PROTOCOL

TITLE:	**A PHASE II OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF UTTR1147A IN PATIENTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS OR CROHN'S DISEASE**
PROTOCOL NUMBER:	GA40209
VERSION NUMBER:	7
EUDRACT NUMBER:	2017-004997-32
IND NUMBER:	136180
NCT NUMBER:	NCT03650413
TEST PRODUCT:	Efmarodocokin alfa (UTTR1147A, RO7021610)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
26-Jul-2021 20:28:59	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol		Associated Country- or Region-Specific Protocols		
Version	**Date Final**	**Country or Region**	**Version**	**Date Final**
7	See electronic date stamp on title page.	China Version 4 protocol has not been amended. China will not be activated for this study.		
6	15 December 2020			
5	9 April 2020			
3	6 April 2018	China	4	11 April 2019
		VHP	4	21 November 2018
		VHP/UK	3	24 August 2018
2	2 March 2018	—	—	—
1	19 December 2017	—	—	—

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol GA40209 has been amended to align with the Investigator Brochure update (Version 8, April 2021) [redacted]

[redacted]

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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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

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PHASE:	II
INDICATION:	Ulcerative colitis and Crohn's disease
SPONSOR:	Genentech, Inc.

OBJECTIVES AND ENDPOINTS

This study will evaluate the long-term safety and tolerability of efmarodocokin alfa in patients with moderate to severe ulcerative colitis (UC) or Crohn's disease (CD). In addition, the study will obtain long-term data on the efficacy, immunogenicity, and exposure of efmarodocokin alfa. Specific objectives and corresponding endpoints for the study are outlined below. For endpoint determination, endoscopic scores will be based on interpretation by a central reader.

Objectives and Corresponding Endpoints

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of efmarodocokin alfa	• 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 efmarodocokin alfa administration

ADA = anti-drug antibody; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; PRO2 = Patient-Reported Outcome-2.

Note: For endpoint determination, endoscopic scores will be based on interpretation by a central reader.

[a] Clinical response during the extension study, as defined in the protocol.

[b] Clinical remission during the extension study, as defined in the protocol.

[c] Efmarodocokin alfa 60 μg/kg IV Q4W.

Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of efmarodocokin alfa	• Clinical response [a] at Weeks 28, 52, 80, and 104 • Clinical remission [b] at Weeks 28, 52, 80, and 104 • Durability of clinical remission, defined as time from achieving clinical remission [b] to loss of clinical remission [b] • Change from baseline (i.e., either the baseline score in the parent study or the last score prior to initiation of the most recent course [c] of efmarodocokin alfa during the extension study, whichever score is the most recent) in PRO2 in patients with Crohn's disease
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between long-term drug exposure and the safety and efficacy of efmarodocokin alfa	• Relationship between serum concentration or PK parameters for efmarodocokin alfa and exploratory efficacy endpoints • Relationship between serum concentration or PK parameters for efmarodocokin alfa and safety endpoints
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to efmarodocokin alfa	• Presence of ADAs to efmarodocokin alfa during the study relative to the presence of ADAs at baseline (Study Week 0)
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers that can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in stool and colonic tissue and efficacy, safety, or immunogenicity endpoints

ADA = anti-drug antibody; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; PRO2 = Patient-Reported Outcome-2.

Note: For endpoint determination, endoscopic scores will be based on interpretation by a central reader.

[a] Clinical response during the extension study, as defined in the protocol.

[b] Clinical remission during the extension study, as defined in the protocol.

[c] Efmarodocokin alfa 60 μg/kg IV Q4W.

STUDY DESIGN

DESCRIPTION OF STUDY

This open-label extension study (GA40209) will evaluate the long-term safety and tolerability of efmarodocokin alfa in patients with moderate to severe UC or CD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, and exposure of efmarodocokin alfa.

Patients enrolled in the extension study will receive efmarodocokin alfa treatment or undergo observation for up to approximately 2 years (through Week 104), as determined on the basis of the patient's disease status. Upon entry into the extension study, patients will receive efmarodocokin alfa 60 μg/kg IV every 4 weeks (Q4W) or undergo observation, depending on their disease status at the time of their last endoscopy in the parent study. The first dose of

efmarodocokin alfa in the extension study may not be administered less than 2 weeks after last dose of study drug in parent study. During the extension study, patients will receive efmarodocokin alfa 60 μg/kg IV Q4W or undergo observation, depending on their disease status at a scheduled visit or a disease evaluation visit.

Efmarodocokin Alfa Treatment Algorithm

Patient's Disease Status	Action to Be Taken
Meets criteria for clinical remission. [a]	• Discontinue efmarodocokin alfa (if applicable) • Undergo observation and assessments per schedule of activities
Does not meet criteria for clinical remission. [a]	• Receive efmarodocokin alfa 60 μg/kg IV Q4W until clinical remission is achieved [b] • Undergo assessments per schedule of activities
Meets criteria for disease flare [c] (off treatment) after entry into the study	• Consult with Medical Monitor to determine appropriate course of action prior to administration of efmarodocokin alfa (if applicable)
Experiences disease worsening as a result of efmarodocokin alfa treatment, in the investigator's judgment, or disease flare while receiving efmarodocokin alfa [c]	• Permanently discontinue efmarodocokin alfa • Initiate rescue therapy at discretion of investigator • Undergo safety follow-up assessments 8 weeks after final dose of efmarodocokin alfa

Q4W = every 4 weeks.

[a] Clinical remission during the extension study, as defined in the protocol.

[b] First dose of efmarodocokin alfa in the extension study to be administered no less than 2 weeks after last dose of study drug in parent study

[c] Disease flare during the extension study, as defined in the protocol.

The duration of the study *has been* extended from 1 year to 2 years with the implementation of Protocol Version 6. Patients who completed the study through Week 52 (Year 1) prior to the implementation of Protocol Version 6 may *still* be eligible for an additional year of treatment and/or observation, provided that certain criteria are met, as outlined in the algorithm below. Participation during Year 2 is not required for such patients, and those who do not participate will be considered to have completed the study per protocol, provided required safety follow-up assessments have been completed.

Algorithm for Continued Study Participation during Year 2

Patient Disposition Status at Time of Implementation of Protocol Version 6	Action to Be Taken
Has not yet reached Week 52	• Patient will continue study drug treatment or observation through Week 104 per efmarodocokin alfa treatment algorithm above.
Has completed Week 52 visit but has not yet completed required safety follow-up assessments	• Patient may resume study drug treatment or observation through Week 104 per efmarodocokin alfa treatment algorithm above. If resuming study treatment, there must be a minimum of 2 weeks since the last dose of efmarodocokin alfa. [a]
Has completed Week 52 visit and required safety follow-up assessments [b]	• Re-consent patient within 8 weeks of implementation of Protocol Version 6. • Conduct study re-entry screening assessments (including endoscopy) over a 3-week period to confirm study eligibility and evaluate disease status. Daily diary recording will be re-initiated to enable collection of patient-reported outcome data for MCS, CDAI, and PRO2 assessments. • If eligible for study re-entry, patient will resume study drug treatment (within 1 week of establishing eligibility) or undergo observation through Week 104 per efmarodocokin alfa treatment algorithm above.

CDAI = Crohn's Disease Activity Index; MCS = Mayo Clinic Score; PRO2 = Patient-Reported Outcome-2.

[a] If resuming study treatment, there will be no visit window deviation if there is a minimum of 2 weeks since the last dose of efmarodocokin alfa.

[b] Also includes patients who have completed Week 52 visit but do not require safety follow-up assessments because they did not receive efmarodocokin alfa during the study.

NUMBER OF PATIENTS

This study will enroll up to approximately 320 patients from Phase Ib Study GA29469 and Phase II Study GA39925 (parent studies). *Enrollment numbers may be less based on the actual number of patients who rollover into Study GA40209.*

TARGET POPULATION

Inclusion Criteria

Inclusion Criteria for Study Entry

Patients must meet the following criteria for study entry:

- Prior enrollment in Study GA29469 or Study GA39925, with one of the following having occurred during that study:

  Patients previously enrolled in Study GA29469

  - Unable to achieve clinical response during the study and completion of the study through at least Day 85
  - Initiation of protocol-defined rescue therapy during the study and completion of the study through at least Day 85
  - Completion of the study through Day 134

Patients previously enrolled in Study GA39925

- Unable to achieve protocol-defined clinical response by Week 8
- Initiation of protocol-defined rescue therapy during the study and completion of the study through at least Week 8
- Protocol-defined disease flare after Week 8
- Completion of the study through Week 30

- Age 18–80 years, inclusive, at time of signing Informed Consent Form

Inclusion Criteria for Study Entry and Study Re-Entry

Patients must meet the following criteria for study entry and study re-entry:

- Signed Informed Consent Form (at time of initial entry and again at time of study re-entry)
- Ability to comply with requirements of the study, in the investigator's judgment
- 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 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925 (due to the possibility of receiving vedolizumab), whichever is longer

  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, Clinical Trial Facilitation Group, final version, dated 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 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925, whichever is longer, 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.

Exclusion Criteria

Exclusion Criteria for Study Entry

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

- Withdrawal of consent from parent study
- Discontinuation of study drug as required by the parent study protocol
- Discontinuation of study drug and withdrawal from Study GA29469 prior to Day 85 or from Study GA39925 prior to Week 8
- Non-compliance in the parent study, specifically defined as missing scheduled visits or non-adherence with background medications and concomitant medications

Exclusion Criteria for Study Entry and Study Re-Entry

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925 (due to the possibility of receiving vedolizumab), whichever is longer
- Any new malignancy since enrolling in the parent study
- Any new significant uncontrolled comorbidity, such as cardiac, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorders, since enrolling in the parent study
- Any new signs or symptoms of infection judged by the investigator to be clinically significant since enrolling in the parent study
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) since enrolling in the parent study
- Prior treatment with etrolizumab, natalizumab, efalizumab, or any other anti-integrin agents (other than vedolizumab)
- Use of IV corticosteroid or topical corticosteroid (i.e., enemas or suppositories) at the time of entry into this study
- Abnormal laboratory value recorded at the last visit in the parent study, as defined below:
  - Hemoglobin < 90 g/L (9 g/dL)
  - Serum creatinine $> 1.5 \times$ upper limit of normal (ULN)
  - ALT, AST, or ALP $> 2.5 \times$ 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 $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.5 \times 10^9$/L (1500/μL)
  - Absolute lymphocyte count $< 0.5 \times 10^9$/L (500/μL)

Exclusion Criterion for Study Re-Entry

Patients who meet the following criterion will be excluded from study re-entry:

- Use of prohibited concomitant therapy since enrolling in the extension study

END OF STUDY

The end of the study is defined as the date when the last patient completes his or her final study visit.

