or 0.9% sodium chloride (normal saline) bags, respectively. For information on the formulation and handling of vedolizumab, see the Summary of Product Characteristics for vedolizumab.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Table 2. Study drug will be administered in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

At clinic visits in which two infusions are administered (Weeks 0, 14, and 22), efmarodocokin alfa or efmarodocokin alfa placebo should be delivered first, followed by a monitoring period of approximately 30 minutes before administration of vedolizumab or vedolizumab placebo.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.4.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Efmarodocokin Alfa and Efmarodocokin Alfa Placebo

Efmarodocokin alfa or efmarodocokin alfa placebo will be administered by IV infusion, with the initiation infusion delivered over approximately 60 ± 10 minutes. If the 60-minute infusion is tolerated without infusion-associated adverse events (e.g., fevers or chills), the second infusion may be delivered over 30 ± 10 minutes. If the 30-minute infusion is tolerated, all subsequent infusions may be delivered over 15 ± 5 minutes.

If a patient experiences an infusion-associated adverse event, refer to the pharmacy manual for management of infusion reactions. All subsequent infusions should be delivered at the previously tolerated rate.

Patients should be monitored for at least 30 minutes after each infusion.

Weight-based infusions of efmarodocokin alfa, with a maximum dose given to be based on 100 kg total body weight, will be prepared per the instructions outlined in the pharmacy manual.

4.3.2.2 Vedolizumab and Vedolizumab Placebo

Vedolizumab 300 mg or vedolizumab placebo will be administered by IV infusion over 30 minutes as specified in the prescribing information.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (efmarodocokin alfa and vedolizumab) will be provided by the Sponsor where required by local health authority regulations. Vedolizumab may be provided by the study site, if applicable. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form. *The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMP received and that any discrepancies have been reported and resolved before use of the IMP. The IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.*

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Efmarodocokin Alfa

Patients may be eligible to receive efmarodocokin alfa as part of an extension study offered by the Sponsor (Genentech, a member of the Roche Group), as described in Section 3.1.5. The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment in the period immediately prior to randomization (as specified in Sections 4.1.1 and 4.1.2) through the final study visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF, along with the reason for their use.

At this time there is no evidence to suggest an interaction between efmarodocokin alfa and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. If a patient in the study elects to have a SARS-CoV-2 vaccine, it should not be given on the same day as study drug dosing, in order to distinguish any possible infusion-related reactions/injection-related reactions from each agent should one occur. The SARS-CoV-2 vaccine should be recorded on the Concomitant Medication eCRF.

If there is any doubt as to whether a medication is permitted during the trial, the study site staff should contact the Medical Monitor.

4.4.1 Concomitant Therapy for UC (Including Rescue Therapy)

Permitted and prohibited concomitant therapies for UC, including rescue therapies, are outlined in Table 3.

Table 3 Permitted and Prohibited Concomitant Therapies for UC

Therapy	Prior to and during Screening [a]	During Part A	During Part B and Safety Follow-Up	Rescue Therapy [b]
Anti-inflammatories				
Topical (rectal) 5-ASA	– May not have received topical (rectal) 5-ASA within 2 weeks prior to randomization	– Initiation of topical (rectal) 5-ASA is not permitted		– Initiation of topical (rectal) 5-ASA is considered rescue therapy
Oral 5-ASA	– May be receiving oral 5-ASA if dose has been stable for at least 4 weeks at the time of randomization (baseline)	– Initiation of oral 5-ASA is not permitted – Baseline level of oral 5-ASA must be maintained during the study		– Initiation of oral 5-ASA or increase in dose of oral 5-ASA compared with baseline is considered rescue therapy
IV corticosteroids and rectal corticosteroids (i.e., enemas or suppositories)	– May not have received rectal corticosteroid within 2 weeks prior to randomization – May not have received IV corticosteroids within 30 days prior to randomization with the exception of a single administration of IV corticosteroids	– Initiation of IV or rectal corticosteroid is not permitted		– Initiation of IV or rectal corticosteroid is considered rescue therapy

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MMF = mycophenolate mofetil; MTX = methotrexate; TNF = tumor necrosis factor.

[a] See inclusion and exclusion criteria in Sections 4.1.1 and Section 4.1.2 for additional details.

[b] See Sections 3.1.2 and Section 3.1.3 for information regarding rescue therapy as it applies to the disposition of patients.

Table 3 Permitted and Prohibited Concomitant Therapies for UC (cont.)

Therapy	Prior to and during Screening [a]	During Part A	During Part B and Safety Follow-Up	Rescue Therapy [b]
Anti-inflammatories (cont.)				
Oral corticosteroids	– May be receiving oral corticosteroid therapy (≤ 20 mg/day prednisone or equivalent) if dose has been stable for at least 2 weeks at the time of randomization (baseline steroid level) [c, d] – > 20 mg/day prednisone or equivalent is exclusionary [c, d]	– Initiation of oral corticosteroids is not permitted – Baseline level of oral corticosteroids must be maintained during the study	– Initiation of oral corticosteroids is not permitted – For patients on oral corticosteroids at baseline, corticosteroid dose will be tapered until discontinuation, starting at Week *8* (see Section 3.1.3) – For patients who cannot tolerate the corticosteroid taper without recurrence of UC symptoms or experience symptoms of corticosteroid withdrawal, the corticosteroid dose can be increased [e]	– Initiation of oral corticosteroids or increase in dose of oral corticosteroids compared with baseline is considered rescue therapy

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MMF = mycophenolate mofetil; MTX = methotrexate; TNF = tumor necrosis factor.

[a] See inclusion and exclusion criteria in Sections 4.1.1 and Section 4.1.2 for additional details.

[b] See Sections 3.1.2 and Section 3.1.3 for information regarding rescue therapy as it applies to the disposition of patients.

[c] The equivalent dose of budesonide to prednisone has not been fully characterized; however, 9 mg/day budesonide has been shown to be as effective as 40 mg/day prednisolone (equivalent to 40 mg/day prednisone) in achieving remission in Crohn's disease (Rutgeerts et al. 1994; Campieri et al. 1997; Edsbäcker et al. 1999; Edsbäcker and Andersson 2004).

[d] There is limited/no data on beclometasone dipropionate equivalency in inflammatory bowel disease. Beclometasone dipropionate should not be used for more than 4 weeks based on the Clipper Summary of Product Characteristics.

[e] If the corticosteroid dose has not been increased above the baseline level, these patients should re-initiate corticosteroid dose tapering per the regimen described in Section 3.1.3. Patients who are unable to tolerate a second taper should discontinue study drug and enroll in OLE Study GA40209, if eligible. Treatment with corticosteroids above the baseline dose will be considered rescue therapy.

Table 3 Permitted and Prohibited Concomitant Therapies for UC (cont.)

Therapy	Prior to and during Screening [a]	During Part A	During Part B and Safety Follow-Up	Rescue Therapy [b]
Immunosuppressants				
AZA, 6-MP, or MTX	– May not have received AZA, 6-MP, or MTX within 2 weeks prior to randomization	– Initiation of AZA, 6-MP, or MTX is not permitted		– Initiation of AZA, 6-MP, or MTX is considered rescue therapy
TNF inhibitors: adalimumab, certolizumab, golimumab, and infliximab	– May not have received a TNF inhibitor within 8 weeks prior to randomization	– Initiation of TNF inhibitors is not permitted		– Initiation of TNF inhibitors is considered rescue therapy
Anti-integrin agents				
Vedolizumab	– May not have received prior treatment with vedolizumab	– Patients in Arm 4 will receive blinded vedolizumab as an investigational medicinal product and active comparator		– Vedolizumab is not permitted as rescue therapy
Natalizumab, etrolizumab, efalizumab, or other anti-integrin agents	– May not have received prior treatment with etrolizumab, natalizumab, efalizumab or other anti-integrin agents	– Initiation of anti-integrin agents (other than vedolizumab for patients in Arm 4) is not permitted		– Anti-integrin agents are not permitted as rescue therapy

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MMF = mycophenolate mofetil; MTX = methotrexate; TNF = tumor necrosis factor.

[a] See inclusion and exclusion criteria in Sections 4.1.1 and Section 4.1.2 for additional details.

[b] See Sections 3.1.2 and Section 3.1.3 for information regarding rescue therapy as it applies to the disposition of patients.

Table 3 Permitted and Prohibited Concomitant Therapies for UC (cont.)

Therapy	Prior to and during Screening [a]	During Part A	During Part B and Safety Follow-Up	Rescue Therapy [b]
Other Therapies				
Oral probiotics	– May be receiving oral probiotics (e.g., Culturelle, *S. boulardii*) if dose has been stable for at least 2 weeks at the time of randomization	– Initiation of oral probiotics is not permitted – Baseline usage of oral probiotics must remain stable during the study		—
Cyclosporine, tacrolimus, sirolimus, and MMF	– May not have received cyclosporine, tacrolimus, sirolimus, or MMF within 4 weeks prior to randomization	– Initiation of cyclosporine, tacrolimus, sirolimus, or MMF is not permitted		– Cyclosporine, tacrolimus, sirolimus, and MMF are not permitted as rescue therapy
Tofacitinib	– *Prohibited within 30 days or 5 half-lives of the drug (whichever is longer) prior to randomization*	– *Initiation of tofacitinib is not permitted*		– *Tofacitinib is not permitted as rescue therapy*
Ustekinumab	– *Prohibited within 90 days or 5 half-lives of the drug (whichever is longer) prior to randomization*	– *Initiation of ustekinumab is not permitted*		– *Ustekinumab is not permitted as rescue therapy*

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; IV = intravenous; MMF = mycophenolate mofetil; MTX = methotrexate; TNF = tumor necrosis factor.

[a] See inclusion and exclusion criteria in Sections 4.1.1 and Section 4.1.2 for additional details.

[b] See Sections 3.1.2 and Section 3.1.3 for information regarding rescue therapy as it applies to the disposition of patients.

4.4.2 Other Concomitant Therapy

4.4.2.1 Other Permitted Concomitant Therapy

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients will be permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Patients may continue on stable regimens of drugs they are receiving as treatment for coexistent stable diseases (e.g., anti-hypertensives, cholesterol-lowering drugs, or bronchodilators).

Over-the-counter preparations deemed acceptable by the Sponsor and the investigator at the beginning of the study will be allowed during the study. Initiation of over-the-counter medications during the study will need to be approved by the investigator and the Sponsor.

4.4.2.2 Other Prohibited Concomitant Therapy

Use of the following therapies is prohibited as specified below:

- Use of rituximab is prohibited prior to and during the study
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab), with the exception of AZA and 6-MP (see Section 4.4.1), is prohibited within 12 months prior to randomization or during the study
- Chronic use of NSAIDs is prohibited prior to and during the study

  Occasional use of NSAIDs and acetaminophen (e.g., headache, arthritis, myalgias, or menstrual cramps) and aspirin up to 325 mg/day is permitted.
- Use of anticoagulants (including, but not limited to, warfarin, heparin, enoxaparin, dabigatran, apixaban, rivaroxaban) is prohibited prior to and during the study

  Use of antiplatelet agents, such as aspirin up to 325 mg/day or clopidogrel, is permitted.
- Apheresis (e.g., Adacolumn® apheresis) is prohibited within 2 weeks prior to randomization and during the study
- Use of a non-biologic investigational drug is prohibited within 30 days or 5 half-lives of the drug (whichever is longer) prior to randomization and during the study

- Use of a biologic investigational drug is prohibited within 90 days or 5 half-lives of the drug (whichever is longer) prior to randomization and during the study

4.4.3 Additional Restrictions

At study visits where fasting lipids are measured, no food or fluids other than water will be allowed for approximately 8 hours prior to the visit and until after study laboratory samples are obtained. On study-drug dosing days, no food will be allowed from at least 2 hours before dosing until 30 minutes after the last infusion, when a light meal will be allowed.

