

Official Title: An Open-Label Extension and Safety Monitoring Study of Patients With Moderately to Severely Active Crohn's Disease Previously Enrolled in the Etrolizumab Phase III Protocol GA29144

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PROTOCOL

TITLE: AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE PREVIOUSLY ENROLLED IN THE ETROLIZUMAB PHASE III PROTOCOL GA29144

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FINAL PROTOCOL APPROVAL

Approver's Name
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Title
Company Signatory

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PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol GA29145 has been amended primarily to address a change in the parent study GA29144. Changes to the protocol, along with a rationale for each change, are summarized below:

- The duration of Part 1 of Study GA29145 has been changed from 6.5 years to approximately 10 years to better ensure continued availability (prior to commercial availability) of open-label etrolizumab for the treatment of Crohn's disease (Sections 3.1.2 and 3.2).
- Eligibility criteria have been changed to account for the closure of enrollment into the Maintenance Phase in parent study GA29144 after the projected sample size for the Maintenance Phase has been achieved. Patients in Study GA29144 who complete the Induction Phase through Week 14 after closure of enrollment into the Maintenance Phase of Study GA29144 may enroll directly into this study, if eligible, as re-randomization into the Maintenance Phase will no longer be possible (Section 4.1.1).
- Antagonists of IL-12 \pm IL-23 (e.g., ustekinumab) have been added to the list of concomitant therapies prohibited for enrollment and during the study (Sections 4.1.2 and 4.3.2).
- Reference to patients with significant liver function test abnormalities has been removed from Section 5.1.1.3 as it is not applicable to this study.
- Language related to safety monitoring for special situations, which had been modified in the last amendment (Version 5), has been reverted back to original protocol text for alignment with a GCP council decision to not implement those modifications for ongoing studies. Sections have been renumbered accordingly (Sections 5.4.6.12, 5.5, and 5.5.4).

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

TITLE: AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE PREVIOUSLY ENROLLED IN THE ETROLIZUMAB PHASE III PROTOCOL GA29144

PROTOCOL NUMBER: GA29145

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EUDRACT NUMBER: 2014-003855-76

IND NUMBER: 119725

TEST PRODUCT: Etrolizumab (PRO145223; RO5490261)

MEDICAL MONITOR: Young (Danny) Oh, M.D., M.S.

SPONSOR: F. Hoffmann-La Roche Ltd

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 to the Sponsor Representative.

PROTOCOL SYNOPSIS

TITLE: AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE PREVIOUSLY ENROLLED IN THE ETROLIZUMAB PHASE III PROTOCOL GA29144

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IND NUMBER: 119725

TEST PRODUCT: Etrolizumab (PRO145223; RO5490261)

PHASE: III

INDICATION: Crohn's Disease

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives

The objectives of this open-label extension-safety monitoring (OLE-SM) study are as follows:

Part 1 (Open-Label Extension; OLE)

- To assess the long-term safety and efficacy of etrolizumab in patients eligible for Part 1 (OLE)

Part 2 (Safety Monitoring; SM)

- Progressive multifocal leukoencephalopathy (PML) safety monitoring in patients who have stopped study treatment

Other Safety Objectives

The other safety objectives for this study are as follows:

Part 1 (OLE)

- To evaluate the incidence, rate per subject-year, and severity of infection-related adverse events
- To evaluate the incidence and rate per subject-year of malignancies
- To evaluate the incidence and severity of hypersensitivity reactions
- To evaluate the incidence and the clinical significance of anti-therapeutic antibodies (ATAs)

Exploratory Objective of the Study

The exploratory objective for this study is as follows:

Part 1 (OLE)

- To assess endoscopic appearance at Week 108

Study Design

Description of Study

This OLE-SM study is composed of two parts:

- Part 1 is the OLE for eligible patients, during which etrolizumab, 105 mg subcutaneous (SC), will be administered every 4 weeks (Q4W) followed by a 12-week safety follow-up post-treatment.
- Part 2 is the 92-week PML SM for all patients, during which no etrolizumab will be administered.

Patients who are enrolled in Part 1 (OLE) should participate in Part 2 (SM).

There may be patients from Study GA29144 who are ineligible for or choose not to participate in Part 1 (OLE) who will be asked to directly enroll in Part 2 (SM).