LENGTH OF STUDY

Patients in this study will receive treatment or undergo observation for up to approximately 2 years.

INVESTIGATIONAL MEDICINAL PRODUCTS

The investigational medicinal product for this study is efmarodocokin alfa.

Treatment with efmarodocokin alfa 60 μg/kg Q4W will be administered by IV infusion.

STATISTICAL METHODS

Data collected from the final visit of the parent study will serve as baseline (Study Week 0) data for the extension study.

PRIMARY ANALYSIS

The safety analysis population will consist of all patients who received at least one dose of study drug.

Safety will be assessed through descriptive summaries of adverse events and laboratory test results.

DETERMINATION OF SAMPLE SIZE

Approximately 48 patients will be enrolled in parent study GA29469, and approximately 270 patients will be enrolled in parent study GA39925. These patients will be potentially eligible for this extension study.

The purpose of this study is to evaluate the long-term safety and tolerability of efmarodocokin alfa; no formal hypothesis testing will be performed. Assumptions for sample size determination are based on a 52-week study period, in line with the study duration prior to the implementation of Protocol Version 6. Assuming approximately 50% of patients from parent study GA39925 will enter this open-label extension study as non-responders (approximately 135 patients) and 20% of those patients will have sustained clinical remission at the end of the 52-week study period, a total of 135 evaluable patients will provide a 95% confidence interval of 13.3% to 26.7% for the point estimate of 20%. In two different 52-week maintenance Phase III studies in patients with moderate to severely active UC, the percentage of patients randomly assigned to the placebo arm and who had at least one severe adverse event was 6.6% (13/198) and 13.5% (37/275) respectively. Assuming a 52-week serious adverse event rate of 6.6% or 13.5% for efmarodocokin alfa in Study GA40209, 135 evaluable patients will provide a 95% confidence interval of 3% to 12% or a 95% confidence interval of 8% to 20%, respectively.

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
AIS	adenocarcinoma in situ
AZA	azathioprine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CIN	cervical intraepithelial neoplasia
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DE	disease evaluation (visit)
DLT	dose-limiting toxicity
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
FDA	Food and Drug Administration
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HSIL	high-grade squamous intraepithelial lesion
HV	healthy volunteer
IBD	inflammatory bowel disease
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
IxRS	interactive voice or web-based response system
LFT	liver function test
MCS	Mayo Clinic Score
mMCS	modified Mayo Clinic Score
MMF	mycophenolate mofetil
MTX	methotrexate
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug

Abbreviation	Definition
PD	pharmacodynamic
PGA	Physician's Global Assessment
PK	pharmacokinetic
pMCS	partial Mayo Clinic Score
PRO	patient-reported outcome
PRO2	Patient-Reported Outcome-2
Q2W	every 2 weeks
Q4W	every 4 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
SARS-CoV-2	*severe acute respiratory syndrome coronavirus 2*
SES-CD	Simple Endoscopic Score for Crohn's Disease
SUSAR	suspected unexpected serious adverse reaction
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON INFLAMMATORY BOWEL DISEASE

Ulcerative colitis (UC) and Crohn's disease (CD), the two most common types of inflammatory bowel disease (IBD), are chronic inflammatory conditions of the colon and gastrointestinal (GI) tract, respectively. Both diseases have the potential for extra-intestinal complications. Although there are many risk factors associated with the development of UC and CD, these diseases fundamentally represent 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. CD is characterized by patchy, transmural inflammation of the GI tract with areas of normal mucosa between diseased areas. Patients with CD can present with a variety of symptoms, including nausea, vomiting, abdominal pain, and diarrhea. In addition, patients can present with intestinal obstructions, fistulas, or abscesses. The incidence of UC ranges globally from 6.3 to 24.3 cases per 100,000 persons per year, and the prevalence ranges globally from 4.9 to 505.0 cases per 100,000 persons. The incidence of CD ranges globally from 0.0 to 20.2 cases per 100,000 persons per year, and the prevalence ranges globally from 0.6 to 322.0 cases per 100,000 persons (Molodecky et al. 2012). The incidence and prevalence vary among regions of the world, with the highest estimates occurring in European and Northern American populations. 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 IBD currently includes anti-inflammatory drugs (corticosteroids and aminosalicylates such as 5-aminosalicylic acid [5-ASA]), tumor necrosis factor (TNF) inhibitors and other immunosuppressants (such as azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]), and anti-$\alpha 4\beta 7$ integrin agents (such as vedolizumab). Newer therapies aim to modify the disease by inducing mucosal healing, decrease dependence on corticosteroids, and 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 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 IBDs such as CD 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–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 in these studies suggest that elevations in REG3A are likely a maximum concentration (C_{max})–driven event (i.e., associated with peak exposure levels) and that this response is reversible and not sustainable in the absence of exposure, making REG3A a PD biomarker suggestive of IL-22R target engagement.

Toxicology studies of up to 6 month's 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 for additional details). At the highest IV dose (120 μg/kg), 3 of 4 HVs experienced protocol-defined dermatologic dose-limiting toxicities (DLTs).

Mild to moderate elevations in C-reactive protein (CRP) (which were predicted on the basis of nonclinical studies) were reported and were assessed by the investigator as related to efmarodocokin alfa in some subjects. All other 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 efmarodocokin alfa. No clinically significant changes or findings were noted from vital signs measurements, 12-lead ECGs, or body weight measurements for this study.

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

Anti-drug antibodies (ADAs) occurred in 1 of 44 subjects (2.3%). 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 in this dose cohort 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

Study GA40209 is an optional, open-label extension study that is part of an ongoing program to collect data on the benefit-risk profile of treatment with efmarodocokin alfa in patients with moderate to severe UC or CD. This study is designed to assess the long-term safety and tolerability of efmarodocokin alfa 60 μg/kg IV and to obtain long-term data on the effectiveness, immunogenicity, and exposure of efmarodocokin alfa.

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 IBD, 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). 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.

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 IBD.

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 clinical and nonclinical studies and additional safety information.

Because efmarodocokin alfa is an agonist, intermittent drug exposure (rather than continuous drug exposure) may be required for a therapeutic effect and a supportive benefit-risk profile. As such, Study GA40209 will enable the Sponsor to gather preliminary data on the benefit-risk profile, including immunogenicity of intermittent treat-to-remission strategy. This study is designed to minimize potentially unnecessary

exposure during Phase III studies and to understand the benefit-risk profile in specific populations from the parent studies GA29469 and GA39925 (described below).

This open-label extension study GA40209 will provide an additional management option for patients and will actively exclude patients only on the basis of potential or identified safety risks of treatment with efmarodocokin alfa. The study design and duration and the inclusion of specific responder and non-responder populations (as defined in Sections 3.1.4.1 and 3.1.4.2 and described below) will allow the Sponsor to assess the potential benefits and risks of the dosing strategy and inform Phase III study designs, dosing, and safety management plans.

Vedolizumab and Placebo Non-Responders

Allowing vedolizumab and placebo non-responders to enter Study GA40209 provides patients an additional disease-management option. In addition, the study enables the Sponsor to gather more data on the benefit-risk profile of treatment with efmarodocokin alfa in patients with active disease who have never been exposed to efmarodocokin alfa.

It is known that patients treated with vedolizumab can take longer to achieve clinical response (up to 10 weeks per summary of product characteristics). For patients randomly allocated to the vedolizumab arm (in parent study GA39925), Study GA40209 provides another option for patients treated with vedolizumab who have not subjectively improved or met protocol-defined response criteria at Week 8 and cannot wait until 10 weeks to assess if vedolizumab is working for them or to receive an additional dose of vedolizumab at Week 14 per label. As Study GA40209 is optional, patients may wait to Week 10 to assess if vedolizumab is working prior to deciding on enrolling in this study or continuing vedolizumab outside of the study.

Efmarodocokin Alfa Non-Responders

Inclusion of efmarodocokin alfa non-responders will enable the Sponsor to gather more data on the benefit-risk profile of continuing efmarodocokin alfa treatment in patients with active disease. The 8-week induction timepoint in parent study GA39925 was chosen to balance seeing a biological effect of efmarodocokin alfa and minimizing time on placebo for patients randomly allocated to the placebo arm. At this time, the optimal induction time period is not known. In addition, patients may subjectively improve with efmarodocokin alfa in parent study GA39925 but be classified per protocol as non-responders (e.g., decline in stool frequency from 20 to 10 times per day with no change in stool frequency subscore). Therefore, protocol-defined non-responders to efmarodocokin alfa are not actively excluded from Study GA40209. Inclusion of these patients from parent study GA39925 enables a preliminary assessment of the benefit-risk of longer duration of treatment, in particular, for more refractory populations (e.g., anti-TNF inadequate responders). In addition, for more refractory populations, combination therapy is often required to induce response and remission.

For all non-responders in parent study GA39925, Study GA40209 will provide a preliminary assessment of combination therapy strategies with concomitant medications prohibited or not used in parent study GA39925 (e.g., use of steroids for patients not on steroids or use of higher doses of steroids). Furthermore, this study will provide an additional option for patients for whom the benefit-risk of continuing in Study GA40209 may be preferred over pursuing other clinical trials or treatment options (e.g., patients who are subjectively improving but do not meet protocol-defined response criteria).