To avoid potential contamination of blood supply with the investigational product, patients will be restricted from donating blood for 6 months after receiving the last dose of efmarodocokin alfa or vedolizumab.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Re-Testing for Laboratory Inclusion and Exclusion Criteria

Two re-tests are permitted in order for potential participants to meet the laboratory inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2). If a patient does not meet laboratory criteria for a third time, he or she will be considered a screen failure.

Laboratory testing that is repeated because of administrative or technical issues (e.g., breakage of a sample vial during transit to the central laboratory or degradation of a sample during transportation) is not considered to be re-screening.

4.5.3 Re-Screening

If a patient does not meet all eligibility criteria within the screening window, one re-screening is permitted. Each patient must be re-consented before re-screening occurs.

The screening endoscopy and colonic biopsies do not need to be repeated during re-screening provided that all of the following criteria are met:

- All endoscopy-related inclusion criteria have been met, with corresponding e-diary data for MCS calculation (see Section 4.5.7.2).
- The initial endoscopy has been performed within 28 days prior to the day of randomization for second screening.
- Colon biopsies as specified by the protocol have been obtained.

If a negative TB screening test result has been documented within 3 months prior to screening or re-screening, no repeat test is required.

Patients who are classified as being screen failures due to the presence of *C. difficile* or CMV infection may be re-screened *with randomization occurring (if eligible) at least* 60 days after successful treatment. For patients who screen fail due to CMV infection, laboratory analysis of CMV from colon biopsy samples is required during re-screening evaluation to rule out CMV infection.

4.5.4 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 2–4 weeks prior to randomization will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

A UC-specific history including complications and surgeries related to UC, and a detailed history of UC medications used by the patient within 1 year prior to the screening visit will be recorded. In addition, a detailed history of biologics used by the patient within 5 years prior to the screening visit (e.g., name and duration of previous biologic therapies and reason for discontinuation) will be recorded.

The extent and duration of the patient's disease, as recorded in the patient's medical record, will be captured in the eCRF. The extent of disease should be identified as one of the following:

- Left-sided colitis (inflammation up to the splenic flexure)
- Extensive colitis (inflammation beyond the splenic flexure but not involving the entire colon)
- Pancolitis (inflammation of the entire colon)

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.5 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations, including an abdominal examination, should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.6 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature while the patient is in a seated position after at least 10 minutes of rest.

4.5.7 Clinical Outcome Assessments

Clinical outcome will be assessed through the MCS (see Section 4.5.7.1), which incorporates stool frequency and rectal bleeding as reported by the patient (see Section 4.5.7.2), the PGA as reported by the clinician (see Section 4.5.7.3), and endoscopic evaluations by a central reader (see Section 4.5.7.4). Clinical outcome will also be assessed through the Inflammatory Bowel Disease Questionnaire (IBDQ) (see Section 4.5.7.2), and the Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) (see Section 4.5.7.2), as well as the Ulcerative Colitis Endoscopic Index of Severity (UCEIS), the Robarts Histopathological Index, the Nancy Histological Index, and the Geboes Score (see Section 4.5.7.5).

4.5.7.1 Mayo Clinic Score, Modified Mayo Clinic Score, and Partial Mayo Clinic Score

The MCS is a composite of four assessments, each having a scoring range of 0–3: stool frequency, rectal bleeding, centrally read endoscopy, and PGA. The MCS has a range of 0–12, with higher scores indicating more severe disease (see Appendix 2).

The mMCS is a composite of three assessments from the MCS, each having a scoring range of 0–3: stool frequency, rectal bleeding, and centrally read endoscopy. The mMCS has a range of 0–9, with higher scores indicating more severe disease (see Appendix 3).

The pMCS is a composite of three assessments from the MCS, each having a scoring range of 0–3: stool frequency, rectal bleeding, and PGA. The pMCS has a range of 0–9, with higher scores indicating more severe disease (see Appendix 4).

mMCS with centrally read endoscopy assessment during screening (i.e., a score of ≥ 2, if Robarts' assessment confirms that a patient is eligible) will be used as efficacy baseline and for inclusion. mMCS using locally read endoscopy assessment will be utilized to assess clinical response at Week 8 and for determination of eligibility in the OLE study or continuation into Part B.

Patients are to report their stool frequency and rectal bleeding on a daily basis, as described in Section 4.5.7.2.

4.5.7.2 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be collected through use of an electronic device (e-diary). The e-diary and/or instructions for completing the questionnaires electronically will be provided by site staff. Data captured between clinic visits should be reviewed with the patient at each clinic visit. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

In cases of device malfunction or failure, data may be captured via paper questionnaires.

The PRO questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and compliance with health authority requirements, questionnaires will be self-administered before the patient receives any information on disease status, before non-PRO assessments are performed, and before administration of study treatment, unless otherwise specified. Study site staff will ensure that questionnaires are provided to the patients for completion per the schedule of assessments (see Appendix 1) and will confirm completion or document any reasons for non-completion before the visit concludes.

Stool Frequency and Rectal Bleeding

Stool frequency and rectal bleeding are components of the MCS, mMCS, and pMCS (see Section 4.5.7.1).

At screening, the investigator will document the patient's normal number of stools, defined as the number of stools passed when a patient is in remission (i.e., not in flare).

Patients are to record stool frequency and rectal bleeding in the e-diary daily throughout the study, beginning with the first screening visit (see Appendix 6). If available, stool frequency and rectal bleeding scores from the three most recent e-diary entries prior to bowel preparation for screening endoscopy and the screening endoscopy will be used as efficacy baseline and for inclusion. The three most recent e-diary entries prior to Day 1 randomization will also be used for inclusion. The screening endoscopy should not be performed without adequate symptoms. Adequate symptoms are defined as meeting both of the following criteria:

- Stool frequency $= 1$ in at least 2 out of 3 days or stool frequency ≥ 2 in at least 1 out of 3 days.
- Rectal bleeding $= 1$ in at least 2 out of 3 days or rectal bleeding ≥ 2 in at least 1 out of 3 days.

In rare cases where there are < 3 days of e-diary data available prior to bowel preparation for screening endoscopy, the minimum number of e-diary entries from day 2 until day 4 post endoscopy may be used in addition to pre-endoscopy entries to obtain 3 total days of entries for baseline and inclusion.

- If 3 days of e-diary data are available prior to screening endoscopy, that data will be used. The patient should have adequate symptoms before endoscopy is performed or it will be considered a protocol deviation.
- If 2 days of e-diary data are available prior to screening endoscopy, that data and the first available e-diary entry 2 days after the endoscopy will be used. The patient should have adequate symptoms (i.e., stool frequency and rectal bleeding scores of 1 on both days) before endoscopy is performed or it will be considered a protocol deviation.
- If 1 day of e-diary data is available prior to screening endoscopy, that data and the first two available e-diary entries 2 days after the endoscopy will be used. The patient should have adequate symptoms (i.e., stool frequency and rectal bleeding scores of ≥ 2) before endoscopy is performed or it will be considered a protocol deviation.
- If 0 days of e-diary data are available prior to screening endoscopy, data from the first three available e-diary entries 2 days after the endoscopy will be used.

Because the endoscopy and associated bowel preparation can interfere with the assessment of PROs, e-diary entries on days of bowel preparation, endoscopy, and the

day after endoscopy will not be used to calculate any stool frequency or rectal bleeding scores.

Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms

Patients are to complete the UC-PRO/SS on the 9 consecutive days preceding each clinic visit in which the UC-PRO/SS is assessed.

The UC-PRO/SS will be used to assess patient-reported UC signs and symptoms. The 9-item questionnaire contains two domains: bowel movement signs and symptoms and abdominal symptoms. The UC-PRO/SS assesses the presence of UC symptoms and in some cases the severity or frequency of the symptoms. The UC-PRO/SS measure has a recall specification of 24 hours. A copy of the UC–PRO/SS measure is provided in Appendix 7.

Inflammatory Bowel Disease Questionnaire

The IBDQ should be administered at the investigational site prior to the completion of other non–PRO assessments and before the patient receives any disease status information or study drug.

The IBDQ will be used to assess patients' health-related quality of life (QOL) (Guyatt et al. 1989; Irvine 1999). The 32-item questionnaire contains four domains: bowel symptoms (10 items), systemic symptoms (5 items), emotional function (12 items), and social function (5 items). The items are scored on a 7-point Likert scale with a higher score indicating better health-related QOL. The IBDQ has a recall specification of 2 weeks. A copy of the IBDQ is provided in Appendix 8.

4.5.7.3 Physician's Global Assessment

PGA data will be collected through use of an electronic device or paper form. The PGA is a component of the MCS and pMCS (see Section 4.5.7.1). The PGA should reflect the clinician's assessment of the patient's current overall status, taking into account stool frequency and rectal bleeding scores, clinician endoscopy findings, patient-reported symptoms, clinician observations, physical examination findings, and other pertinent findings. The clinician who completes the PGA should not be the same clinician who assesses adverse events.

4.5.7.4 Colonoscopy or Flexible Sigmoidoscopy with Colonic Biopsies

All patients will undergo a flexible sigmoidoscopy with collection of colonic biopsies at baseline/screening, at Weeks 8 and 30, and at the disease evaluation/early termination visit. Patients without documentation of colon cancer surveillance within 1 year prior to randomization will have a screening colonoscopy in lieu of a flexible sigmoidoscopy. Every effort should be made to schedule on-treatment endoscopies on the same day as the protocol-specified study visit. Stool frequency and rectal bleeding scores from the three most recent e-diary entries and the screening endoscopy will be used as efficacy

baseline and for inclusion. The screening endoscopy should not be performed without adequate symptoms (see Section 4.5.7.2).

Bowel preparation prior to the colonoscopy and flexible sigmoidoscopy procedures should be done per local practice. Medications used for bowel preparation should be reported on the Concomitant Medications eCRF. Scheduled stool samples should be taken prior to bowel preparation.

For each patient, a video recording will be performed during the colonoscopy (if colon cancer surveillance performed during screening) or flexible sigmoidoscopy procedure through use of a medical DVD recorder in the high-quality mode per the endoscopy manual. Video recordings should be taken of the entire endoscopic procedure, starting from insertion into the bowel. Biopsies should be performed upon withdrawal of the endoscope from the bowel. *The endoscopist should ensure that the video recording of the procedure will allow for adequate assessment of disease activity, taking into consideration the possibility of minor bleeding associated with biopsies.* Technical instructions for video recording and biopsy collection will be provided in the laboratory manual.

The clinician who performs the endoscopy will take into account endoscopy findings when completing the PGA (see Section 4.5.7.3).

All video recordings will be submitted to a central reading facility to be centrally reviewed for mucosal lesions and endoscopic severity by an independent gastroenterologist experienced in UC who is blinded to the patient's clinical activity, study visit, and treatment allocation. Endoscopic videos will be assessed to determine if patients meet the endoscopic inclusion criterion as well as to objectively document subsequent disease activity. For efficacy assessment of primary, secondary, and exploratory endpoints, Mayo endoscopic subscore and UCEIS will be calculated on the basis of centrally read patient videos. Locally read endoscopic videos will be used to inform investigator-determined clinical or treatment decisions.