Number of Patients

The OLE-SM study will be conducted in investigational sites that have participated in Study GA29144. The maximum number of patients potentially enrolling in this study will be all patients from Study GA29144, approximately 1150 patients.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Part 1 (OLE)

- Patients who were previously enrolled in Study GA29144 and experienced any of the following:
 - Disease worsening in the Induction Phase of Study GA29144, defined as both Crohn's Disease Activity Index (CDAI) and Patient-Reported Outcomes-2 (PRO2) scores at Week 10 or later in the Induction Phase being greater than the patient's baseline (Week 0) score
 - Not eligible for the Maintenance Phase in Study GA29144
 - Completed the Week 14 visit in Study GA29144 and could not subsequently enter the Maintenance Phase, because the sample size for the Maintenance Phase has been achieved*
 - A clinical relapse during the Maintenance Phase of Study GA29144, defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores ≥ 220 :
 - CDAI score \geq the baseline (Week 0) score
 - CDAI score ≥ 100 points higher than the Week 14 score
 - Completed the Maintenance Phase including the Week 66 or Week 74 clinic visit in Study GA29144
- Ability and willingness to provide written informed consent and comply with the requirements of the OLE-SM protocol.
- For women who are not postmenopausal (at least 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or to use a highly effective method of contraception (e.g., combined oral contraceptive pill or transdermal patch, spermicide and barrier [condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, or surgical tubal ligation) during the treatment period and for at least 24 weeks after the last dose of study drug.
 - Abstinence is acceptable only if it is in line with 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 or to use a condom, as well as not donate sperm, during the treatment period and for at least 24 weeks after the last dose of study drug
 Abstinance is acceptable only if it is in line with 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.

PART 2 (SM)

- Patients who participated in Study GA29144 and are not eligible or chose not to enroll in Part 1 (OLE)
- Patients who participated in Part 1 (OLE) of this protocol
- Ability and willingness to provide written informed consent and comply with the requirements of Part 2 (SM) of the OLE-SM protocol

All patients must have completed the 12-week safety follow-up in either GA29144 or GA29145, Part 1 (OLE), as applicable, prior to entering Part 2 (SM).

Exclusion Criteria

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

Part 1 (OLE)

- Patients who leave Study GA29144 before Week 10
- Patients who discontinue study drug in the Induction Phase of Study GA29144, except for those escaping between and including Weeks 10 and 14 due to disease worsening
- Inability to comply with the study protocol, in the opinion of the investigator
- Pregnancy or lactation
- Patients who developed an anaphylactic/anaphylactoid or severe allergic reaction to study medication during Study GA29144
- Patients who have an untreated or unresolved serious infection event
- Patients who experienced a de novo or reactivated serious viral infection such as hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV during Study GA29144
- Patients who developed cytomegalovirus (CMV) colitis leading to early treatment discontinuation during Study GA29144
- Patients who developed life-threatening infections during Study GA29144
- Patients who developed a malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) or who develop adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade > 1 on cervical Pap smear or who develop colonic dysplasia during Study GA29144
- Receipt of the following prohibited medications since commencement of Study GA29144:
 - Any investigational treatment, including investigational vaccines
 - Use of T or B cell depleting agents (e.g., rituximab, alemtuzumab, or visilizumab), with the exception of azathioprine (AZA) and 6-mercaptopurine (6-MP), or equivalent
 - Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF)
 - Use of natalizumab or vedolizumab
 - Use of TNF antagonists
 - Use of antagonists of IL-12 ± IL-23 (e.g., ustekinumab)*
 - Immunization with a live/attenuated vaccine
 - Use of anti-adhesion molecules (e.g., anti-MAdCAM-1)

- In the opinion of the investigator, any new (since enrolling in Study GA29144), significant, uncontrolled comorbidity, such as neurological, cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal (GI) disorders (excluding CD)
- Any patient who developed PML in Study GA29144
- Any patient with neurological symptoms where suspected PML has not been ruled out

Part 2 (SM)

- No exclusion criteria

Length of Study

Patients will be enrolled into this study from Study GA29144. Part 1 (OLE) of OLE-SM will continue for up to *approximately 10* years after the first patient is enrolled into the study, until commercial availability, or until the Sponsor's decision to terminate the study, *whichever is earlier*. Following Part 1 (OLE), patients will enter Part 2 (SM) for a period of 92 weeks. The study will end when the last patient has the final telephone visit in Part 2 (SM).