Vedolizumab Responders

Vedolizumab responders from parent study GA39925 are not excluded should the patient want to switch to efmarodocokin alfa. Those patients also have the option to continue vedolizumab outside of the study. For vedolizumab responders (in particular for those who have not achieved clinical remission), Study GA40209 is a preliminary assessment of the benefit-risk of switching to efmarodocokin alfa.

Placebo Responders

Placebo responders are not excluded should the patient choose to receive efmarodocokin alfa, in particular those patients who have not achieved clinical remission. Inclusion of placebo responders will provide further data on the benefit-risk of treatment with efmarodocokin alfa.

Efmarodocokin Alfa Responders

For patients who responded to efmarodocokin alfa in the parent studies, Study GA40209 provides the option to continue efmarodocokin alfa treatment as they would be excluded from future controlled trials with efmarodocokin alfa. Study GA40209 will provide preliminary data to understand the benefit-risk of further treatment for patients who respond to efmarodocokin alfa and the durability of remission off-treatment to help assess the benefit-risk including immunogenicity of a treat-to-remission strategy. Study GA40209 will provide preliminary information as to whether or not this dosing strategy should be studied further in Phase III.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the long-term safety and tolerability of efmarodocokin alfa in patients with moderate to severe UC or CD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, and exposure of efmarodocokin alfa. Specific objectives and corresponding endpoints for the study are outlined below. For endpoint determination, endoscopic scores will be based on interpretation by a central reader.

In this protocol, "study drug" refers to efmarodocokin alfa.

Table 1 Objectives and Corresponding Endpoints

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of efmarodocokin alfa	• 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 efmarodocokin alfa administration
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of efmarodocokin alfa	• Clinical response [a] at Weeks 28, 52, 80, and 104 • Clinical remission [b] at Weeks 28, 52, 80, and 104 • Durability of clinical remission, defined as time from achieving clinical remission [b] to loss of clinical remission [b] • Change from baseline (i.e., either the baseline score in the parent study or the last score prior to initiation of the most recent course [c] of efmarodocokin alfa during the extension study, whichever score is the most recent) in PRO2 in patients with Crohn's disease
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between long-term drug exposure and the safety and efficacy of efmarodocokin alfa	• Relationship between serum concentration or PK parameters for efmarodocokin alfa and exploratory efficacy endpoints • Relationship between serum concentration or PK parameters for efmarodocokin alfa and safety endpoints
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to efmarodocokin alfa	• Presence of ADAs to efmarodocokin alfa during the study relative to the presence of ADAs at baseline (Study Week 0)
• **Exploratory Biomarker Objective**	• **Corresponding Endpoint**
• To identify biomarkers that can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in stool and colonic tissue (listed in Section 4.5.6) and efficacy, safety, or immunogenicity endpoints

ADA = anti-drug antibody; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PK = pharmacokinetic; PRO2 = Patient-Reported Outcome-2.

Note: For endpoint determination, endoscopic scores will be based on interpretation by a central reader.

[a] Clinical response during the extension study, as defined in Section 3.1.4.2.

[b] Clinical remission during the extension study, as defined in Section 3.1.4.3.

[c] Efmarodocokin alfa 60 μg/kg IV Q4W.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This open-label extension study (GA40209) will evaluate the long-term safety and tolerability of efmarodocokin alfa in patients with moderate to severe UC or CD. In addition, the study will obtain long-term data on the efficacy, immunogenicity, and exposure of efmarodocokin alfa. This study will enroll up to approximately 320 patients from Phase Ib Study GA29469 and Phase II Study GA39925 (parent studies). *Enrollment numbers may be less based on the actual number of patients who rollover into Study GA40209.* Criteria for enrollment in the extension study are outlined in Sections 4.1.1 and 4.1.2.

3.1.2 Efmarodocokin Alfa Administration

Patients enrolled in the extension study will receive efmarodocokin alfa treatment or undergo observation for up to approximately 2 years (through Week 104), as determined on the basis of the patient's disease status, as outlined in Table 2. Upon entry into the extension study, patients will receive efmarodocokin alfa 60 μg/kg IV Q4W or undergo observation, depending on their disease status at the time of their last endoscopy in the parent study. The first dose of efmarodocokin alfa in the extension study may not be administered less than 2 weeks after last dose of study drug in parent study. During the extension study, patients will receive efmarodocokin alfa 60 μg/kg IV Q4W or undergo observation, depending on their disease status at a scheduled visit or a disease evaluation visit (details on disease evaluation visits are provided in Section 3.1.5).

Table 2 Efmarodocokin Alfa Treatment Algorithm

Patient's Disease Status	Action to Be Taken
Meets criteria for clinical remission [a]	• Discontinue efmarodocokin alfa (if applicable) • Undergo observation and assessments per schedule of activities (see Appendix 1)
Does not meet criteria for clinical remission [a]	• Receive efmarodocokin alfa 60 μg/kg IV Q4W until clinical remission is achieved [b] • Undergo assessments per schedule of activities (see Appendix 1)
Meets criteria for disease flare [c] (off treatment) after entry into study	• Consult with Medical Monitor to determine appropriate course of action prior to administration of efmarodocokin alfa (if applicable)
Experiences disease worsening as a result of efmarodocokin alfa treatment, in the investigator's judgment, or disease flare while receiving efmarodocokin alfa [c]	• Permanently discontinue efmarodocokin alfa • Initiate rescue therapy at discretion of investigator • Undergo safety follow-up assessments 8 weeks after final dose of efmarodocokin alfa [d]

Q4W = every 4 weeks.

[a] Clinical remission during the extension study, as defined in Section 3.1.4.3.

[b] First dose of efmarodocokin alfa in the extension study to be administered no less than 2 weeks after last dose of study drug in parent study

[c] Disease flare during the extension study, as defined in Section 3.1.4.4.

[d] See Section 3.1.6 and Appendix 1 for details regarding safety follow-up.

3.1.3 Study Participation during Year 2

The duration of the study *has been* extended from 1 year to 2 years with the implementation of Protocol Version 6. Patients who completed the study through Week 52 (Year 1) prior to the implementation of Protocol Version 6 may *still* be eligible for an additional year of treatment and/or observation, provided that certain criteria are met, as outlined in Table 4. Participation during Year 2 is not required for such patients, and those who do not participate will be considered to have completed the study per protocol, provided required safety follow-up assessments have been completed.

Table 3 Algorithm for Continued Study Participation during Year 2

Patient Disposition Status at Time of Implementation of Protocol Version 6	Action to Be Taken
Has not yet reached Week 52	• Patient will continue study treatment or observation through Week 104 per algorithm in Table 2.
Has completed Week 52 visit but has not yet completed required safety follow-up assessments	• Patient may resume study treatment or observation through Week 104 per algorithm in Table 2. If resuming study treatment, there must be a minimum of 2 weeks since the last dose of efmarodocokin alfa. [a]
Has completed Week 52 visit and required safety follow-up assessments [b]	• Re-consent patient within 8 weeks of implementation of Protocol Version 6. • Conduct study re-entry screening assessments (including endoscopy) over a 3-week period to confirm study eligibility per criteria outlined in Section 4.1 and evaluate disease status. Daily diary recording will be re-initiated to enable collection of patient-reported outcome data for MCS, CDAI, and PRO2 assessments (see Section 4.5.4). • If eligible for study re-entry, patient will resume study treatment (within 1 week of establishing eligibility) or undergo observation through Week 104 per algorithm in Table 2.

CDAI = Crohn's Disease Activity Index; MCS = Mayo Clinic Score; PRO2 = Patient-Reported Outcome-2.

[a] If resuming study treatment, there will be no visit window deviation if there is a minimum of 2 weeks since the last dose of efmarodocokin alfa.

[b] Also includes patients who have completed Week 52 visit but do not require safety follow-up assessments because they did not receive efmarodocokin alfa during the study.

3.1.4 Key Definitions for the Study

3.1.4.1 Definitions for Clinical Response during Study GA29469

For some patients from Study GA29469, entry into the extension study will be based on whether the patient met criteria for clinical response (see Section 4.1.1). Definitions for clinical response during Study GA29469 are provided below for patients with UC and patients with CD. In these definitions, "baseline" refers to the baseline score in the parent study.

For patients with UC, clinical response during the parent study is defined as meeting both of the following:

- A ≥ 3-point decrease from baseline in modified Mayo Clinic Score (mMCS)

  mMCS is a composite of three Mayo Clinic Score (MCS) assessments: stool frequency, rectal bleeding, and centrally read endoscopy (see Appendix 2).

- A ≥1-point decrease from baseline in Mayo rectal bleeding subscore or a Mayo rectal bleeding subscore of 0 or 1

For patients with CD, clinical response during the parent study is defined as meeting any one of the following:

- A ≥100-point decrease from baseline in Crohn's Disease Activity Index (CDAI) (see Appendix 6)
- For patients with a baseline CDAI of <250: a CDAI of <150 combined with a ≥70-point decrease from baseline in CDAI
- A ≥50% decrease from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) (see Appendix 7)

3.1.4.2 Definitions for Clinical Response during the Extension Study

Definitions for clinical response during the extension study are provided below for patients with UC and patients with CD. In these definitions, "baseline" refers to either the baseline score in the parent study or the last score prior to initiation of the most recent course of efmarodocokin alfa 60 μg/kg IV Q4W during the extension study, whichever score is the most recent.

For patients with UC, clinical response during the extension study is defined as meeting one of the following:

- A ≥3-point decrease from baseline in mMCS and a ≥1-point decrease from baseline in Mayo rectal bleeding subscore or a Mayo rectal bleeding subscore of 0 or 1
- Achievement of clinical remission as defined in Section 3.1.4.3

For patients with CD, clinical response during the extension study is defined as meeting any one of the following:

- A ≥100-point decrease from baseline in CDAI
- For patients with a baseline CDAI of <250: a CDAI of <150 combined with a ≥70-point decrease from baseline in CDAI
- A ≥50% decrease from baseline in SES-CD
- Achievement of clinical remission as defined in Section 3.1.4.3

3.1.4.3 Definitions for Clinical Remission during the Extension Study

Definitions for clinical remission during the extension study are provided below for patients with UC and patients with CD.