4.5.7.5 Other Clinical Indices

The UCEIS is a scoring system used to predict the overall assessment of endoscopic severity based on three descriptors: vascular pattern, bleeding, and erosions and ulcers. The descriptors are scored on a Likert scale with a higher score indicating more endoscopic severity (Travis et al. 2012).

The Robarts Histopathological Index is used to evaluate histological disease activity in UC based on four components: chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in epithelium, and erosion or ulceration. The components are scored on a 0–3 Likert scale with a higher score indicating more severe disease activity (Mosli et al. 2017).

The Nancy Histological Index is used to evaluate histological disease activity in UC based on three histological components: ulceration, acute inflammatory infiltrate, and chronic inflammatory infiltrate. The components are scored on a 0–5 Likert scale with a higher score indicating more severe disease activity (Marchal-Bressenot et al. 2017).

The Geboes Score is used to evaluate histological disease severity in UC based on a six-grade classification system: 0-structural change only; 1-chronic inflammation; 2-lamina propria neutrophils; 3-neutrophils in epithelium; 4-crypt destruction; 5-erosions or ulcers. A higher grade indicates more severe disease activity (Geboes et al. 2000).

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis. Samples may be analyzed at a central laboratory if local analysis is not available.

- Urinalysis: specific gravity, pH, blood, quantitative protein, ketones, glucose, bilirubin, nitrite, leukocyte esterase, color, and appearance

  If urinalysis is abnormal, the same urine sample will be sent to the laboratory for microscopic analysis (sediment, WBCs, RBCs, casts, crystals, epithelial cells, and bacteria), culture, and sensitivity.

- Urine pregnancy test

  All women of childbearing potential will have a urine pregnancy test performed monthly during the study. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Stool sample analysis: culture and sensitivity, ova and parasites, and *C. difficile* toxin
- Analysis of colonic tissue sample obtained by biopsy performed during screening endoscopic procedure (flexible sigmoidoscopy or colonoscopy):
  - CMV, as determined by histologic examination or immunohistochemistry per local standards
  - Patients without a prior histopathology report: histopathologic examination
- Patients with no documentation of colonic cancer surveillance within 1 year prior to randomization: analysis of multiple random mucosal tissue samples obtained during screening colonoscopy to evaluate for dysplasia

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Patients with a history of drug abuse: urine drug screening
- Serum pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening.

- HIV serology
- HBV serology: HBsAg, total HBcAb

  If a patient has a negative HBsAg test and a positive HBcAb test, an HBV DNA test will be performed.
- HCV serology: HCV antibody test

  If a patient has a positive HCV antibody test, an HCV RNA test will be performed.
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH
- Lipase and CRP

  Site and Sponsor personnel, with the exception of the IMC, will be blinded to CRP test results.
- Coagulation: INR, aPTT, PT, fibrinogen

  Site and Sponsor personnel, with the exception of the IMC, will be blinded to fibrinogen test results.
- Lipids (fasting): cholesterol, LDL cholesterol, HDL cholesterol, triglycerides

  No food or fluids other than water will be allowed for approximately 8 hours prior to the visit and until after sample collection.
- TB test: QFT or, if QFT is unavailable, PPD skin test

  Test may be performed locally.
- Patients with known diabetes: HbA_{1c}

The following samples will be sent to the Sponsor or a designee for analysis:

- Serum samples for PK analysis

  Serum ADA may be measured using PK samples if ADA samples have not been collected at the same timepoint.
- Serum samples for immunogenicity (ADA) analysis

  Serum drug concentrations may be measured in ADA samples if PK samples have not been collected at the same timepoint.

  Baseline ADA samples will be analyzed for all patients.

  Post-baseline ADA samples will be analyzed for all patients receiving efmarodocokin alfa.

- Serum samples for exploratory research on biomarkers that may include, but will not be limited to, IL-22, IL-22BP, REG3A, and sMAdCAM

  Site and Sponsor personnel, with the exception of the IMC, will be blinded to REG3A test results.
- Plasma samples for exploratory research on biomarkers that may include, but will not be limited to, propionate, 4β-hydroxycholesterol, and cholesterol
- Stool samples for exploratory research on biomarkers that may include, but will not be limited to, bacterial DNA and calprotectin
- Colonic tissue samples obtained by biopsy performed during screening and subsequent endoscopic procedures (flexible sigmoidoscopy or colonoscopy) for exploratory research on tissue histology and on biomarkers that may involve extraction of DNA or RNA and bacterial DNA and may include, but will not be limited to, analysis of IL-22RA2, IL-22RA1, and DMBT1

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Serum, plasma, stool, and colonic tissue samples collected for biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements)

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.9 Chest X-Ray

A chest X-ray will be performed during screening or within 3 months prior to screening to rule out TB for patients who have a positive or indeterminate QFT and patients with no

history of BCG vaccination who have a positive PPD skin test (see Section 4.1.2 for details on requirements for TB testing).

4.5.10 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using an electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal, if possible. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following *will* be *transmitted to a central ECG vendor*: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. *Clinically significant* waveform changes or other ECG abnormalities must be documented *as an adverse event* on the *Adverse Event* eCRF. *An ECG finding must be reported as an adverse event if it meets any of the following criteria:*

- *Is accompanied by clinical symptoms*
- *Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*
- *Results in a medical intervention or a change in concomitant therapy*
- *Is clinically significant in the investigator's judgment*

It is the investigator's responsibility to review all ECG findings. Medical and scientific judgment should be exercised in deciding whether an isolated ECG finding should be classified as an adverse event. If a clinically significant finding is a sign of a disease or syndrome, only the diagnosis should be recorded on the Adverse Event eCRF.

If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two

successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.11 Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable whole genome sequencing (WGS) to identify germline mutations and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the WGS analyses, data derived from these analyses will generally not be provided to study investigators or patients unless

required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

4.5.12 Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to efmarodocokin alfa or diseases:

- Leftover serum, plasma, stool, and colonic biopsy tissue samples and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. *After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient.* However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. *If a patient wishes to withdraw consent to the testing of his or her RBR sample after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:*

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study GA39925 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GA39925.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study drug if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study drug
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Drug-related anaphylaxis or other severe (Grade 3 or 4) drug-related hypersensitivity reaction
- Unresectable colonic mucosal dysplasia
- High-grade colonic mucosal dysplasia or colon cancer
- Requirement for rescue therapy outside defined limits of the protocol (see Section 4.4.1)
- Malignancy or cervical Pap test with CIN of Grade $>$1,AIS, or HSILs
- De novo or reactivated serious viral infection, such as hepatitis B virus, hepatitis C virus, HIV, disseminated varicella zoster virus, or disseminated herpes simplex virus, should discontinue study medication. For other serious or severe infections, see Section 5.1.3.3 and Table 4
- Severe liver injury as defined by Hy's Law (see Section 5.3.5.7)
- *Grade 4 thromboembolism or deep vein thrombosis*

The primary reason for study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced. Patients who discontinue study drug prematurely for the reasons listed above will be asked to return to the clinic for an early termination visit within 1 week of the event and will undergo assessments at 4 and 8 weeks after their last dose of study drug (safety follow-up period; see Section 3.1.4 and Appendix 1 for additional details).

Patients who receive rescue therapy or do not meet the criteria for clinical response during Part A will discontinue study drug but may be eligible to receive treatment in OLE Study GA40209 (see Section 3.1.2).

Patients who receive rescue therapy, experience disease flare (see Section 3.1.1), or cannot tolerate corticosteroid tapering during Part B will discontinue study drug but may be eligible to receive treatment in OLE Study GA40209 (see Section 3.1.3).

Patients who experience disease flare or receive rescue therapy and discontinue study drug should return to the clinic for a disease evaluation visit no later than 1 week after initiation of rescue therapy (see Appendix 1 for additional details).

Patients who discontinue study drug without entering OLE Study GA40209 will undergo assessments at 4 and 8 weeks after their last dose of study drug (safety follow-up period). Patients who are unwilling to complete the safety follow-up period should return to the clinic for an early termination visit as soon as possible and no later than 30 days after the final dose (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, specifically defined as missing scheduled visits or non-adherence with concomitant medications for UC

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study *or stop enrollment* at any time. Reasons for terminating the study *or stopping enrollment* may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH E6 guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Efmarodocokin alfa is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with efmarodocokin alfa in completed and ongoing studies. The anticipated important safety risks for efmarodocokin alfa are outlined below. Please refer to the Efmarodocokin Alfa Investigator's Brochure for a complete summary of safety information.

Vedolizumab is an approved biologic therapy for patients with moderate to severe UC. The important safety risks for vedolizumab are available in the vedolizumab prescribing information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for clinically significant adverse events. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Efmarodocokin Alfa

The general risks associated with biologic agents and the potential or hypothetical risks of efmarodocokin alfa are based on available clinical and nonclinical data. Risks are summarized below and are described in detail in the Efmarodocokin Alfa Investigator's Brochure.

5.1.1.1 Dermatologic Reactions

Results from Study GA29468, a Phase Ia single-dose study in HVs, showed that IV efmarodocokin alfa induced reversible skin changes, including dry lips and skin, patchy erythema, scaling skin (primarily on the face and upper body), and skin discomfort. At doses of up to 90 μg/kg, the MTD for HVs in Study GA29468, most dermatologic manifestations were mild (Grade 1) and sometimes moderate (Grade 2). These cutaneous adverse events were manageable with topical emollients that provided

symptomatic relief when needed and were fully reversible (i.e., resolving within approximately 2 weeks of onset).

In the Phase Ib multiple-dose study (GA29469) in HVs and patients with UC, skin changes similar in nature and duration to those occurring in Study GA29468 have been observed at tolerated dose levels. Dermatologic manifestations at tolerated dose levels (e.g., dry, erythematous, scaling skin and skin discomfort) have been reversible and managed with topical emollients. In two HVs, a dose level of 90 μg/kg Q2W induced protocol-defined dermatologic dose-limiting adverse events that occurred after the second dose of blinded efmarodocokin alfa or placebo. The dermatologic manifestations included severe (Grade 3) skin discomfort and severe (Grade 3) dry skin; topical emollients and topical corticosteroids provided minimal relief. The adverse events were fully reversible. For additional details, refer to the Efmarodocokin Alfa Investigator's Brochure.

Patients with a history of psoriasis and other inflammatory skin disorders requiring oral corticosteroids, immunosuppressants, or biologic therapy within the past year will be excluded from the study.

Guidelines for management of patients who develop dermatologic reactions are provided in Section 5.1.3.3.

5.1.1.2 Infusion-Related Reactions

With the introduction of a foreign biological molecule such as efmarodocokin alfa, there is a potential risk of infusion-related reactions. Infusion-related reactions may include both acute allergic/hypersensitivity (e.g., anaphylactic) reactions and acute pseudoallergic/hypersensitivity-like (e.g., anaphylactoid) reactions. Anaphylactic and anaphylactoid reactions are the more severe forms of allergic and pseudoallergic reactions, respectively. However, in the Phase Ia single-dose study and the Phase Ib multiple-dose study, no anaphylactic or anaphylactoid reactions were observed.