End of Study

The end of the study is defined as the date when the last patient completes the 92-week PML safety-monitoring period.

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

Part 1 (OLE)

- CDAI remission assessed at 12-week intervals during Part 1 (OLE)
- Clinical remission assessed at 12-week intervals during Part 1 (OLE), as defined by a stool frequency (SF) mean daily score ≤ 3 and an abdominal pain (AP) mean daily score ≤ 1 with no worsening in either subscore compared to baseline, averaged over 7 days prior to visit
- Simplified Endoscopic Score for Crohn's disease (SES-CD) score assessed at Week 108 or at early withdrawal, if prior to Week 108, during Part 1 (OLE)

Safety Outcome Measures

The safety outcome measures for this study are as follows:

Part 1 (OLE)

- Incidence and severity of adverse events
- Incidence of serious adverse events
- Incidence, rate per subject-year, and severity of infection-related adverse events
- Incidence of serious infection-related adverse events
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to etrolizumab discontinuation
- Incidence of laboratory abnormalities
- Incidence and rate per subject-year of malignancies
- Incidence of ATAs to etrolizumab
- Incidence and severity of hypersensitivity reactions

Part 2 (SM)

- Incidence of suspected or confirmed PML events

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

Part 1 (OLE)

- SES-CD ≤ 4 (≤ 2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1 , at Week 108
- Change in SES-CD score between Week 0 (Study GA29144) and Week 108 or early withdrawal (Study GA29145, Part 1; OLE)

Investigational Medicinal Products

Test Product

Etrolizumab prefilled syringe (PFS): containing 105 mg will be administered by SC injection every 4 weeks.

Non-Investigational Medicinal Products

None

Statistical Methods

Primary Analysis

Because of the non-comparative character of the study, no statistical tests are planned; all efficacy parameters will be summarized descriptively. Efficacy in Part 1 (OLE) will be assessed across visits using absolute values and change from baseline for continuous outcomes, and dichotomous data (e.g., CDAI remission, clinical remission) will be evaluated using frequency counts and proportions. Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants, duration of disease, and CDAI, SF and AP scores will be summarized by use of descriptive statistics.

Determination of Sample Size

The maximum number of patients enrolled in the OLE-SM study is approximately 1150 (i.e., all patients enrolled in Study GA29144). No formal sample size calculations were performed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6-MP	6-mercaptopurine
AIS	adenocarcinoma in situ
APQ	abdominal pain questionnaire
AP	abdominal pain
ATA	anti-therapeutic antibody
AZA	azathioprine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CRO	contract research organization
CRP	C-reactive protein
CSF	cerebrospinal fluid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
e-diary	electronic diary
ePRO	electronic patient-reported outcome
FDA	U.S. Food and Drug Administration
GI	gastrointestinal
HBV	hepatitis B virus
HCP	health care professional
HCV	hepatitis C virus
HIPAA	U.S. Health Insurance Portability and Accountability Act
HSIL	high-grade squamous intraepithelial lesion
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
IxRS	interactive voice/Web-based response system
JCV	John Cunningham virus

mAb	monoclonal antibody
MAdCAM-1	Mucosal addressin cell adhesion molecule 1
MOA	mechanism of action
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	open-label extension
OLE-SM	open-label extension–safety monitoring
PCR	polymerase chain reaction
PFS	prefilled syringe
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
Q4W	every 4 weeks
RCR	Roche Clinical Repository
SC	subcutaneous
SES-CD	Simple Endoscopic Score for Crohn’s disease
SF	stool frequency
SM	safety monitoring
SUSAR	suspected unexpected serious adverse reaction
TNF	tumor necrosis factor
TNF-IR	non-responsive or refractory to anti-TNF therapy
UC	ulcerative colitis
ULN	upper limit of normal

1. **BACKGROUND**

1.1 **BACKGROUND CROHN'S DISEASE**

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease (IBD) that can affect any portion of the gastrointestinal tract, with 40%–50% of cases affecting the small bowel. CD is characterized by patchy, transmural inflammation, ulcers, and granulomatous lesions that are interspersed with healthy sections of bowel (skip lesions). The disease is progressive; uncontrolled inflammation develops into stricturing or penetrating complications such as prestenotic dilatation, obstruction (stricturing), and intra-abdominal or perianal fistula and abscesses (penetrating). Clinical signs and symptoms include chronic diarrhea, abdominal pain, cachexia, abdominal mass, or tenderness as well as the overt signs of fistulae. The disease course is variable; patients can experience a severe initial flare followed by few symptoms over the next 10 years (43%), symptoms that are chronic and persistent (19%), or relapsing-remitting (32%) (Baumgart and Sandborn 2012).