For patients with UC, clinical remission is defined as meeting both of the following:

- mMCS of ≤2
- Mayo rectal bleeding subscore of 0 and other Mayo subscores of ≤1

For patients with CD, clinical remission is defined as meeting one of the following:

- Patients with disease restricted to the ileum: CDAI of <150 and SES-CD of ≤ 2
- Patients with disease not restricted to the ileum: CDAI of <150, SES-CD of ≤ 4, and no ulcerations

3.1.4.4 Definitions for Disease Flare during the Extension Study

Definitions for disease flare during the extension study are provided below for patients with UC and patients with CD. In these definitions, "lowest pMCS" and "lowest CDAI" refer to the lowest score after completion of treatment in either Study GA29469 or Part A of Study GA39925, or completion of the most recent course of efmarodocokin alfa 60 μg/kg IV Q4W during the extension study, whichever is the most recent.

For patients with UC, disease flare is defined as meeting any one of the following:

- A ≥ 3-point increase in partial MCS (pMCS) relative to the lowest pMCS and an absolute pMCS of ≥ 5 and a locally read 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 a locally read endoscopy subscore of ≥ 2

For patients with CD, disease flare is defined as meeting both the following:

- A CDAI of ≥ 220 at two consecutive visits (may include unscheduled visits)
- A ≥ 70-point increase in CDAI, at two consecutive visits (may include unscheduled visits), relative to the lowest CDAI

The schedule of activities is provided in Appendix 1.

3.1.5 Disease Evaluation Visits

Patients with worsening disease, as determined by the investigator, should return to the clinic as soon as possible for a disease evaluation visit. The investigator may also schedule a disease evaluation visit to determine if a patient has achieved clinical remission. Patients with UC will undergo a flexible sigmoidoscopy and MCS evaluation at the disease evaluation visit. Patients with CD will undergo an ileocolonoscopy and CDAI evaluation, with one exception: Patients who experience worsening disease while receiving efmarodocokin alfa will not undergo an ileocolonoscopy unless the visit corresponds to a time when an ileocolonoscopy is already scheduled to occur.

After determination of the patient's disease status, the investigator may initiate or discontinue treatment with efmarodocokin alfa as appropriate (see efmarodocokin alfa treatment algorithm in Table 2).

3.1.6 Safety Follow-Up Visit and Early Termination Visit

Patients will undergo safety follow-up or early termination assessments as outlined below:

- Patients who receive at least one dose of efmarodocokin alfa must undergo safety follow-up assessments 8 weeks after their final dose of study drug.

  Patients who discontinue the study prematurely (prior to Week 104) and have received at least one dose of efmarodocokin alfa should return to the clinic for an early termination visit within 1 week. Patients who discontinue prematurely without having undergone at least 8 weeks of follow-up (observation) after their final dose of efmarodocokin alfa should also return to the clinic for a safety follow-up visit 8 weeks after their final dose.

  Patients who are unwilling to complete the safety follow-up visit should return to the clinic for an early termination visit no later than 30 days after their final dose.

- Patients who discontinue the study prematurely (prior to Week 104) and have not received efmarodocokin alfa should return to the clinic for an early termination visit within 30 days. Follow-up assessments are not required for patients who discontinue the study at Week 104 without having received efmarodocokin alfa.

For patients who complete Week 52 and safety follow-up assessments prior to the implementation of Protocol Version 6 and re-enter the study, safety follow-up is to be repeated for Year 2, as outlined above. Details regarding assessments at the safety follow-up visit and the early termination visit are provided in Appendix 1.

Patients who permanently discontinue study drug can receive rescue therapy at the investigator's discretion.

3.1.7 Corticosteroids

For patients on concomitant oral corticosteroids, the corticosteroid dose should be tapered until discontinuation. The corticosteroid tapering schedule may be at the discretion of the investigator. For patients who receive a course of efmarodocokin alfa 60 μg/kg IV Q4W, tapering should be initiated once the patient is stable, based on the investigator's judgment. Patients who cannot tolerate up to two corticosteroid taper attempts without experiencing recurrence of IBD symptoms or symptoms of corticosteroid withdrawal will be discontinued from the study as outlined in Section 4.6.1. Any patient requiring corticosteroids above the baseline dose (with baseline defined as either the baseline dose in the parent study or the last dose prior to initiation of the most recent course of efmarodocokin alfa 60 μg/kg IV Q4W during the extension study, whichever dose is the most recent) should be discontinued from the study.

3.1.8 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, Biostatistics, and Statistical Programming and Analysis, and may invite representatives from other functional areas (e.g., Clinical Pharmacology, Research) or external experts on an ad hoc basis. 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. 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. In addition to reviews on a periodic basis, ad hoc reviews may be requested by the IMC or the Sponsor at any time to address potential safety concerns. An interim efficacy analysis for parent Study GA39925 will be performed by the IMC (see Protocol GA39925, 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.
- 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, including making further dose and duration adjustments to optimize benefit-risk. 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 Institutional Review Boards (IRBs)/Executive Committees (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

Patients in this study will receive treatment or undergo observation for up to approximately 2 years. The end of the study is defined as the date when the last patient completes his or her final study visit.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Efmarodocokin Alfa Dose and Schedule

The dose regimen of efmarodocokin alfa 60 μg/kg IV Q4W was selected on the basis of an integrated analysis of the clinical, PK, and PD data from the completed Phase Ia study (GA29468) and data from the Phase Ib study (GA29469). The 60 μg/kg IV Q4W regimen would provide a preliminary assessment of the benefit-risk of a treat-to-remission strategy to help inform the Phase III studies. The 60 μg/kg Q4W regimen enables drug exposure within the tolerable exposure range to evaluate whether efmarodocokin alfa is safe and efficacious in patients with UC or CD.

The dose regimen tested in Study GA40209 is similar to the highest dose regimen tested in the Phase II parent study GA39925 (90 μg/kg IV Q4W in the first 8 weeks of treatment and 60 μg/kg IV Q8W during the 4−month maintenance phase). The benefit-risk profile of the 60 μg/kg IV Q4W regimen is anticipated to be similar to this regimen with a 33% lower C_{max} (60 μg/kg IV Q4W vs. 90 μg/kg IV Q8W, respectively) during the first 8 weeks, but 2 times higher exposure over the subsequent 4 months (60 μg/kg IV Q4W vs. 60 μg/kg IV Q8W, respectively). The dose regimen in Study GA40209 may be adjusted on the basis of emerging data from the parent study GA39925 as described above.

3.3.2 Rationale for Pharmacokinetic Sample Collection

This study will employ a sparse PK sampling schedule to allow for assessment of potential relationships between long-term drug exposure and the safety and efficacy of the study drug.

3.3.3 Rationale for Biomarker Assessments

Biomarkers will be assessed in stool and colonic tissue to demonstrate evidence of biologic activity of efmarodocokin alfa in patients with UC and CD. The relationship between stool and colonic tissue biomarkers and safety and immunogenicity endpoints may also be explored. The assessment of biomarkers may include, but not be limited to, measurement of DMBT1 in colonic tissue biopsies.

4. MATERIALS AND METHODS

4.1 PATIENTS

Up to approximately 320 patients with moderate to severe UC or CD from Study GA29469 or Study GA39925 will be enrolled in this study.

4.1.1 Inclusion Criteria

4.1.1.1 Inclusion Criteria for Study Entry

Patients must meet the following criteria for study entry:

- Prior enrollment in Study GA29469 or Study GA39925, with one of the following having occurred during that study:

  Patients previously enrolled in Study GA29469

  - Unable to achieve clinical response (defined for patients with UC and CD in Section 3.1.4.1) during the study and completion of the study through at least Day 85
  - Initiation of protocol-defined rescue therapy during the study and completion of the study through at least Day 85
  - Completion of the study through Day 134

  Patients previously enrolled in Study GA39925

  - Unable to achieve protocol-defined clinical response by Week 8
  - Initiation of protocol-defined rescue therapy during the study and completion of the study through at least Week 8
  - Protocol-defined disease flare after Week 8
  - Completion of the study through Week 30
- Age 18–80 years, inclusive, at time of signing Informed Consent Form

4.1.1.2 Inclusion Criteria for Study Entry and Study Re-Entry

Patients must meet the following criteria for study entry and study re-entry:

- Signed Informed Consent Form (at time of initial entry and again at time of study re-entry)
- Ability to comply with requirements of the study, in the investigator's judgment
- 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 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925 (due to the possibility of receiving vedolizumab), whichever is longer

  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, Clinical Trial Facilitation Group, final version, dated 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 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925, whichever is longer, 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.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusion Criteria for Study Entry

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

- Withdrawal of consent from parent study
- Discontinuation of study drug as required by the parent study protocol
- Discontinuation of study drug and withdrawal from Study GA29469 prior to Day 85 or from Study GA39925 prior to Week 8
- Non-compliance in the parent study, specifically defined as missing scheduled visits or non-adherence with background medications and concomitant medications

4.1.2.2 Exclusion Criteria for Study Entry and Study Re-Entry

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925 (due to the possibility of receiving vedolizumab), whichever is longer
- Any new malignancy since enrolling in the parent study
- Any new significant uncontrolled comorbidity, such as cardiac, pulmonary, renal, hepatic, endocrine, or GI disorders, since enrolling in the parent study
- Any new signs or symptoms of infection judged by the investigator to be clinically significant since enrolling in the parent study
- Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF) since enrolling in the parent study
- Prior treatment with etrolizumab, natalizumab, efalizumab, or any other anti-integrin agents (other than vedolizumab)

- Use of IV corticosteroid or topical corticosteroid (i.e., enemas or suppositories) at the time of entry into this study
- Abnormal laboratory value recorded at the last visit in the parent study, as defined below:
  - Hemoglobin < 90 g/L (9 g/dL)
  - Serum creatinine $> 1.5 \times$ upper limit of normal (ULN)
  - ALT, AST, or ALP $> 2.5 \times$ 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 $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.5 \times 10^9$/L (1500/μL)
  - Absolute lymphocyte count $< 0.5 \times 10^9$/L (500/μL)

4.1.2.3 Exclusion Criterion for Study Re-Entry

Patients who meet the following criterion will be excluded from study re-entry:

- Use of prohibited concomitant therapy, as outlined in Section 4.4.2.2, since enrolling in the extension study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

All patients in this study will have the opportunity to receive treatment with efmarodocokin alfa at a dose of 60 μg/kg IV Q4W until remission is achieved. All patients, study site personnel, Sponsor agents, and Sponsor personnel will be unblinded to the treatment assignment of this study; however, the treatment assignment from the parent study will remain blinded until the parent study is unblinded.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for this study is efmarodocokin alfa.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Efmarodocokin Alfa

Efmarodocokin alfa 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.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimen is summarized in Section 3.1.2. 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.