Patients with a history of moderate or severe allergic, anaphylactic, or anaphylactoid reactions to chimeric, human, or humanized antibodies, fusion proteins, or murine proteins or hypersensitivity to efmarodocokin alfa or any of the excipients (sucrose, methionine, sodium phosphate, or polysorbate 20) are not eligible for this study. Anaphylaxis and hypersensitivity reactions will be closely monitored.

Guidelines for management of patients who develop infusion-related reactions are provided in Section 5.1.3.3.

5.1.1.3 Epithelial Tumor Promotion

IL-22 has been reported to promote epithelial tumor progression, including squamous cell and basal cell carcinoma (Nardinocchi et. al. 2015) and colorectal cancer (Kryczek et. al. 2014; Kirchberger et al. 2013). There has been no evidence of epithelial

tumor promotion in the Phase Ia study, the Phase Ib study, or nonclinical studies to date. Nevertheless, given the a priori elevated risk of malignancy in this patient population, and the potential for epithelial tumor promotion with IL-22 in tumor cells that may express the IL22 receptor (refer to the Efmarodocokin Alfa Investigator's Brochure), the trial includes selection criteria and additional safety monitoring to minimize any hypothetical risk.

Patients with a history of cancer within the past 5 years are to be excluded from the study. In addition, patients with a history of non-melanoma skin cancer or GI and/or colon cancer, or a known family history of GI and/or colon cancer (defined as one first-degree relative or two second-degree relatives) will be excluded. Patients must have documentation of colon cancer surveillance within 1 year prior to randomization. Patients who have evidence of unresectable colonic mucosal dysplasia or high-grade colonic mucosal dysplasia will be excluded from the study. Furthermore, patients are excluded who have a history of CIN of Grade >1, cervical smear indicating the presence of AIS, or HSIL.

Guidelines for management of patients who develop epithelial tumor promotion are provided in Section 5.1.3.3.

5.1.1.4 Neutralization of Endogenous IL-22 by ADAs

Though not seen in nonclinical and human studies to date, there is a possibility that efmarodocokin alfa may induce ADAs that neutralize endogenous IL-22 and thus be associated with an increased risk for opportunistic infections (including bacterial and fungal infections). ADAs may also reduce the therapeutic effect of efmarodocokin alfa. In addition, because IL-22 is involved in stimulating epithelial barrier repair, ADAs that neutralize endogenous IL-22 could impair epithelial barrier repair in the GI epithelium. These potential effects could be long-lasting if neutralizing ADAs are persistent.

Any patient who is found to test positive for ADAs to efmarodocokin alfa, including ADAs that may neutralize endogenous IL22, should be followed, when possible, every 2 months for up to 6 months after the last dose of study drug, or until ADA titers are below the assay-cut point level, whichever occurs first.

Guidelines for management of patients who develop infections are provided in Section 5.1.3.3.

5.1.1.5 *Worsening Of Clotting/Coagulation Dysfunction In High Risk Populations Due To Increased Fibrinogen*

Fibrinogen increases along with CRP are consistent with acute phase protein response, and are considered on-target effects of IL-22 signaling. A meta-analysis of clinical studies reported associations between plasma fibrinogen levels and the risks of coronary heart disease, stroke, other vascular mortality, and nonvascular mortality. However, whether the high fibrinogen levels are causal or are an effect of inflammation is not

established (FSC 2005). In mice, infusion of fibrinogen was shown to induce a state of hyperfibrinogenemia, which was then associated with an increased risk of coagulation dysfunction and thrombosis (Machlus et al. 2011) but the translatability to humans remains uncertain (Ariens 2011; Klovaite et al. 2011).

Dose dependent increases in fibrinogen have been observed following efmarodocokin alfa treatment in the nonclinical studies with cynomolgus monkeys and in the Phase I studies (GA29468 and GA29469) which included HVs, patients with UC, and patients with CD. These increases in fibrinogen were considered on-target effects of IL-22 signaling, with peak mean cohort values within 2-fold of baseline. The fibrinogen increases were not accompanied by changes in other clotting parameters measured (prothrombin time, activated partial thromboplastin time, and internal normalized ratio), or by clinical signs or adverse events of clotting/coagulation abnormalities. As of the data cutoff of 05 February 2021 in the ongoing blinded Phase II Study GA39925, there has been 1 serious adverse event of deep venous thrombosis in 1 patient (out of 161 patients enrolled) that was considered unrelated to the study drug/placebo by the investigator. In a preliminary data analysis from the Phase II Study GA42969 in patients with severe COVID-19 pneumonia, the number of thrombotic or embolic adverse events were comparable between efmarodocokin alfa, comparator, and placebo arms.

Relative to the healthy population, a higher incidence of coagulation dysfunction and thromboembolic phenomena is reported in patients with IBD (Danese et al. 2007; Grainge et al. 2010). It is unclear but possible that a fibrinogen increase observed with efmarodocokin alfa treatment may contribute to worsening the risk of clotting/coagulation dysfunction in high-risk populations. To minimize the risk of clotting/coagulation dysfunction, investigators are advised to closely monitor patients for signs and symptoms suggestive of thromboembolism or deep vein thrombosis. If any Grade 2 or 3 thromboembolism or deep vein thrombosis occur, efmarodocokin alfa should be withheld until the event resolves to Grade 1 or lower. Efmarodocokin alfa should be permanently discontinued in any patient who develops a Grade 4 thromboembolism or deep vein thrombosis. Grade 2 or higher thromboembolism or deep vein thrombosis should be reported to the Sponsor in an expedited manner as an adverse event of special interest (see Section 5.2.3). Based on current data and literature, it is not believed that excluding patients with other risk factors such as use of oral contraceptives is justified. The association between fibrinogen and coagulation/clotting dysfunction is correlative, and it is important to assess if these risk factors, which are common in the general population, pose an enhanced risk in a controlled clinical trial setting.

Guidelines for management of patients who develop Grade ≥2 thromboembolism or deep vein thrombosis are provided in Section 5.1.3.3.

5.1.2 Risks Associated with Vedolizumab

Investigators should be aware of the risks associated with vedolizumab and guidelines for managing those risks (see vedolizumab prescribing information).

5.1.3 Management of Patients Who Experience Specific Adverse Events

Guidelines for the monitoring and management of patients who experience specific adverse events are provided in Table 4.

5.1.3.1 Dose Modifications

The dose of efmarodocokin alfa or vedolizumab should not be modified when managing individual patients who experience adverse events.

5.1.3.2 Treatment Interruption

Study treatment may be temporarily suspended in patients who experience a treatment-emergent adverse event considered to be related to study drug. If the event resolves to Grade 2 or better, treatment will resume at the next scheduled dose. If more than one scheduled dose will be missed because of an on-going adverse event, the patient should be permanently discontinued from treatment, unless resumption of treatment is *determined* following investigator discussion with the Medical Monitor. Study treatment may be suspended for reasons other than a treatment-emergent adverse event (e.g., surgical procedures) *after discussion* with *the* Medical Monitor. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.3.3 Management Guidelines

Dermatologic Reactions

Investigators should remain vigilant for dermatologic signs or symptoms at scheduled study visits. Symptomatic relief of dermatologic manifestations can include topical emollients for mild to moderate skin effects and topical corticosteroids and/or oral antihistamines for more severe skin effects. Inability to achieve symptomatic relief may require local dermatologic assessment for further evaluation, including recommended biopsy and management.

Guidelines for the management of patients who develop dermatologic reactions are provided in Table 4.

Infusion-Related Reactions

All infusions will be administered in the clinic to enable monitoring for possible infusion-related reactions. Patients must be monitored for approximately 30 minutes after each study drug infusion. Medicinal products for the treatment of severe reactions (e.g., epinephrine, antihistamines, and glucocorticoids) must be available for immediate use in the clinic. Resuscitation equipment should also be available.

Infusion-related reactions may include both acute allergic/hypersensitivity (e.g., anaphylactic) reactions and acute pseudoallergic/hypersensitivity-like (e.g., anaphylactoid) reactions. These may have similar clinical manifestations, but they have different mechanisms (e.g., only allergic reactions are IgE mediated) and risks of re-challenge. Differentiating allergic reactions from pseudoallergic reactions is important because it may impact the understanding of the risk profile of the drug. In instances where the reaction occurs with the first infusion of the study drug without any suspicion of prior sensitization, it is less likely to be an allergic reaction. When a new reaction is seen with the second or subsequent infusions, or if there is an atypical presentation (e.g., rapid onset within 15 minutes or increase in severity when compared with previous reactions), there is a higher likelihood that the reaction is allergic. Investigators should report infusion-related reactions using the most appropriate term, based on their medical judgment. The investigator should also discuss with the Medical Monitor the possibility of obtaining additional supportive data, if available, to inform the diagnosis of allergic versus pseudoallergic reaction (e.g., serum histamine, serial tryptase measurements).

Patients should be instructed to recognize the symptoms of a severe allergic (e.g., anaphylactic) or pseudoallergic (e.g., anaphylactoid) reaction and to contact a healthcare provider or seek immediate care in case of any such symptoms. Patients are to be provided with alert cards to remind them and a caregiver or partner of these instructions.

Guidelines for the management of patients who develop infusion-related reactions are provided in Table 4.

Epithelial Tumors

Investigators should remain vigilant for signs or symptoms of cancer in scheduled study visits. Any signs or symptoms that could be suggestive of malignancy should be promptly and aggressively evaluated and reported to the Sponsor. If a patient develops malignancy or high-grade colonic dysplasia during the study, study drug must be discontinued permanently. In cases of newly diagnosed malignancy or epithelial high grade dysplasia, unstained slides and/or representative tissue blocks may be requested by the Sponsor for further evaluation and characterization.

Guidelines for the management of patients who develop epithelial tumors are provided in Table 4.

Serious Infections

To assess for the potential development of an immune response, including neutralizing ADAs against endogenous IL-22, antibody samples will be obtained at baseline, at regular intervals during treatment, and during the safety follow-up period (see Appendix 1) and stored appropriately for further evaluation as needed.

Guidelines for the management of patients who develop infections are provided

in Table 4.

Hepatic Events

If treatment-emergent ALT or AST elevations are observed, ALT, AST, alkaline phosphatase, and total bilirubin tests (i.e. liver function tests [LFT]) should be repeated within 48–72 hours to confirm the abnormality and to determine whether transaminases are increasing or decreasing.

For re-testing done locally or at a central laboratory facility, normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the eCRF.

If treatment-emergent ALT or AST elevations are confirmed, other laboratory tests should be performed to rule out acute viral hepatitis (i.e., hepatitis A, B, C, D, or E), autoimmune hepatitis (i.e., antinuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, or anti–LKM-1 antibody), or functional hepatic impairment (i.e., INR or fractionated bilirubin). Further LFT monitoring to ensure patient safety should be performed on the basis of clinical judgement and local practice. Imaging tests and hepatology consultation should be considered. In addition, a more detailed history of the event should be obtained, including symptoms, prior or current diseases, concomitant drug use (including nonprescription medications and herbal and dietary supplements), alcohol use, recreational drug use, and special diets.

Guidelines for the management of patients who develop treatment-emergent ALT or AST elevations are provided in Table 4. For patients with suspected or confirmed severe liver injury as defined by Hy's Law, refer to Section 5.3.5.7.