The annual incidences of CD reported in Europe, Asia and the Middle East, and North America were 12.7, 5.0, and 20.2 per 100,000 person-years, respectively (Molodecky et al. 2012). Current prevalence rates in North America are reported to be 319 per 100,000 persons (Molodecky et al. 2012). Disease-related mortality in CD accounts for approximately 30% of deaths in this population, resulting from clinical and/or surgical complications that occur early in the disease course or intestinal cancer occurring later. The global incidence of CD is expected to continue increasing substantially, affecting individuals in the most formative and productive years of life, with long-term costs to patients, healthcare systems, and society (Duricova et al. 2010).

So far, there is no cure for CD. The treatment goals for CD are to induce and maintain symptom improvement, induce mucosal healing, avoid surgery, and improve quality of life (Lichtenstein et al. 2009; Van Assche et al. 2010).

Systemic corticosteroids have been the mainstay treatment for inducing remission and are effective in approximately 80% of patients (Summers et al. 1979; Malchow et al. 1984). However, they are less effective as a maintenance therapy, with only 28% of patients achieving a prolonged response after 1 year of treatment and 32% of patients becoming steroid dependent (Faubion et al. 2001; Peyrin-Biroulet et al. 2010). Even if patients' symptoms improve, fewer than 30% are expected to achieve endoscopic improvement with steroid treatment (Modigliani et al. 1990). The adverse effects of steroids are well documented, and 50% of patients will stop their treatment because of this; long-term safety outcomes include osteoporosis, cataracts, and diabetes.

Immunosuppressants (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) are typically administered to induce remission in patients who are intolerant of or refractory to steroids and to maintain remission in patients who achieve

quiescent CD. Immunosuppressants are given with or without a steroid bridge, depending on a patient's symptoms during the 2–4-month onset of immunosuppressant efficacy. In patients with ileal or ascending colonic disease, budesonide presents a less toxic, more tolerable bridge because of its low systemic bioavailability resulting from a rapid first-pass metabolism. An earlier initiation of immunosuppressant to alter the inflammatory disease course has been advocated over the past 20 years. However, a decrease in the rate of intestinal resections and complications has not been observed during this time (Cosnes et al. 2005). This may reflect poor adoption of this top-down treatment over concern for systemic toxicities, including leukopenia, thrombocytopenia, and increased risk for lymphoma with AZA and 6-MP (Prefontaine et al. 2009) and hepatotoxicity and hair loss with MTX (Hausmann et al. 2010).

The development of monoclonal antibodies (mAbs) against tumor necrosis factor (TNF)- α has provided an additional treatment option. Although anti-TNFs are effective in a significant proportion of patients, efficacy is suboptimal; remission rates after 4 weeks of induction therapy are fewer than 35%, and among patients who respond to induction therapy, fewer than 50% achieve remission when assessed in maintenance at 20–30 weeks (Peyrin-Biroulet et al. 2011). Furthermore, 30% of patients are reported to be primary non-responders to anti-TNF therapy when assessed after 4 weeks of induction therapy (Targan et al. 1997; Sandborn et al. 2007), possibly because of an underlying pathobiology that is not TNF- α driven and as such may benefit from a different mechanistic class of drug. It is estimated that 30%–40% of patients will be secondary non-responders (i.e., initially responsive), but lose response or become intolerant in their first year of treatment (Colombel et al. 2007). Secondary non-response has been attributed to the development of neutralizing antibodies, resulting in low drug serum levels, to accelerated drug clearance, or to a biological escape mechanism that may benefit from a therapy with a different pharmacological target. These agents are also associated with significant side effects, including serious infection, opportunistic infection, lupus-like reactions, and an increased risk of lymphoma (Siegal et al. 2009). Tolerability concerns include infusion reactions (occurring in 9%–17% of patients treated with infliximab, de Vries et al. 2011) and injection site reactions (occurring in 10% of patients receiving adalimumab, van der Heijde et al. 2006). Overall, the benefits versus risks are considered acceptable for this drug class, but there continues to be a need for treatments with better benefit-risk profiles that attenuate inflammation and the clinical sequelae and improve the long-term prognosis of patients with CD.