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 5.1.2.

4.3.2.1 Efmarodocokin Alfa

Efmarodocokin alfa will be administered by IV infusion, with the initial infusion in this study 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, the next infusion may be delivered over 15 (±5) minutes. If the 15-minute infusion is tolerated, all subsequent infusions may be delivered over 5 (±1) minutes. For patients who re-enter the study for the second year, the infusion time upon study re-entry can be reduced to 5 (±1) minutes if the 15-minute infusion was tolerated during the first year of the study; otherwise, the infusion time will be equivalent to the last tolerated infusion time prior to study re-entry.

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 efmarodocokin alfa infusions, 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.

4.3.3 Investigational Medicinal Product Accountability

The IMP required for completion of this study (efmarodocokin alfa) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMP supplied by the Sponsor, using the interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP 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 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

Currently, the Sponsor (Genentech, a member of the Roche Group) does not have any plans to provide Genentech IMP (efmarodocokin alfa) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing efmarodocokin alfa in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, 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 from entry into the extension study to the final visit of the extension study. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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 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 Rescue Therapy

The initiation of rescue therapy for patients with UC or CD will require permanent discontinuation of study treatment. Rescue therapy is defined as follows:

- Initiation of IV corticosteroid or rectal corticosteroid (i.e., enemas or suppositories)
- Initiation of oral corticosteroid or increase in dose of oral corticosteroid compared with baseline, with baseline defined as either the baseline dose in the parent study or the last dose prior to initiation of the most recent course of efmarodocokin alfa 60 μg/kg IV Q4W during the extension study, whichever dose is the most recent

  For patients receiving ongoing concomitant oral corticosteroids upon entry into the study, the corticosteroid dose should be tapered until discontinuation as described in Section 3.1.7.
- Initiation of immunosuppressants (i.e., AZA, 6-MP, MTX, or TNF inhibitors)
- Initiation of natalizumab, etrolizumab, efalizumab, or other anti-integrin agents
- Initiation of cyclosporine, tacrolimus, sirolimus, or MMF
- Initiation of tofacitinib
- Initiation of ustekinumab

4.4.2 Other Concomitant Therapy

4.4.2.1 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
- Topical or oral 5-ASA

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 Prohibited Concomitant Therapy

Use of the following therapies is prohibited as specified below:

- Initiation of oral probiotics or increase in dose of oral probiotics compared with baseline, with baseline defined as either the baseline dose in the parent study or the last dose prior to initiation of the most recent course of efmarodocokin alfa 60 μg/kg IV Q4W during the extension study, whichever dose is the most recent
- Use of rituximab
- Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab)
- Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs)

  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)

  Use of antiplatelet agents, such as aspirin up to 325 mg/day or clopidogrel, is permitted.
- Apheresis (e.g., Adacolumn® apheresis)
- Use of an investigational drug

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 final dose of efmarodocokin alfa.

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.

Data collected from the final visit of the parent study will serve as Study Week 0 (initial visit) data for the extension study. Procedures and assessments that were performed at the final visit of the parent study do not need to be repeated at Study Week 0, with the exception of the ADA sample. A baseline ADA sample should be collected at baseline (Study Week 0).

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 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 the extension study (Study Week 0). In addition, medication use (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) from the time the patient exited the parent study to the time the patient entered the extension study will be recorded. Past resolved adverse events will be recorded in the medical history if clinically significant. Refer to Section 5.3.5.4 for information on recording adverse events that had not resolved at the end of the parent study. 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.

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

For patients who re-enter the study (see Section 3.1.3), adverse events that occur after completion of Week 52 and required safety follow-up assessments but prior to obtaining informed consent for study re-entry should be captured on the General Medical History and Baseline Conditions eCRF (rather than the Adverse Event eCRF), unless it is a serious adverse event related to prior study treatment.

4.5.3 Physical Examinations

A complete physical examination, performed at baseline in the extension study (Study Week 0) 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 postbaseline visits and as clinically indicated. Changes from baseline (Study Week 0) abnormalities should be recorded in patient

notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

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

4.5.5 Clinical Outcome Assessments

Clinical outcome for UC will be assessed through the MCS (see Section 4.5.5.1), which incorporates stool frequency and rectal bleeding as reported by the patient (see Section 4.5.5.4), the PGA as reported by the clinician (see Section 4.5.5.5), and endoscopic evaluations (see Section 4.5.5.6). Clinical outcome for CD will be assessed through the CDAI (see Section 4.5.5.2), which incorporates loose-stool frequency, abdominal pain severity, and general well-being as reported by the patient (see Section 4.5.5.4) as well as other factors assessed by the clinician, and the SES-CD (see Section 4.5.5.3).

4.5.5.1 Mayo Clinic Score, Modified Mayo Clinic Score, and Partial Mayo Clinic Score

The MCS (including mMCS and pMCS) will be assessed in patients with UC.

The MCS is a composite of four assessments, each having a scoring range of 0–3: stool frequency, rectal bleeding, 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).

UC patients are to report their stool frequency and rectal bleeding on a daily basis, as described in Section 4.5.5.4 (see Appendix 5).

4.5.5.2 Crohn's Disease Activity Index and Patient-Reported Outcome-2 Score

The CDAI quantifies the signs and symptoms of patients with CD. The CDAI consists of eight factors; each factor is summed after adjustment with a weighting factor (Best et al. 1979). The components of the CDAI include number of liquid or soft stools (loose-stool frequency), abdominal pain severity, general well-being, presence of complications, use of diphenoxylate/atropine (Lomotil®) or other opiates for diarrhea,

presence of an abdominal mass, hematocrit, and percent deviation from standard weight (see Appendix 6). It is preferred, but not required, that the clinician who completes the CDAI not be the same clinician who assesses adverse events.

The Patient-Reported Outcome-2 (PRO2) evaluates two patient-reported factors: loose-stool frequency and abdominal pain severity (Khanna et al. 2015). The score is calculated using the CDAI-weighted sum of the average loose-stool frequency and abdominal pain scores in a 7-day period.

CD patients are to report their loose-stool frequency, abdominal pain severity, and general well-being on a daily basis, as described in Section 4.5.5.4.

4.5.5.3 Simple Endoscopic Score for Crohn's Disease

The SES-CD will be assessed in patients with CD. SES-CD is assessed through endoscopy and is a composite of four factors, each having a scoring range of 0–3: ulcer size, percentage of ulcerated surface, percentage of surface affected by other lesions, and extent of stenosis. These factors are scored in up to five ileocolonic segments (Daperno et al. 2004). Higher scores indicate more severe disease (see Appendix 7). It is preferred, but not required, that the clinician who completes the SES-CD not be the same clinician who assesses adverse events.

4.5.5.4 Patient-Reported Outcomes

Patient-reported outcome (PRO) data will be collected through use of a diary and/or paper questionnaires. Site staff will provide the diary and/or instructions for completing the questionnaires. Data captured between clinic visits should be reviewed with the patient at each clinic visit. The data will be available for access by appropriate study personnel.

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 4.5.5.1). Patients with UC are to record stool frequency and rectal bleeding in the daily diary throughout the study (see Appendix 5). Because the endoscopy and associated bowel preparation can interfere with the assessment of patient-reported outcomes, diary entries on days of bowel preparation, endoscopy, and the day after

endoscopy will not be used to calculate any stool frequency scores. Stool frequency and rectal bleeding scores from the three most recent diary entries (prior to bowel preparation), the endoscopy, and PGA will be used to calculate an MCS.

Loose-Stool Frequency, Abdominal Pain Severity, and General Well-Being

Loose-stool frequency, abdominal pain severity, and general well-being are components of the CDAI, and abdominal pain severity and loose-stool frequency are components of the PRO2 (see Section 4.5.5.2). Patients with CD are to record loose-stool frequency, abdominal pain severity, and general well-being in the daily diary throughout the study (see Appendix 6). The Bristol Stool Scale will be provided to patients as a reference for determining loose stools (Types 6 and 7 on the Bristol Stool Scale; see Appendix 8). Because the endoscopy and associated bowel preparation can interfere with the assessment of other clinical parameters, diary entries on days of bowel preparation, the day of endoscopy, and the day after endoscopy will not be used to calculate scores for loose-stool frequency, abdominal pain severity, and general well-being.

4.5.5.5 Physician's Global Assessment

PGA data will be collected through use of a paper questionnaire. The PGA is a component of the MCS and pMCS (see Section 4.5.5.1). 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. It is preferred, but not required, that the clinician who completes the PGA not be the same clinician who assesses adverse events.