Thromboembolism or Deep Vein Thrombosis

Investigators should remain vigilant for signs and symptoms suggestive of thromboembolism or deep vein thrombosis in scheduled study visits. Any signs or symptoms that could be suggestive of thromboembolism or deep vein thrombosis should be promptly and aggressively evaluated and reported in an expedited manner to the Sponsor (see Section 5.2.3). Guidelines for the management of patients who develop Grade ≥2 thromboembolism or deep vein thrombosis are provided in Table 4.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Dermatologic adverse event	
Grade 1 or 2	• Continue study drug. • Treat with topical emollients.
Grade 3	• Withhold study drug. • Treat with topical emollients and with topical corticosteroids and/or oral antihistamines. • If no symptomatic relief, refer patient to dermatologist for further assessment and treatment. • If treatment with oral immunosuppressants is required, discontinue study drug. • If event resolves to Grade 2 or better with topical treatment, resume study drug at the next scheduled dose. If more than one scheduled dose will be missed because of an on-going adverse event, permanently discontinue study drug.
Grade 4	• Permanently discontinue study drug. • Refer patient to dermatologist for assessment and treatment.
Infusion-related reactions	
Grade 1 or 2	• Reduce infusion rate to ≤ 50% of original infusion rate. • Interrupt infusion if symptoms persist. • Provide supportive treatment if indicated. • If infusion was interrupted, resume infusion at 50% of original infusion rate upon symptom resolution. • If infusion reaction reoccurs, *discuss with* Medical Monitor before premedicating with acetaminophen or diphenhydramine at subsequent infusions.
Grade 3 and 4	• Stop infusion immediately and administer supportive treatment as per local or institutional standard operating procedures (see Appendix 9 for guidance on anaphylaxis). • Permanently discontinue study drug. • Discuss with the Medical Monitor the possibility of obtaining additional supportive data, if available, to inform the diagnosis of allergic versus pseudoallergic reaction (e.g., serum histamine, serial tryptase measurements).

ADA = anti-drug antibody; AESI = adverse event of special interest; IRR = infusion-related reaction; LFT = liver function test; PK = pharmacokinetic; ULN = upper limit of normal.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Infection	
Grade 1 or 2	• Continue study drug.
Grade 3	• Withhold study drug. • Collect PK and ADA sample if not collected at study visit, and treat according to local standards. • If the infection is clearly not study-drug related (i.e., there is a clear alternative explanation for the infection), the infection and symptoms are fully resolved at least 1 week prior to the next scheduled dose, and any treatment for the infection has been completed at least 1 week prior to the next scheduled dose, consult the Medical Monitor to determine if study drug can be resumed. If these conditions are not met or the Medical Monitor indicates that study drug should not be resumed, permanently discontinue study drug.
Grade 4	• Permanently discontinue study drug. • Collect PK and ADA sample if not collected at study visit, and treat according to local standards.
Suspected or confirmed COVID-19 infection	
Grades 1–3	• Withhold study drug • If the infection and symptoms are fully resolved at least 1 week prior to the next scheduled dose, and any treatment for the infection has been completed at least 1 week prior to the next scheduled dose, consult the Medical Monitor to determine if study drug can be resumed. If these conditions are not met or the Medical Monitor indicates that study drug should not be resumed, permanently discontinue study drug.
Grade 4	• Permanently discontinue study drug.
Epithelial tumor	
New malignancy, unresectable colonic mucosal dysplasia, or any high-grade colonic mucosal dysplasia	• Permanently discontinue study drug.
New cervical intraepithelial neoplasia of Grade > 1, cervical smear indicating the presence of adenocarcinoma in situ, or high-grade squamous intraepithelial lesion	• Permanently discontinue study drug.

ADA = anti-drug antibody; AESI = adverse event of special interest; IRR = infusion-related reaction; LFT = liver function test; PK = pharmacokinetic; ULN = upper limit of normal.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Hepatic event	
ALT or AST > 3 × ULN to ≤ 5 × ULN	• Continue study drug. • Repeat LFTs within 48-72 hours. • If LFT results confirmed, test for alternative cause(s) as described in Section 5.1.3.3.
ALT or AST > 5 × ULN to ≤ 8 × ULN	• Withhold study drug. • Repeat LFTs within 48-72 hours. • If LFTs confirmed, test for alternative cause(s) as described in Section 5.1.3.3. • Monitor LFTs weekly until AST and ALT ≤ 5 × ULN. • If event resolves to AST or ALT ≤5x ULN within 2 weeks after event onset, resume study drug. If not, monitor as described in the next category.
Any one of the following: • ALT or AST elevation > 8 × ULN • ALT or AST > 5 × ULN for more than 2 weeks • ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5 • ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%), or jaundice	• Withhold study drug. • Repeat LFTs within 48-72 hours. • If LFTs confirmed, test for alternative cause(s) as described in Section 5.1.3.3. • Monitor LFTs two to three times per week until decreasing or stabilized, then monitor LFTs weekly until AST and ALT are ≤ 5 × ULN and total bilirubin is ≤ 2 × ULN. • Discontinuation of study drug should be considered. However, if event resolves to AST and ALT ≤ 5 × ULN with total bilirubin ≤ 2 × ULN, study drug may be resumed after consultation with the Medical Monitor. If a decision is made to permanently discontinue study drug, offer medical management per local standard of care and follow for safety.
Thromboembolism or deep vein thrombosis	
Grade 1	• *Continue study drug and monitor closely for worsening of symptoms.*
Grade 2 or 3	• *Treat as per local standard of care. Withhold study drug until the event resolves to a Grade 1 or lower* • *Report event to Sponsor in an expedited manner as an AESI (Section 5.2.3)*
Grade 4	• *Permanently discontinue study drug* • *Notify Medical Monitor and offer medical management per local standard of care, and follow for safety.* • *Report event to Sponsor in an expedited manner as an AESI (Section 5.2.3)*

ADA = anti-drug antibody; AESI = adverse event of special interest; IRR = infusion-related reaction; LFT = liver function test; PK = pharmacokinetic; ULN = upper limit of normal.

Table 4 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Efmarodocokin alfa- and vedolizumab-related adverse events not described above	
Grade 1 or 2	• Continue study drug.
Grade 3	• Withhold study drug. • If event resolves to Grade 2 or better, resume study drug at the next scheduled dose. If more than one scheduled dose will be missed because of an on-going adverse event, permanently discontinue study drug.
Grade 4	• Permanently discontinue study drug, offer medical management per local standard of care, and follow for safety.

ADA = anti-drug antibody; AESI = adverse event of special interest; IRR = infusion-related reaction; LFT = liver function test; PK = pharmacokinetic; ULN = upper limit of normal.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH E6 guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- New or worsening neurologic signs and symptoms that are consistent with a diagnosis of PML
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Any adverse event leading to discontinuation of study drug
- Suspected or confirmed COVID-19 infection
- *Grade ≥2 thromboembolism or deep vein thrombosis*

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The clinician who assesses adverse events should not be the same clinician who assesses UC efficacy outcomes (e.g., PROs and endoscopic evaluation).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 6 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events

based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 *Abnormal ECG Findings*

Not every ECG abnormality qualifies as an adverse event. An ECG finding must be reported as an adverse event if it meets any of the following criteria:

- *Is accompanied by clinical symptoms*
- *Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*
- *Results in a medical intervention or a change in concomitant therapy*
- *Is clinically significant in the investigator's judgment*

It is the investigator's responsibility to review all ECG findings. Medical and scientific judgment should be exercised in deciding whether an isolated ECG abnormality should be classified as an adverse event.

If a clinically significant ECG abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant ECG abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (See Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.9 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of UC.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of UC, "ulcerative colitis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF. Medical conditions (serious or non-serious) that occur after screening but before study drug administration and are not due to a protocol-mandated intervention should not be recorded as adverse events but should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.11 Lack of Efficacy or Worsening of Ulcerative Colitis

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on the MCS, which includes endoscopic disease evaluation. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Planned hospitalization required by the protocol (e.g., for study drug administration, insertion of access device for study drug administration, or procedure required by the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed through use of PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

- Accidental overdoses or medication errors (see Section 5.4.4 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Pharmaceutical Product Development (PPD) Medical Monitor contact information:

	Telephone Number (24-Hour Safety Hotline)	Fax Number
North America	+1 888 483 7729	+1 888 529 3580
North America (Alternate)	+1 800 201 8725	+1 888 488 9697
EMEA/Asia Pacific	+44 1223 374 240	+44 1223 374 102

Alternate Medical Monitor contact information for all sites:

Medical Monitor: [redacted], M.D., Ph.D

Telephone Nos.: Mobile: [redacted]

Office: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), by faxing the form using the fax number provided below:

Region	Fax Number
North America	+1 888 529 3580
EMEA/Asia Pacific	+44 1223 374 102

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 8 weeks after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), by faxing the form using the fax number provided in Section 5.4.2.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 8 weeks after the last dose of study drug are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 18 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), by faxing the form using the fax number provided in Section 5.4.2.1. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible

effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 18 weeks after the last dose of study drug. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), by faxing the form using the fax number provided in Section 5.4.2.1. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.4 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. All special situations associated with efmarodocokin alfa, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

For efmarodocokin alfa and vedolizumab, each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For efmarodocokin alfa, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 8 weeks after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, by faxing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the email/fax numbers provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events *through* the *use of the* reference *safety information in the* documents *listed below:*

Drug	*Document*
Efmarodocokin alfa	*Efmarodocokin Alfa Investigator's Brochure*
Vedolizumab	*Summary of Product Characteristics*

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Currently there are no expected serious adverse drug reactions for efmarodocokin alfa described in the Efmarodocokin Alfa Investigator’s Brochure. Thus, any treatment-emergent serious adverse event deemed related to efmarodocokin alfa will be reported as a suspected unexpected serious adverse reaction (SUSAR). Reporting of individual SUSARs to investigators, IRBs, ECs, and applicable health authorities will be done in accordance with applicable legislation.

For the purpose of SUSAR reporting, the version of the Efmarodocokin Alfa Investigator’s Brochure valid at the time of SUSAR occurs will apply. SUSARs will be

kept blinded unless required for medical safety reasons and/or country regulatory reasons. Unblinding to study personnel and Genentech study team members will be documented.

Six-month SUSAR reports related to efmarodocokin alfa will be provided as per local regulatory requirements. If a significant safety issue arises altering the benefit-risk profile of efmarodocokin alfa, the investigators, IRBs, ECs, and applicable health authorities will be informed prior to the next update of the Efmarodocokin Alfa Investigator's Brochure, in accordance with applicable legislation.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, those associated with the progression of UC.

The IMC will monitor the incidence of events associated with progression of UC during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A target of approximately 270 patients will be enrolled and randomly assigned in a 1:1:1:1:1:1:2:1 ratio to Arms 1A, 1B, 2A, 2B, 3A, 3B, 4, and 5. The A and B arms for each efmarodocokin alfa dose will be pooled (i.e., 1A + 1B; 2A + 2B; 3A + 3B) for analyses of endpoints at or before Week 8. Thus, the primary efficacy analysis of clinical remission at Week 8 will compare data for pooled Arm 1 (1A + 1B), pooled Arm 2 (2A + 2B), and pooled Arm 3 (3A + 3B), versus Arm 4 and versus Arm 5. The sample size of 60 patients per pooled efmarodocokin alfa arm provides approximately 80% power to detect an improvement of 16 percentage points over the vedolizumab arm (Arm 4; $n = 60$) and approximately 80% power to detect an improvement of 26 percentage points over the placebo arm (Arm 5; $n = 30$) in the proportion of patients with clinical remission at Week 8, assuming a clinical remission rate of approximately 15%–20% in a vedolizumab-treated population and approximately 5%–10% in a placebo-treated population with both populations consisting of 25% TNF-α naive patients and 75% TNF-IR patients (derived from data presented by Feagan et al. 2013) and a two-sided type I error rate of 0.2.

6.2 SUMMARIES OF CONDUCT OF STUDY

The numbers of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and self-reported race/ethnicity) will be summarized through use of means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm.

6.4 EFFICACY ANALYSES

The efficacy analysis population will consist of all randomized patients who received at least one dose of study drug and have at least one postbaseline efficacy measurement, with patients grouped according to their treatment assigned at randomization. Unless otherwise noted, analyses of efficacy endpoints will be stratified by the stratification factor used at randomization (i.e., prior treatment with TNF inhibitors [yes/no]).

Patients who are non-evaluable for a response- or remission-type efficacy endpoint at a specific timepoint (e.g., due to missing data or early discontinuation from study) will be considered non-responders for that endpoint.

Because the study is hypothesis-generating in nature, no adjustment for multiplicity will be performed. Hypothesis testing will be carried out in an exploratory fashion, at a two-sided 0.20 significance level. Sensitivity analyses, through use of last observation carried forward, baseline observation carried forward, or worst observation carried forward may be performed. A separate Data Analysis Plan will contain more details on the statistical analyses.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is clinical remission at Week 8 (see definition of clinical remission in Section 2, Table 1). The primary analysis will be conducted by first comparing the efmarodocokin alfa arms versus the placebo arm. A comparison between the efmarodocokin alfa arms and the vedolizumab arm will be carried out secondarily. The difference between pooled Arm 1, pooled Arm 2, and pooled Arm 3, versus Arm 4 and versus Arm 5 in the proportion of patients with clinical remission at Week 8 will be evaluated by the Mantel-Haenszel test statistic, stratified by prior treatment with TNF inhibitors (yes/no). Additional stratification variables may be used if appropriate (e.g., if a large number of very small strata are not generated), such as concomitant treatment with corticosteroids (yes/no) or prior treatment with immunomodulators (AZA, 6-MP, or MTX) (yes/no). An 80% two-sided confidence interval of the differences in the proportion of patients with clinical remission at Week 8 will be provided to aid in the interpretation of the study results.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are defined in Section 2, Table 1. The secondary efficacy endpoints will be summarized by descriptive statistics based on the following calculations:

- Proportion of patients with sustained remission (clinical remission at both Week 8 and Week 30)
- Proportion of patients with clinical response at Week 8 and Week 30 (separate proportion calculated for each timepoint)
- Proportion of patients with endoscopic healing at Week 8 and Week 30 (separate proportion calculated for each timepoint)
- Proportion of patients with endoscopic remission at Week 8 and Week 30 (separate proportion calculated for each timepoint)
- Average change from baseline in UC bowel movement signs and symptoms at Week 8 and at Week 30, as assessed by UC-PRO/SS score (separate average calculated for each timepoint)
- Average change from baseline in UC abdominal symptoms at Week 8 and at Week 30, as assessed by UC-PRO/SS score (separate average calculated for each timepoint)
- Average change from baseline in patient-reported health-related QOL at Week 8 and at Week 30, as assessed by the IBDQ score (separate average calculated for each timepoint)

Data will be summarized for pooled Arms 1, 2, and 3, for Arm 4, and for Arm 5 if the endpoint is at or before Week 8. Data will be summarized separately for all arms if the endpoint is after Week 8.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are defined in Section 2, Table 1. The exploratory efficacy endpoints will be summarized by descriptive statistics based on the following calculations:

- Proportion of patients with mucosal healing at Week 8 and Week 30 (separate proportion calculated for each timepoint)
- Average change from baseline in UC endoscopic index severity at Week 8 and at Week 30 (separate average calculated for each timepoint)
- Proportion of patients with histological healing, defined as Nancy score of 0 or 1 as per Nancy Histological Index, at Week 8 and Week 30 (separate proportion calculated for each timepoint)
- Average change from baseline in Geboes Score at Week 8 and at Week 30 (separate average calculated for each timepoint).
- Average change from baseline in Robarts Histological Index at Week 8 and at Week 30 (separate average calculated for each timepoint)

Data will be summarized for pooled Arms 1, 2, and 3, for Arm 4, and for Arm 5 if the endpoint is at or before Week 8. Data will be summarized separately for all arms if the endpoint is after Week 8.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all randomized patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed by recording adverse events and conducting clinical laboratory evaluations.

Separate summaries of adverse events will be provided for the screening period, the 8-week induction treatment period (Part A), and the 22-week maintenance period (Part B). Adverse events will be summarized by treatment arm.

Clinical laboratory data will also be summarized by treatment arm through use of appropriate descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0.

6.6 PHARMACOKINETIC ANALYSES

The efmarodocokin alfa PK analysis population will consist of patients who received at least one dose of efmarodocokin alfa and have at least one postdose blood draw to determine serum concentration of efmarodocokin alfa.

The following PK parameters will be measured and reported:

- Maximum serum concentration after the first dose ($C_{max,wk0}$) during Part A
- Maximum serum concentration after the last dose ($C_{max,wk8}$) during Part A
- Predose concentration at Weeks 4, and 8 (C_{wk4}, C_{wk8}) during Part A
- Trough (predose) concentration at Weeks 14 and 22($C_{wk14,}$ C_{wk22}) during Part B
- Serum concentration at Week 26 (C_{wk26}) during safety follow-up

Individual and mean serum efmarodocokin alfa concentration-versus-time data will be tabulated and plotted by arm. The PK parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, and range). Additional PK analyses will be conducted as appropriate.

Exploratory vedolizumab PK analyses may also be performed.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one postdose ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment arm. When determining postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

6.8 BIOMARKER ANALYSES

The PD biomarker analyses will include all patients with one pre-treatment and at least one post-treatment biomarker assessment, with patients grouped according to the treatment actually received. PD biomarker analyses will include examination of changes from baseline (pre-treatment) in biomarkers over time. PD biomarkers will be assessed as an absolute increase over time, and/or as a percent change relative to original baseline for each patient. In addition, efforts will be made to perform PK/PD analyses based on PD and PK exposure data. Results will be summarized through use of summary statistics and or other graphs as required. Descriptive statistics will be listed by dose, treatment arm, and response status. Additional PD analyses will be conducted as appropriate.

Non-PD (e.g., predictive and prognostic) biomarker analyses will include all patients with one pre-treatment biomarker assessment, with patients grouped according to the treatment actually received, provided there are sufficient data in each biomarker arm to facilitate a meaningful analysis. Baseline values will be used to evaluate predictive biomarkers in the context of activity (clinical and/or pharmacological), drug levels, safety, and/or immunogenicity endpoints. Results will be summarized descriptively.

6.9 INTERIM ANALYSES

6.9.1 Planned Interim Analysis

An interim analysis will be performed when approximately 50% of patients have completed Part A (through Week 8). The interim results will be evaluated on the basis of descriptive summaries of the primary and key secondary outcomes for Part A, including estimated rates, between-group differences in rates, 80% CIs, and exploratory p-values with no type I error adjustments or formal stopping criteria.

Results of the interim analysis may inform potential early stopping of enrollment if the benefit-risk profile for the efmarodocokin alfa arms is considerably unfavorable. The interim analysis will be conducted by the IMC (see Section 3.1.6). Recruitment of patients will continue during the period of the interim analysis.

6.9.2 Optional Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and all other electronic data, including endoscopy and ECG data, will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and clinician-reported outcome (ClinRO) data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT- AND CLINICIAN-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO and, at applicable sites, ClinRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

In cases of device malfunction or failure, data may be captured via paper questionnaires.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes,

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered on the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO and ClinRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Genentech will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and the General Data Protection Regulation (GDPR).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

After discussion of the study with the investigator, patients must be given ample time to review what has been discussed and have their questions answered prior to signing Consent Forms. Patients must be told that they are free to refuse to participate and may withdraw their consent at any time for any reason without penalty or loss of benefits to which they are otherwise entitled. The Consent Forms must be signed and dated by the patient before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

8.6 PATIENT RECRUITMENT

Recruitment procedures will follow the ICH E6 guideline for Good Clinical Practice and are customized in accordance with local requirements and regulations. Recruitment strategies for this study may include, but are not necessarily limited to, recruitment from the investigator's local practice or referrals from other physicians. All patient recruitment materials must be reviewed and approved by the IRB/EC prior to study use (see Section 8.3).

To ensure that patients are adequately informed and free from coercion, patient recruitment procedures must adhere to the following guidelines:

- After discussion of the study with the investigator, patients must be given ample time to review what has been discussed and have their questions answered prior to signing Consent Forms (see Section 8.2)
- Patients must be told that they are free to refuse to participate and may withdraw their consent at any time for any reason without penalty or loss of benefits to which they are otherwise entitled (see Section 8.2)
- Patients must be provided with IRB/EC-approved study educational material and a copy of each signed Consent Form (see Section 8.2)
- Patients with the potential of exposure to any coercion will be excluded from the study (see Section 4.1.2)

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by Genentech. A contract research organization will be contracted to manage the study and perform monitoring activities. Centralized facilities (vendors) will perform endoscopy reading and interpretation; however, the investigator or a designee will also read the endoscopy as part of the MCS and mMCS evaluation. In addition, a central vendor will collect ECG data.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected. A selected group of assessments will be performed on site or by a local laboratory and urine pregnancy tests will be conducted by the patient at home if appropriate.

The eCRF data will be recorded via a Sponsor-designated EDC system. An IxRS will be used for study treatment inventory management and to randomly assign patients to study treatment.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Assessment or Procedure	Screening −28 to −1 [a]	Study Week (± 3 days)												DE/ET Visit [e]	UV Visit [f]
		Part A						Part B				Safety Follow-Up			
		0 [b] (D 1)	1 (D 8)	2 (D 15)	4 (D 29)	6 (D 43)	8 (D 57)	11 [c] (D 78)	14 (D 99)	18 [c] (D 127)	22 (D 155)	4 wks [d] 26 (D 183)	8 wks [d] 30 (D 211)		
Informed consent	x														
Review eligibility criteria	x	x													
Demographic data	x														
Medical history and baseline conditions	x														
Concomitant medications	x	x	x	x	x	x	x		x		x	x	x	x	x
Adverse events [g]	x	x	x	x	x	x	x		x		x	x	x	x	x
IBDQ		x					x		x		x		x	x	
UC-PRO/SS [h]		x					x				x		x	x	
Vital signs [i]	x	x	x	x	x	x	x		x		x	x	x	x	x
Height	x														
Weight		x		x	x	x	x		x		x		x		
Physical examination [j]	x										x		x	x	x
ECG [k]		x					x				x		x		
Hematology [l] and chemistry [m]	x	x	x	x		x	x		x		x		x		

Appendix 1
Schedule of Activities (cont.)