4.5.5.6 Endoscopy with Biopsies

All patients will undergo an endoscopy, consisting of a flexible sigmoidoscopy for patients with UC and an ileocolonoscopy for patients with CD, with collection of biopsies at specified timepoints during the study and at the disease evaluation/early termination visit. Endoscopy at the early termination visit should be conducted if the investigator deems it necessary. All patients will undergo annual endoscopies for colon cancer surveillance. The endoscopies should include the following:

- Removal of any adenomatous polyps
- Performance of multiple random mucosal biopsies to evaluate for dysplasia

    Annual dysplasia surveillance should be performed according to local guidelines, taking into consideration endoscopic technique as well as the appropriateness of performing surveillance for dysplasia in the presence of active inflammation. Surveillance may be delayed per local guidelines (i.e., if there is extensive active inflammation) to enable more accurate pathologic diagnosis.

Every effort should be made to schedule on-treatment endoscopies on the same day as the protocol-specified study visit.

Bowel preparation prior to the endoscopy 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 endoscopy 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 are provided in the laboratory manual.

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 objectively document disease activity. Mayo endoscopic subscore (for patients with UC) and the endoscopy-based components of the SES-CD (for patients with CD) will be calculated on the basis of centrally read patient videos, with one exception: for the determination of disease flare in patients with UC, the Mayo endoscopic subscore should be locally read to inform treatment decisions.

The clinician who performs the endoscopy will take into account endoscopy findings when completing the PGA (see Section 4.5.5.5).

4.5.6 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 undergo urine pregnancy tests monthly during the study. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Serum pregnancy test, to confirm positive urine pregnancy test
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, LDH
- Lipase and CRP
- Coagulation: INR, aPTT, PT, fibrinogen
- 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.

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

- Serum samples for study drug PK analysis

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

- Serum samples for study drug immunogenicity (ADA) analysis

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

    Baseline (Study Week 0) samples will be analyzed for all patients.

    Postbaseline ADA samples will be analyzed for all patients receiving study drug.

- Stool samples for exploratory research on biomarkers that may include, but will not be limited to, bacterial DNA
- Colonic tissue samples obtained by biopsy performed during screening and subsequent endoscopic procedures (flexible sigmoidoscopy, ileocolonoscopy, 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 4.5.8), 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 assay characterization as well as assay development and validation. Therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- 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.

4.5.7 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 QT interval corrected through use of Fridericia's formula (QTcF), based on the machine readings of the individual ECG tracings. Clinically significant waveform changes or other ECG abnormalities (see Section 5.3.5.7) must be documented as adverse events 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 value at Study Week 0 (initial visit), 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).

4.5.8 Optional Samples for Research Biosample Repository

4.5.8.1 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

4.5.8.2 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 4.5.8) will not be applicable at that site.

4.5.8.3 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 disease biology:

- 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, 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).

4.5.8.4 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.

4.5.8.5 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.

4.5.8.6 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 samples 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 GA40209 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 GA40209.

4.5.8.7 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)
- Inability to tolerate corticosteroid taper (see Section 3.1.7)
- Disease flare (as defined in Section 3.1.4.4) while receiving efmarodocokin alfa
- Disease worsening as a result of efmarodocokin alfa treatment, in the investigator's judgment
- Malignancy or cervical Pap test with cervical intraepithelial neoplasia (CIN) of Grade >1, adenocarcinoma in situ (AIS), or high-grade squamous intraepithelial lesions (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. For other serious or severe infections, see Section 5.1.2.3 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 treatment discontinuation should be documented on the appropriate eCRF. Patients who receive at least one dose of efmarodocokin alfa must

undergo safety follow-up assessments 8 weeks after their final dose of study drug (see Section 3.1.6 and Appendix 1 for more information).

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 or CD

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. Patients who withdraw from the study may be replaced.

Follow-up assessments for patients who discontinue from the study prematurely are described in Section 3.1.6 and Appendix 1.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. For details on cessation of enrollment or stopping of the study, refer to Section 3.1.8 (Internal Monitoring Committee). Reasons for terminating the study 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 International Council for Harmonisation (ICH) 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.

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 maximum tolerated dose 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 were excluded from the parent studies.

Guidelines for management of patients who develop dermatologic reactions are provided in Section 5.1.2.3.

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 (GA29468) and the Phase Ib multiple-dose study (GA29469), 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) were excluded from Study GA39925. Patients with a history of anaphylaxis, hypersensitivity, or drug allergies to human or humanized antibodies or fusion proteins were excluded from Study GA29469. Anaphylaxis and hypersensitivity reactions will be closely monitored.

Guidelines for management of patients who develop infusion-related reactions are provided in Section 5.1.2.3.

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 (Kirchberger et al. 2013; Kryczek et al. 2014). There has been no evidence of epithelial tumor promotion in the Phase Ia study (GA29468), the Phase Ib study (GA29469), 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 IL-22 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 any history of cancer were excluded from Study GA29469. Patients with a history of cancer within the past 5 years and 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) were excluded from Study GA39925. In addition, patients with a history of CIN of Grade >1,

cervical smear indicating the presence of AIS or HSILs, and patients who had evidence of unresectable colonic mucosal dysplasia or high-grade colonic mucosal dysplasia were excluded from Study GA39925. Patients in both parent studies had to have documentation of colon cancer surveillance within 1 year prior to enrollment.

Guidelines for management of patients who develop epithelial tumor promotion are provided in Section 5.1.2.3.

5.1.1.4 Neutralization of Endogenous IL-22 by Anti-Drug Antibodies

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 IL-22, 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 5.1.2.3.

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 occurs, 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 5.1.2.3.

5.1.2 Management of Patients Who Experience Adverse Events

At this stage of development, the efmarodocokin alfa safety profile is not completely characterized. For any treatment–emergent adverse event that the investigator believes may be related to efmarodocokin alfa, the investigator should consider whether the benefit-risk favors continued dosing for that individual patient (i.e., if the adverse event is improving and if a clear alternate cause can be identified).

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

5.1.2.1 Dose Modifications

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

5.1.2.2 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.

5.1.2.3 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 epithelial tumors (as defined in Table 4) 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 (Study Week 0), at regular intervals during treatment, and during the safety follow-up period 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 [LFTs]) 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., anti-nuclear 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 judgment and local practice. Imaging tests and hepatology consultation should be considered. In addition, a more detailed history of the event should be obtained, including the following: symptoms, prior or current diseases, concomitant drug use (including nonprescription medications and herbal and dietary supplements), alcohol use, recreational drug use, and special diets.

Regarding re-initiation of study drug, the benefit-risk assessment takes alternate causes (e.g., acute viral hepatitis, newly initiated concomitant medication, treated gallstone disease) and reversibility into consideration, but the recommendations for a specific patient are complex and require medical judgment (i.e., consultation between the investigator, medical monitor, and the IMC). In general, re-initiation of study drug can be considered if there is clear evidence that the liver injury is not related to study drug or clearly attributable to other causes (as determined by the IMC), is showing signs of reversibility, and that the benefit-risk of continuing to receive study drug remains favorable. Because establishing a diagnosis of drug-induced liver injury is frequently challenging, the IMC may involve outside hepatology experts or consultants as necessary. If the study drug is re-initiated, there remains a potential risk of recurrence of liver injury due to the possibility of an erroneous causality assessment. Hence, patients will need to be monitored carefully after re-initiation of study drug. If LFTs worsen significantly after re-initiation, study drug should be permanently discontinued.

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 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; 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; 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 $>3\times$ULN to $\leq 5\times$ULN	• Continue study drug. • Repeat LFTs within 48-72 hours. • If LFT results confirmed, test for alternative cause(s) as described in Section 5.1.2.3.
ALT or AST $>5\times$ULN to $\leq 8\times$ULN	• Withhold study drug. • Repeat LFTs within 48-72 hours. • If LFTs confirmed, test for alternative cause(s) as described in Section 5.1.2.3. • Monitor LFTs weekly until AST and ALT $\leq 5\times$ULN. • If event resolves to AST or ALT $\leq 5\times$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 $>8\times$ULN • ALT or AST $>5\times$ULN for more than 2 weeks • ALT or AST $>3\times$ULN and (total bilirubin $>2\times$ULN or INR >1.5) • ALT or AST $>3\times$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 5.1.2.3. • Monitor LFTs two to three times per week until decreasing or stabilized, then monitor LFTs weekly until AST and ALT are $\leq 5\times$ULN and total bilirubin is $\leq 2\times$ULN. • Discontinuation of study drug should be considered. However, if event resolves to AST and ALT $\leq 5\times$ULN with total bilirubin $\leq 2\times$ULN, study drug may be resumed after consultation with the Medical Monitor. In general, re-initiation of study drug can be considered if there is clear evidence that the liver injury is not related to study drug or clearly attributable to other causes (as determined by the IMC), is showing signs of reversibility, and that the benefit-risk of continuing to receive study drug remains favorable (see Section 5.1.2.3). If a decision is made to 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; 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
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 (see 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 (see Section 5.2.3).*
Efmarodocokin alfa-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; 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 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 (Study Week 0)
- 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:

- 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
- New or worsening neurologic signs and symptoms that are consistent with a diagnosis of progressive multifocal leukoencephalopathy
- 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. It is preferred, but not required, that the clinician who assesses adverse events not be the

same clinician who assesses UC or CD 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 for study entry 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 informed consent for study re-entry has been obtained (see Section 3.1.3) 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) or prior study treatment should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug following study entry or study re-entry, all adverse events will be reported until 8 weeks after the final dose of study drug.

Any adverse event that occurs after completion of Week 52 and required safety follow-up assessments but prior to obtaining informed consent for study re-entry should be captured on the General Medical History and Baseline Conditions eCRF rather than the Adverse Event eCRF, unless it is a serious adverse event related to prior study treatment.

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 6):

- 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 gastrointestinal 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

Persistent Adverse Events First Reported in Study GA40209 or in Parent Study

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.