Assessment or Procedure	Screening −28 to −1 [a]	Study Week (± 3 days)												DE/ET Visit [e]	UV Visit [f]
		Part A						Part B				Safety Follow-Up			
		0 [b] (D 1)	1 (D 8)	2 (D 15)	4 (D 29)	6 (D 43)	8 (D 57)	11 [c] (D 78)	14 (D 99)	18 [c] (D 127)	22 (D 155)	4 wks [d] 26 (D 183)	8 wks [d] 30 (D 211)		
Lipase, coagulation, [n] and lipids (fasting) [o]		x [n]				x [o]	x [o]				x [o]		x [n]		
CRP [p]	x	x	x	x	x	x	x		x		x		x		
HbA_{1c} [q]	x										x		x		
Pregnancy test [r]	x	x			x		x	x	x	x	x	x	x	x	
Urinalysis [s]	x	x					x				x		x		
Urine drug screening [t]	x														
Viral serology	x [u]														
TB testing (may include chest X-ray) [v]	x														
PK [w] and/or ADA [w, x] (serum)	See Appendix 2.														
Biomarkers (plasma and/or serum) [p]	See Appendix 2.														
WGS (blood) [y]		x													
Stool sample [z]	x	x			x		x [y]		x		x	x	x		
Endoscopy [aa] with biopsy [bb]	x [y]						x [cc]						x [dd]	x	

Appendix 1
Schedule of Activities (cont.)

Assessment or Procedure	Screening −28 to −1 [a]	Study Week (± 3 days)												DE/ET Visit [e]	UV Visit [f]
		Part A						Part B				Safety Follow-Up			
		0 [b] (D 1)	1 (D 8)	2 (D 15)	4 (D 29)	6 (D 43)	8 (D 57)	11 [c] (D 78)	14 (D 99)	18 [c] (D 127)	22 (D 155)	4 wks [d] 26 (D 183)	8 wks [d] 30 (D 211)		
Stool frequency and rectal bleeding	x [ee]														
MCS (pMCS plus endoscopy) [ff]	x						x						x [dd]	x	
pMCS [gg]		x	x	x	x	x			x		x	x	x [dd]		
Efmarodocokin alfa or efmarodocokin alfa placebo administration		x			x		x [hh]		x [hh]		x [hh]				
Vedolizumab or vedolizumab placebo administration		x		x		x			x		x				

ADA = anti-drug antibody; CMV = cytomegalovirus; CRP = C-reactive protein; D = day; DE = disease evaluation; eCRF = electronic Case Report Form; ET = early termination; HBV = hepatitis B virus; HbA_{1c} = glycosylated hemoglobin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IBDQ = Inflammatory Bowel Disease Questionnaire; IMC = Internal Monitoring Committee; MCS = Mayo Clinic Score; OLE = open-label extension; PD = pharmacodynamic; PGA = Physician's Global Assessment; PK = pharmacokinetic; pMCS = partial Mayo Clinic Score; PPD = purified protein derivative; QFT = QuantiFERON®-TB Gold test; TB = tuberculosis; UC = ulcerative colitis; UC-PRO/SS = Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms; UV = unscheduled visit; WGS = whole genome sequencing; Wks = weeks.

Note: All assessments should be performed prior to study drug administration, unless otherwise stated.

[a] Informed consent must be documented before any study-specific screening procedure is performed. Screening window begins after the first procedure is performed. Screening may be extended to accommodate an unanticipated delay in CMV results. Local safety laboratory results (i.e., chemistry, hematology, urinalysis, urine pregnancy [for women of childbearing potential only]) would have to be reconfirmed prior to randomization.

[b] Day 1 of Week 0.

[c] Weeks 11 and 18 visits (±1 week) for women of childbearing potential only.

[d] Patients who complete the treatment period (Parts A and B) and patients who discontinue study drug without entering OLE Study GA40209 will undergo assessments at 4 and 8 weeks after their last dose of study drug.

[e] A disease evaluation visit is required if a patient receives rescue therapy or experiences persistent or worsening disease for which rescue therapy is indicated, as determined by the investigator. A disease evaluation visit should occur no later than 1 week after initiation of rescue therapy. All indicated assessments are required for a disease evaluation visit, with the exception of the UC-PRO/SS, which is not required if it has not been completed for 9 consecutive days prior to visit. Patients who discontinue study drug prematurely for the reasons listed in Section 4.6.1 should return to the clinic for an early termination visit within 1 week of the event and will then enter the safety follow-up period. Patients who are unwilling to complete the safety follow-up period should return to the clinic for an early termination visit no later than 30 days after their final dose. All indicated assessments should be completed for an early termination visit.

[f] An unscheduled visit represents a visit that is not specified by the protocol but is determined to be necessary by the investigator or Sponsor (e.g., for evaluation of an adverse event). The indicated assessments are required for an unscheduled visit. Other assessments are optional for an unscheduled visit, per investigator discretion.

[g] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 8 weeks after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[h] Patients are to complete the UC-PRO/SS on the 9 consecutive days preceding the clinic visit.

[i] Vital signs include measurements of respiratory rate, pulse rate, systolic blood pressure, diastolic blood pressure, and temperature. Patient should be in a seated position after at least 10 minutes of rest prior to measuring vital signs.

[j] A complete physical examination is required at screening and includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. A limited, symptom-driven physical examination, including an abdominal examination, is required at all other indicated timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Patient must be resting in a supine position for at least 10 minutes prior to ECG assessment. The Day 1 ECG can be taken anytime from Day −28 to Day 1 prior to study drug administration.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[m] Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH.

[n] Coagulation includes INR, aPTT, PT, and fibrinogen. Site and Sponsor personnel, with the exception of the IMC, will be blinded to fibrinogen test results.

[o] Lipid panel includes cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Patients must be fasting (no food or fluids other than water will be allowed for approximately 8 hours prior to the visit and until after sample collection).

[p] Site and Sponsor personnel, with the exception of the IMC, will be blinded to CRP and exploratory biomarker REG3A test results.

[q] Test for HbA_{1c} will be performed only for patients with known diabetes.

[r] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed monthly and at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[s] Urinalysis includes specific gravity, pH, blood, qualitative protein, ketones, glucose, bilirubin, nitrite, leukocyte esterase, color, and appearance. If urinalysis is abnormal, the same urine sample will be sent to the laboratory for microscopic analysis (sediment, WBCs, RBCs, casts, crystals, epithelial cells, and bacteria), culture, and sensitivity.

[t] Patients with a history of drug abuse will undergo urine drug screening.

[u] At screening, patients will be tested for HIV, HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must be performed.

[v] Patients must have a negative TB test during screening or within 3 months prior to screening. TB testing will consist of the QFT, if available, or the PPD test. A chest X-ray will be performed to rule out TB for patients with a positive or indeterminant QFT and patients with no history of BCG vaccination who have a positive PPD skin test (see Section 4.1.2 for details on TB testing).

[w] PK and ADA samples should be collected in patients with signs and symptoms of serious opportunistic infections, if not already scheduled to be collected at that timepoint. See Appendix 2 for additional details.

[x] ADA samples may be used to assess PK if needed. ADA samples should be collected in patients with signs and symptoms of infusion-related reactions, if not scheduled to be collected at that timepoint. See Appendix 2 for additional details.

[y] Collect blood sample for WGS after all other predose samples are taken. Not applicable for a site that has not been granted approval for WGS.

[z] Stool samples scheduled for Weeks 8 and 30 should be obtained prior to bowel preparation for sigmoidoscopy. Samples will be analyzed for culture and sensitivity, ova and parasites, and *C. difficile* at screening. Samples collected at screening and subsequent timepoints will be used for exploratory biomarker research.

[aa] All patients will undergo a flexible sigmoidoscopy at screening, with the exception of patients without documentation of colon cancer surveillance within 1 year prior to randomization. Such patients will undergo a colonoscopy in lieu of a flexible sigmoidoscopy at screening. Stool frequency and rectal bleeding scores from the three most recent e-diary entries and the screening endoscopy will be used as efficacy baseline and for inclusion. The screening endoscopy should not be performed without adequate symptoms (see Section 4.5.7.2). A flexible sigmoidoscopy will be performed for all other scheduled endoscopies. Video recordings should be taken of the entire endoscopic procedure (colonoscopy or flexible sigmoidoscopy), starting from with insertion into the bowel. Biopsies should be performed upon withdrawal of the endoscope from the bowel. Technical instructions for video recording and biopsy collection will be provided in the laboratory manual.

[bb] Tissue collected at screening will be analyzed for CMV, as determined by histologic examination or immunohistochemistry per local standards, and will undergo histopathologic examination for patients without a prior histopathology report. Tissue collected at screening and subsequent timepoints will be used for exploratory biomarker research. For patients who undergo a screening colonoscopy, multiple random mucosal tissue samples will be evaluated for dysplasia.

[cc] Not performed for patients who have undergone a flexible sigmoidoscopy as part of a disease evaluation visit.

[dd] Full MCS (i.e., pMCS plus endoscopy) to be performed only if patient has completed Parts A and B and 8-week safety follow-up, otherwise, pMCS should be performed.

[ee] At screening, the investigator will document the patient's normal number of stools, defined as the number of stools passed when a patient is in remission (i.e., not in flare). Patients are to record stool frequency and rectal bleeding (MCS and pMCS components) in the e-diary daily throughout the study, beginning with the first screening visit. However, e-diary entries on days of bowel preparation and endoscopy will not be used to calculate stool frequency scores, and rectal bleeding scores will be derived from e-diary entries prior to endoscopy. Stool frequency and rectal bleeding scores from the three most recent e-diary entries and the screening endoscopy will be used as efficacy baseline and for inclusion (see Section 4.5.7.2).

[ff] MCS is a composite of four assessments, each having a scoring range of 0–3: stool frequency, rectal bleeding, endoscopy, and PGA.

[gg] pMCS is a composite of three assessments from the MCS, each having a scoring range of 0–3: stool frequency, rectal bleeding, and PGA.

[hh] Study drug should not be administered if determination is made at visit that patient will enroll in OLE Study GA40209.

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Blood Samples

Visit (± 3 days)	Timepoint	Sample Type
Screening (Day –28 to Day –1)	NA	• Biomarker (serum) including sample for diagnostic biomarkers [a] • Biomarker (plasma)
Week 0 (Day 1)	Prior to the first infusion	• PK (serum) • Biomarker (serum) including sample for diagnostic biomarkers [a] • Biomarker (plasma) including sample for 4β-hydroxycholesterol and cholesterol [a] • ADA (serum)
	30 minutes (±5 minutes) after the end of the first infusion	• PK (serum)
Week 1 (Day 8)	NA	• PK (serum) • Biomarker (serum) • Biomarker (plasma) for 4β-hydroxycholesterol and cholesterol only [a]
Week 2 (Day 15)	Prior to the first infusion	• PK (serum) • Biomarker (serum) • ADA (serum)
Week 4 (Day 29)	Prior to the first infusion	• PK (serum) • Biomarker (serum) • Biomarker (plasma) • ADA (serum)
Week 8 (Day 57)	Prior to the first infusion	• PK (serum) • Biomarker (serum) • Biomarker (plasma) including sample for 4β-hydroxycholesterol and cholesterol [a] • ADA (serum)
	30 minutes (± 5 minutes) after the end of the efmarodocokin alfa infusion	• PK (serum)
Week 14 (Day 99)	Prior to the first infusion	• PK (serum) • Biomarker (serum) • Biomarker (plasma) including sample for 4β-hydroxycholesterol and cholesterol [a] • ADA (serum)

Appendix 2
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Blood Samples (cont.)