Persistent Adverse Events First Reported in the Parent Study

An adverse event that is ongoing at the end of a parent study will be marked as not resolved in the eCRF for that study and will be reopened in Study GA40209 with the same start date, adverse event term, and severity recorded in the parent study. The severity (NCI CTCAE grade) should be evaluated by the investigator at the start of Study GA40209 and updated in the Adverse Event Intensity or Grade Changes eCRF if applicable.

Recurrent 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., ALP and bilirubin $5 \times$ 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 or CD.

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. If the death is attributed to progression of CD, "Crohn's disease 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 (Study Week 0) visit for this study. Such conditions 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 or Crohn's Disease

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 for patients with UC and the SES-CD for patients with CD, 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
Europe, Middle East, Africa, or 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 No.: [redacted]

Mobile Telephone No.: [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 for study entry has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After informed consent for study re-entry has been obtained (see Section 3.1.3) but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention or prior study treatment 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
Europe, Middle East, Africa, or Asia Pacific	+44 1223 374 102

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug following study entry or study re-entry, serious adverse events and adverse events of special interest will be reported until 8 weeks after the final 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 final dose of study treatment 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 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925, whichever is longer. 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 5.4.1. 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 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 8 weeks after the final dose of study drug or 18 weeks after final dose of study drug from Study GA39925, whichever is longer. 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 5.4.1. 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. 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.

In addition, 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.

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

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 final 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 fax number 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 document listed below:*

Drug	*Document*
Efmarodocokin alfa	*Efmarodocokin Alfa Investigator's Brochure*

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 the 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Data collected from the final visit of the parent study will serve as baseline (Study Week 0) data for the extension study.

Participation during Year 2 is not required for patients who completed the study through Week 52 (Year 1) prior to the implementation of Protocol Version 6, and those who do not participate will be considered to have completed the study per protocol, provided required safety follow-up assessments have been completed.

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 48 patients will be enrolled in parent study GA29469, and approximately 270 patients will be enrolled in parent study GA39925. These patients will be potentially eligible for this extension study.

The purpose of this study is to evaluate the long-term safety and tolerability of efmarodocokin alfa; no formal hypothesis testing will be performed. Assumptions for sample size determination are based on a 52-week study period, in line with the study duration prior to the implementation of Protocol Version 6. Assuming approximately 50%

of patients from parent study GA39925 will enter this open-label extension study as non-responders (approximately 135 patients) and 20% of those patients will have sustained clinical remission at the end of the 52-week study period, a total of 135 evaluable patients will provide a 95% confidence interval of 13.3% to 26.7% for the point estimate of 20%. In two different 52-week maintenance Phase III studies in patients with moderate to severely active ulcerative colitis, the percentage of patients randomly assigned to the placebo arm and who had at least one serious adverse event was 6.6% (13/198) and 13.5% (37/275) respectively (Sandborn et al.; 2017; Feagan et al., 2013). Assuming a 52-week serious adverse event rate of 6.6% or 13.5% for efmarodocokin alfa in Study GA40209, 135 evaluable patients will provide a 95% confidence interval of 3% to 12% or a 95% confidence interval of 8% to 20%, respectively.

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. Eligibility and other major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

Patients who withdraw from the study, irrespective of final outcome, will be considered as non-responders at analysis. All patients who received efmarodocokin alfa in this study will be pooled for analysis. Further subgroup analysis by dose change during the study or baseline characteristics may be performed if the sample size per subgroup is sufficient.

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.

6.4 SAFETY ANALYSES

The safety analysis population will consist of all patients who received at least one dose of study drug.

The safety analysis will contribute to the evaluation of the dosing strategy in the enrolled population over the study period, the impact of total cumulative dose received in consecutive months, the impact of intermittent dosing, the impact of total amount of drug received (including dose adjustments) or total number of infusions during the study. Safety will be analyzed through descriptive summaries of adverse events, laboratory test results, and clinical data on the basis of, but not limited to, the following:

- All patients who receive at least one dose of study drug

- Total dose received overall
- Total number of infusions overall
- Total number of consecutive monthly doses
- Maximum total cumulative dose received in consecutive months

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.

6.5 EXPLORATORY EFFICACY ANALYSES

The analysis population for the efficacy analyses will consist of all patients.

The exploratory efficacy endpoints will be summarized by descriptive statistics based on the following calculations, with clinical response and clinical remission as defined in Sections 3.1.4.2 and 3.1.4.3.

- Proportion of patients with a clinical response
- Proportion of patients with a clinical remission
- Time from clinical remission to loss of clinical remission
- Change from baseline (i.e., either the baseline score in the parent study or the last score prior to initiation of the most recent course of efmarodocokin alfa 60 μg/kg IV Q4W during the extension study, whichever score is the most recent) in PRO2 for patients with CD

6.6 EXPLORATORY PHARMACOKINETIC ANALYSES

Serum study drug concentrations at selected timepoints will be summarized by descriptive statistics. Some of the covariate effects (e.g. patient demographics or disease status at the time of entry) on exposure will also be evaluated. The relationship between serum concentration and some efficacy or safety endpoints will be explored.

6.7 EXPLORATORY IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one postbaseline ADA assessment.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (Study Week 0) (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized. 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, safety, PK, and biomarker endpoints will be analyzed and reported via descriptive statistics.

6.8 EXPLORATORY BIOMARKER ANALYSES

The biomarker data may be summarized descriptively.

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 paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 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 7.5.

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.

7.4 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.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, 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.

The Sponsor 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), the General Data Protection Regulation (2016/679), and applicable local, regional, and national laws.

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 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 Informed Consent Form (see Section 8.2).
- Patients with the potential of exposure to any coercion will be excluded from the parent study (see Study GA39925, Section 4.1.2); therefore, they will not be eligible for Study GA40209.

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, mMCS, and SES-CD 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 4.5.6. 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.

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 Study Information 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).

10. REFERENCES

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Appendix 1
Schedule of Activities

Activity	Baseline	Efmarodocokin Alfa-Specific Activities [b, c] (±5 days)			Q8W, When Not Undergoing Efmarodocokin Alfa-Specific Activities [e] (±1 week)	Ongoing Activities [f]				DE/ET Visit [g]	UV Visit [h]	Re-entry Screening (3 weeks) [i]	Safety FU [j] (±5 days)
	Study Week					Study Week (±2 weeks)							
	0 [a]	Treatment Initiation [d]	Q4W When Not in Clinical Remission	4 and 8 Weeks after Achieving Clinical Remission		28	52	80	104				
Informed consent	x											x [k]	
Review eligibility criteria	x											x	
Medical history and baseline conditions	x											x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [l]	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [m]	x		x	x	x					x	x	x	x
Weight	x	x	x	x	x					x	x	x	x
Complete physical examination [n]	x											x	
Limited physical examination [o]			x	x	x					x	x		x
ECG [p]	x	x	x [p]			x	x	x	x	x		x	x
Hematology [q] and chemistry [r]	x		x	x	x					x		x	x
Lipase, coagulation, and lipids [s] (fasting)	x		x	x		x	x	x	x	x		x	x
CRP	x		x		x					x		x	

Appendix 1
Schedule of Activities (cont.)

Activity	Baseline	Efmarodocokin Alfa-Specific Activities [b, c] (±5 days)			Q8W, When Not Undergoing Efmarodocokin Alfa-Specific Activities [e] (±1 week)	Ongoing Activities [f]				DE/ET Visit [g]	UV Visit [h]	Re-entry Screening (3 weeks) [i]	Safety FU [j] (±5 days)
	Study Week					Study Week (±2 weeks)							
	0 [a]	Treatment Initiation [d]	Q4W When Not in Clinical Remission	4 and 8 Weeks after Achieving Clinical Remission		28	52	80	104				
Pregnancy test [t]	x		x	x	Q4W					x		x	x
Urinalysis [u]	x			x						x		x	x
PK sample [v]	x		x	x		x		x		x			x
ADA sample [w]	x [a]		Q12W [w]	x		x		x		x			x
Stool sample [x]	x		x			x	x	x	x	x		x	
Diary	x [i, y]												
Efmarodocokin alfa [c, z]		x [d]	x										
Annual colon surveillance colonoscopy with biopsy [aa]	x [bb]												
UC-Specific Activities													
Flexible sigmoidoscopy with biopsy [aa]	x					x	x	x	x	x		x	
MCS (pMCS plus endoscopy) [cc]	x					x	x	x	x	x		x	
pMCS [dd]			x	x	x						x [ee]		x

Appendix 1
Schedule of Activities (cont.)

Activity	Baseline	Efmarodocokin Alfa-Specific Activities [b, c] (±5 days)			Q8W, When Not Undergoing Efmarodocokin Alfa-Specific Activities [e] (±1 week)	Ongoing Activities [f]				DE/ET Visit [g]	UV Visit [h]	Re-entry Screening (3 weeks) [i]	Safety FU [j] (±5 days)
	Study Week					Study Week (±2 weeks)							
	0 [a]	Treatment Initiation [d]	Q4W When Not in Clinical Remission	4 and 8 Weeks after Achieving Clinical Remission		28	52	80	104				
CD-Specific Activities													
Ileocolonoscopy with biopsy [aa]	x					x	x	x	x	x		x	
CDAI (including PRO2)	x	x	x	x	x	x	x	x	x	x	x	x	x
SES-CD	x		x			x	x	x	x	x	x	x	

ADA = anti-drug antibody; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; DE = disease evaluation; eCRF = electronic Case Report Form; ET = early termination; FU = follow-up; MCS = Mayo Clinic Score; PGA = Physician's Global Assessment; PK = pharmacokinetic; pMCS = partial Mayo Clinic Score; PRO2 = Patient-Reported Outcome-2; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; QTcF = QT interval corrected through use of Fridericia's formula; SES-CD = Simple Endoscopic Score for Crohn's Disease; UC = ulcerative colitis; UV = unscheduled visit.

Notes: All activities should be performed prior to study drug administration, unless otherwise stated.

The duration of the study *has been* extended from 1 year to 2 years with the implementation of Protocol Version 6. Patients who completed the study through Week 52 (Year 1) prior to the implementation of Protocol Version 6 may *still* be eligible for an additional year of treatment and/or observation, provided that certain criteria are met, as outlined in Table 3. Participation during Year 2 is not required for such patients, and those who do not participate will be considered to have completed the study per protocol, provided required safety follow-up assessments have been completed.

[a] Day 1 of Study Week 0. Data collected from the final visit of the parent study will serve as baseline Study Week 0 (initial visit) data for the extension study. Activities that were performed at the final visit of the parent study do not need to be repeated at Study Week 0, with the exception of the ADA sample. A baseline ADA sample should be collected at Study Week 0.

[b] Efmarodocokin alfa-specific activities to be performed while patients are receiving efmarodocokin alfa 60 μg/kg IV Q4W or undergoing follow-up 4 and 8 weeks after achieving clinical remission.

[c] Efmarodocokin alfa 60 μg/kg IV Q4W will be administered in patients who do not meet criteria for clinical remission, with the first dose occurring after loss of clinical remission is confirmed. For patients who were not in clinical remission at the time of their final endoscopy in the parent study, the first dose of efmarodocokin alfa in the extension study will occur at Study Week 0 (initial visit).

Appendix 1
Schedule of Activities (cont.)

[d] Treatment initiation (i.e., first visit of period in which patient receives efmarodocokin alfa) may coincide with the Study Week 0 (baseline) visit or a subsequent scheduled visit that confirms the patient is not in clinical remission. The first dose of efmarodocokin alfa in the extension study is to be administered no less than 2 weeks after the last dose of study drug in parent study. For patients who complete the Week 52 visit but have not yet completed required safety assessments prior to the implementation of Protocol Version 6 (see Section 3.1.3): If treatment is resumed *(follow "Q4W When Not in Clinical Remission" column)*, there must be a minimum of 2 weeks since the last dose of efmarodocokin alfa. For patients who complete the Week 52 visit and (if required) safety follow-up assessments prior to the implementation of Protocol Version 6: If the patient qualifies for study re-entry and is not in clinical remission, efmarodocokin alfa must be given within 1 week of establishing eligibility *(follow "Q4W When Not in Clinical Remission" column)*.

[e] For patients who achieve clinical remission while receiving efmarodocokin alfa, Q8W visits begin 16 weeks after *achieving clinical remission*.

[f] Additional activities to be performed in all patients.

[g] Patients with worsening disease, as determined by the investigator, should return to the clinic as soon as possible for a disease evaluation visit. The investigator may also schedule a disease evaluation visit to determine if a patient has achieved clinical remission. Patients who discontinue study drug prematurely (prior to Week 104) for the reasons listed in Section 4.6.1 and have received at least one dose of efmarodocokin alfa 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. Patients who discontinue the study prematurely (prior to Week 104) and have not received efmarodocokin alfa should return to the clinic for an early termination visit within 30 days. Endoscopy at the early termination visit should be conducted if the investigator deems it necessary.

[h] 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.

[i] Patients who complete Week 52 and (if required) safety follow-up assessments prior to the implementation of Protocol Version 6 and agree to participate during Year 2 will undergo re-entry screening over a 3-week period to confirm study eligibility per criteria outlined in Section 4.1 and evaluate disease status. Daily diary recording will be re-initiated during re-entry screening to enable collection of patient-reported outcome data for MCS, CDAI, and PRO2 assessments (see Section 4.5.5).

[j] Patients who receive at least one dose of efmarodocokin alfa must undergo safety follow-up assessments 8 weeks after their final dose. Patients who discontinue prematurely without having undergone at least 8 weeks of follow-up (observation) after their final dose of efmarodocokin alfa should return to the clinic for a safety follow-up visit 8 weeks after their final dose. Patients who are unwilling to return the clinic for the safety follow-up visit should undergo assessments indicated for an early termination visit no later than 30 days after their final dose. For patients who complete Week 52 and safety follow-up assessments prior to the implementation of Protocol Version 6 and re-enter the study, safety follow-up is to be repeated for Year 2.

[k] Patients who complete Week 52 and (if required) safety follow-up assessments prior to the implementation of Protocol Version 6 and agree to participate during Year 2 must be re-consented within 8 weeks of implementation of Protocol Version 6.

Appendix 1
Schedule of Activities (cont.)

[l] After informed consent for study entry has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After informed consent for study re-entry has been obtained (see Section 3.1.3) 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) or prior study treatment should be reported. After initiation of study drug following study entry or study re-entry, all adverse events will be reported until 8 weeks after the final 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). Any adverse event that occurs after completion of Week 52 and required safety follow-up assessments but prior to obtaining informed consent for study re-entry should be captured on the General Medical History and Baseline Conditions eCRF rather than the Adverse Event eCRF, unless it is a serious adverse event related to prior study treatment.

[m] 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.

[n] A complete physical examination 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 (Study Week 0) on the General Medical History and Baseline Conditions eCRF.

[o] Perform a limited, symptom-directed examination, including an abdominal examination, at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[p] Patient must be resting in a supine position for at least 10 minutes prior to ECG assessment. 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. ECGs should be performed at each dosing visit until after the shortest tolerated infusion delivery time is reached (i.e., infusion is tolerated without infusion-associated adverse event).

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

[r] 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.

[s] 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).

[t] For women of childbearing potential undergoing efmarodocokin alfa treatment, urine pregnancy tests will be performed monthly, at specified subsequent visits. For women of childbearing potential not undergoing efmarodocokin alfa treatment, urine pregnancy tests will be performed Q4W. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] 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.

[v] PK samples should be collected in patients with signs and symptoms of serious opportunistic infections or if the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline (Study Week 0) value, if not already scheduled to be collected at that timepoint.

[w] ADA samples may be used to assess PK if needed. ADA samples should be collected in patients with signs and symptoms of serious opportunistic infections or infusion-related reactions, if not already scheduled to be collected at that timepoint. For patients receiving efmarodocokin alfa Q4W, ADA samples should be collected at treatment initiation (prior to dosing) and every 12 weeks thereafter.

[x] Stool samples should be obtained prior to bowel preparation.

[y] Patients with UC are to record stool frequency and rectal bleeding in the daily diary throughout the study (see Section 4.5.5.4). Patients with CD are to record loose-stool frequency, abdominal pain severity, and general well-being in the daily diary throughout the study (see Section 4.5.5.4).

[z] Patients who do not meet criteria for clinical remission will receive efmarodocokin alfa 60 μg/kg IV Q4W until clinical remission is achieved.

[aa] 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. Technical instructions for video recording and biopsy collection are provided in the laboratory manual.

[bb] Patients will undergo annual colonoscopies for colon cancer surveillance. The colonoscopies should include removal of any adenomatous polyps and performance of multiple random mucosal tissue samples (see Section 4.5.5.6). This colonoscopy can substitute for the flexible sigmoidoscopy (for patients with UC) or be part of the ileocolonoscopy (for patients with CD) if the procedures are scheduled to occur during the same time period.

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

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

[ee] pMCS may be performed at an unscheduled visit as determined by the investigator or Sponsor.

Appendix 2
Mayo Clinic Score

Please respond to the following questions after reviewing the patient's Signs and Symptoms of Ulcerative Colitis 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 3
Modified Mayo Clinic Score

Please respond to the following questions after reviewing the patient's Signs and Symptoms of Ulcerative Colitis 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 4
Partial Mayo Clinic Score

Please respond to the following questions after reviewing the patient's Signs and Symptoms of Ulcerative Colitis 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 5
Signs and Symptoms in Ulcerative Colitis Daily Diary: Stool Frequency and Rectal Bleeding

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 6
Crohn's Disease Activity Index
(Includes Patient-Reported Outcome-2 Score)

Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		× 2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe (reported on the 7 days immediately prior to the study visit)		× 5	
General well-being	7-day total of daily general well-being scores on a 4-point scale: 0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible (reported on the 7 days immediately prior to the study visit)		× 7	
Extra-intestinal manifestations of Crohn's disease	Total number of checked boxes (check <u>all</u> that apply): ❒ Arthritis/arthralgia ❒ Iritis/uveitis ❒ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ❒ Anal fissure, fistula, or abscess ❒ Other fistula ❒ Fever over 37.8°C during past week		× 20	
Lomotil/Imodium/ opiates for diarrhea	Yes = 1 No = 0		× 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		× 10	
Hematocrit (%)[a]	Males: subtract value from 47 Females: subtract value from 42		× 6	
Body weight [b]	[1 − (Body weight/Standard weight)] × 100		× 1	
Final score			Add totals:	

[a] If hematocrit subtotal < 0, enter 0.

[b] If body weight subtotal < −10, enter −10.

Adapted from: Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439–44.

Appendix 7
Simple Endoscopic Score for Crohn's Disease

Table 1 Definitions of Simple Endoscopic Score for Crohn's Disease

Variable	Simple Endoscopic Score for Crohn's Disease Values			
	0	1	2	3
Size of ulcers	None	Aphthous ulcers (Ø 0.1 to 0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø > 2 cm)
Ulcerated surface	None	< 10%	10%–30%	> 30%
Affected surface	Unaffected segment	< 50%	50%–75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Ø = diameter.

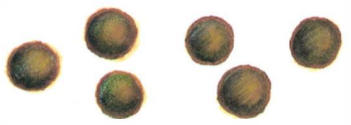
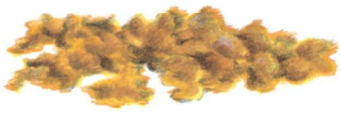
Table 2 Example of SES-CD Scoring Form

	Ileum	Right colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0–3)						
Extent of ulcerated surface (0–3)						
Extent of affected surface (0–3)						
Presence and type of narrowings (0–3)						
					SES-CD =	

Adapted from: Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505–12.

Appendix 8
Bristol Stool Form Scale

THE BRISTOL STOOL FORM SCALE

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces ENTIRELY LIQUID

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.