Visit (± 3 days)	Timepoint	Sample Type
Week 22 (Day 155)	Prior to the first infusion	• PK (serum) • Biomarker (serum) • Biomarker (plasma) including sample for 4β-hydroxycholesterol and cholesterol [a] • ADA (serum)
	30 minutes (± 5 minutes) after the end of the efmarodocokin alfa infusion	• PK (serum)
Week 26 Safety follow-up 4 weeks (Day 183)	NA	• PK (serum) • Biomarker (plasma) including sample for 4β-hydroxycholesterol and cholesterol [a]
Week 30 Safety follow-up 8 weeks (Day 211)	NA	• Biomarker (serum) • Biomarker (plasma) including sample for 4β-hydroxycholesterol and cholesterol [a] • ADA (serum)
Unscheduled [b] or DE/ET Visit	NA	• PK (serum) • Biomarker (serum) • Biomarker (plasma) • ADA (serum)

ADA = anti-drug antibody; DE = disease evaluation; ET = early termination; NA = not applicable; PK = pharmacokinetic.

Notes: Samples may be used for exploratory research (see Section 4.5.8). ADA samples may be used to assess PK if needed. Serum ADA may be measured in PK samples if ADA samples have not been collected at the same timepoint. PK and ADA samples should be collected in patients with signs and symptoms of serious opportunistic infections, if not already scheduled to be collected at that timepoint. ADA samples should be collected in patients with signs and symptoms of infusion-related reactions, if not scheduled to be collected at that timepoint. Site and Sponsor personnel, with the exception of the IMC, will be blinded to exploratory biomarker REG3A test results

[a] See laboratory manual for specific sample handling procedures

[b] For unscheduled visits, PK, ADA, or biomarker samples may be collected per investigator discretion.

Appendix 3
Mayo Clinic Score

Please respond to the following questions after reviewing the patient's Signs and Symptoms of UC Daily Diary at each visit as per the schedule of activities.

1. **Stool frequency**
   0 = Normal
   1 = 1-2 stools/day more than normal
   2 = 3-4 stools/day more than normal
   3 = >4 stools/day more than normal

2. **Rectal bleeding**
   0 = None
   1 = Visible blood with stool less than half the time
   2 = Visible blood with stool half of the time or more
   3 = Passing blood alone

3. **Mucosal appearance at endoscopy**
   0 = Normal or inactive disease
   1 = Mild disease (erythema, decreased vascular pattern)
   2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
   3 = Severe disease (spontaneous bleeding, ulceration)

4. **Physician's Global Assessment**
   0 = Normal
   1 = Mild
   2 = Moderate
   3 = Severe

Appendix 4
Modified Mayo Clinic Score

Please respond to the following questions after reviewing the patient's Signs and Symptoms of UC Daily Diary at each visit as per the schedule of activities.

1. **Stool frequency**
   0 = Normal
   1 = 1-2 stools/day more than normal
   2 = 3-4 stools/day more than normal
   3 = >4 stools/day more than normal

2. **Rectal bleeding**
   0 = None
   1 = Visible blood with stool less than half the time
   2 = Visible blood with stool half of the time or more
   3 = Passing blood alone

3. **Mucosal appearance at endoscopy**
   0 = Normal or inactive disease
   1 = Mild disease (erythema, decreased vascular pattern)
   2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
   3 = Severe disease (spontaneous bleeding, ulceration)

Appendix 5
Partial Mayo Clinic Score

Please respond to the following questions after reviewing the patient's Signs and Symptoms of UC Daily Diary at each visit as per the schedule of activities.

1. **Stool frequency**
   0 = Normal
   1 = 1-2 stools/day more than normal
   2 = 3-4 stools/day more than normal
   3 = >4 stools/day more than normal

2. **Rectal bleeding**
   0 = None
   1 = Visible blood with stool less than half the time
   2 = Visible blood with stool half of the time or more
   3 = Passing blood alone

3. **Physician's Global Assessment**
   0 = Normal
   1 = Mild
   2 = Moderate
   3 = Severe

Appendix 6
Signs and Symptoms of UC Daily Diary

Please respond to the following questions before you go to bed each evening.

1. **How many stools/bowel movements did you have today, compared to your normal number?**
   0 = Normal
   1 = 1-2 stools/day more than normal
   2 = 3-4 stools/day more than normal
   3 = >4 stools/day more than normal

2. **How much rectal bleeding did you experience today?**
   0 = None
   1 = Visible blood with stool less than half the time
   2 = Visible blood with stool half of the time or more
   3 = Passing blood alone

Appendix 7
Ulcerative Colitis Patient-Reported Outcome Signs and Symptoms (UC-PRO/SS) Instrument

Appendix A: UC-PRO/SS Measure (ePRO Format)

You and Your Ulcerative Colitis

The following questions ask about your bowel movements in the past 24 hours.

For these questions, a ***bowel movement*** is defined as any time you pass solid or liquid including stool, blood, mucus (white material), or water. Passing gas alone is not considered a bowel movement.

1. In the past 24 hours, how many bowel movements did you have?

- ☐ 0
- ☐ 1–2
- ☐ 3–4
- ☐ 5–6
- ☐ 7–9
- ☐ 10–12
- ☐ 13–17
- ☐ 18 or more

2. In the past 24 hours, how often were your bowel movements mostly or completely liquid?

- 0 ☐ Never
- 1 ☐ Rarely
- 2 ☐ Sometimes
- 3 ☐ Often
- 4 ☐ Always

The following questions ask about the presence and how often you experienced your ulcerative colitis symptoms in the **past 24 hours**.

3. In the past 24 hours, did you have blood in your bowel movements?

☐ Yes

☐ No

(If Yes)

How often did you experience blood in your bowel movements?

1 ☐ Rarely

2 ☐ Sometimes

3 ☐ Often

4 ☐ Always

4. In the past 24 hours, did you have mucus (white material) in your bowel movements?

☐ Yes

☐ No

(If Yes)

How often did you experience mucus (white material) in your bowel movements?

1 ☐ Rarely

2 ☐ Sometimes

3 ☐ Often

4 ☐ Always

5. In the past 24 hours, did stool, blood, or liquid leak out before you reached a toilet?

☐ Yes

☐ No

(If Yes)

How often did you experience having stool, blood, or liquid leak out before you reached a toilet?

1 ☐ Rarely
2 ☐ Sometimes
3 ☐ Often
4 ☐ Always

6. In the past 24 hours, did you pass gas?

☐ Yes
☐ No

(If Yes)

How often did you experience passing gas?

1 ☐ Rarely
2 ☐ Sometimes
3 ☐ Often
4 ☐ Very often

The following questions ask about the presence and severity of your ulcerative colitis symptoms in the **past 24 hours**.

7. In the past 24 hours, did you feel the need to have a bowel movement right away?

- ☐ Yes
- ☐ No

(If Yes)

How severe was the need to have a bowel movement right away at its worst?

- 1 ☐ Mild
- 2 ☐ Moderate
- 3 ☐ Severe
- 4 ☐ Very severe

8. In the past 24 hours, did you feel pain in your belly?

☐ Yes

☐ No

(If Yes)

How severe was the pain in your belly at its worst?

1 ☐ Mild

2 ☐ Moderate

3 ☐ Severe

4 ☐ Very severe

9. In the past 24 hours, did you feel bloating in your belly?

☐ Yes

☐ No

(If Yes)

How severe was the bloating in your belly at its worst?

1 ☐ Mild

2 ☐ Moderate

3 ☐ Severe

4 ☐ Very severe

Appendix 8
Inflammatory Bowel Disease Questionnaire (IBDQ)

The Inflammatory Bowel Disease Questionnaire[2] (IBDQ)

Patient Name: ..... File No: ..... Date: .....

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general and how your mood has been. Please tick **one** answer for each of the questions. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate.

1 How frequent have your bowel movements been during the last 2 weeks?
Please choose an option from:

Bowel movements as or more frequent than they have ever been	1
Extremely frequent	2
Very frequent	3
Moderate increase in frequency of bowel movements	4
Some increase in frequency of bowel movements	5
Slight increase in frequency of bowel movements	6
Normal, no increase in frequency of bowel movements	7

2 How often has the feeling of fatigue or of being tired and worn out been a problem for you during the past 2 weeks?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

3 How often during the last 2 weeks have you felt frustrated, impatient, or restless?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

4 How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

5 How much of the time during the last 2 weeks have your bowel movements been loose?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

6 How much energy have you had during the last 2 weeks?
Please choose an option from:

No energy at all	1
Very little energy	2
A little energy	3
Some energy	4
A moderate amount of energy	5
A lot of energy	6
Full of energy	7

7 How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

8 How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

9 How often during the last 2 weeks have you been troubled by cramps in your abdomen?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

10 How often during the last 2 weeks have you felt generally unwell?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

11 How often during the last 2 weeks have you been troubled because of fear of not finding a washroom (bathroom, toilet)?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

12 How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

A great deal of difficulty; activities made impossible	1
A lot of difficulty	2
A fair bit of difficulty	3
Some difficulty	4
A little difficulty	5
Hardly any difficulty	6
No difficulty; the bowel problems did not limit sports or leisure	7

13 How often during the last 2 weeks have you been troubled by pain in the abdomen?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

14 How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night?
Please choose an option from:

All of the time	1
Most of the time	2
A good bit of the time	3
Some of the time	4
A little of the time	5
Hardly any of the time	6
None of the time	7

15 How often during the last 2 weeks have you felt depressed or discouraged?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

16 How often during the last 2 weeks have you had to avoid attending events where there was no washroom (bathroom, toilet) close to hand?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

17 Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas?
Please choose an option from:

- A major problem — 1
- A big problem — 2
- A significant problem — 3
- Some trouble — 4
- A little trouble — 5
- Hardly any trouble — 6
- No trouble — 7

18 Overall, in the last 2 weeks, how much of a problem have you had in maintaining, or getting to, the weight you would like to be at?
Please choose an option from:

- A major problem — 1
- A big problem — 2
- A significant problem — 3
- Some trouble — 4
- A little trouble — 5
- Hardly any trouble — 6
- No trouble — 7

19 Many patients with bowel problems often have worries and anxieties related to their illness. Worries about getting cancer, never feeling any better and having a relapse. How often during the last 2 weeks have you felt worried or anxious? Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

20 How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

21 How often during the last 2 weeks have you felt relaxed and free of tension?
Please choose an option from:

- None of the time — 1
- A little of the time — 2
- Some of the time — 3
- A good bit of the time — 4
- Most of the time — 5
- Almost all of the time — 6
- All of the time — 7

22 How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

23 How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

24 How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

25 How much of the time during the last 2 weeks have you felt tearful or upset?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

26 How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

27 How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

28 To what extent **has your bowel problem** limited sexual activity during the last 2 weeks?
Please choose an option from:

- No sex as a result of bowel disease — 1
- Major limitation as a result of bowel disease — 2
- Moderate limitation as a result of bowel disease — 3
- Some limitation as a result of bowel disease — 4
- A little limitation as a result of bowel disease — 5
- Hardly any limitation as a result of bowel disease — 6
- No limitation as a result of bowel disease — 7

29 How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

30 How much of the time during the last 2 weeks have you felt irritable?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

31 How often during the past 2 weeks have you felt a lack of understanding from others?
Please choose an option from:

- All of the time — 1
- Most of the time — 2
- A good bit of the time — 3
- Some of the time — 4
- A little of the time — 5
- Hardly any of the time — 6
- None of the time — 7

32 How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks?
Please choose one of the following options from:

- Very dissatisfied, unhappy most of the time — 1
- Generally dissatisfied, unhappy — 2
- Somewhat dissatisfied, unhappy — 3
- Generally satisfied, pleased — 4
- Satisfied most of the time, happy — 5
- Very satisfied most of the time, happy — 6
- Extremely satisfied, could not have been more happy or pleased — 7

Appendix 9
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.