The anti-integrins are another class of biologics approved for the treatment of CD. Natalizumab is an anti-integrin approved in the United States for the treatment of moderately to severely active CD. The use of natalizumab, which blocks both α 4 β 1 and α 4 β 7, has been limited because of concerns that inhibition of α 4 β 1/VCAM-1 binding increases the risk of progressive multifocal leukoencephalopathy (PML), a rare but serious infection of the CNS. Vedolizumab is the most recently approved gut-selective anti-integrin for CD, but this targets only the α 4 β 7 integrin receptor, inhibiting

T-lymphocyte binding to the cell adhesion molecule MAdCAM-1, and is administered as an intravenous (IV) infusion. In the pivotal trials for vedolizumab, 31% of patients had a clinical response with 6 weeks of induction treatment; up to 39% of the vedolizumab responders achieved remission with 46 weeks of maintenance treatment, compared with 22% of patients given placebo (Sandborn et al. 2013). While vedolizumab shows promise as a new treatment for CD, there remains a need for a more convenient therapy that is gut selective and achieves better response and remission rates.

1.2 BACKGROUND ON ETROLIZUMAB

Etrolizumab, a subcutaneously administered mAb, is a novel anti-integrin that, like vedolizumab, targets the $\alpha 4\beta 7$ receptors that regulates trafficking of T-cell subsets in the intestinal mucosa, but unlike vedolizumab, etrolizumab also targets the $\alpha E\beta 7$ receptors that regulate retention of T-cell subsets in the intestinal mucosa. Thus, etrolizumab offers the potential of an additive therapeutic effect in CD via a dual mechanism of action (MOA) without generalized immunosuppression.

Etrolizumab is a humanized mAb based on the IgG1 subgroup-III V_H , κ subgroup-I V_L consensus sequences and is directed specifically against the $\beta 7$ subunit of the integrin heterodimer (Andrew et al. 1994). Etrolizumab binds with high affinity to $\alpha 4\beta 7$ (Holzmann et al. 1989; Hu et al. 1992) and $\alpha E\beta 7$ (Cepek et al. 1993). By this mechanism, it blocks the homing and retention of leukocyte subpopulations in the intestinal mucosa that occur via binding with the cell adhesion molecules (MAdCAM-1) and E-cadherin, respectively. As such, it represents a novel gut mucosal-selective anti-trafficking agent whose selectivity may eliminate generalized immunosuppression by preferentially targeting trafficking to the gut rather than to other organs and tissues. Data from multiple, non-clinical, general toxicity studies of up to 6 months' duration demonstrated that etrolizumab had no adverse effects in any organ system. In addition, etrolizumab had no adverse effects in the embryo fetal developmental toxicity studies or general reproductive toxicity study (see Etrolizumab Investigator's Brochure).

It is important to note that unlike natalizumab, etrolizumab does not bind to $\alpha 4\beta 1$ or inhibit either the interaction of $\alpha 4\beta 1$ and VCAM-1 or the distribution and homing of lymphocytes to the CNS and peripheral lymphoid tissue (see Etrolizumab Investigator's Brochure). As such, etrolizumab is not expected to increase the risk of PML. Safety assessments for etrolizumab have been completed in adult Phase I and Phase II studies, in which patients with moderately to severely active ulcerative colitis (UC) received either single or multiple doses of IV or subcutaneous (SC) etrolizumab. Safety evaluation is ongoing in a Phase II open-label extension (OLE) study. A total of 158 patients have been exposed to etrolizumab with no significant adverse safety signals, including any evidence of increased rates of serious or opportunistic infections, being associated with etrolizumab treatment. No events of PML have been reported in patients treated with etrolizumab.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This open-label extension–safety monitoring (OLE-SM) study consists of two parts.

1.3.1 Study Rationale for Part 1 (Open-Label Extension or “OLE”)

Part 1 (OLE) of this study is designed to assess the long-term safety and tolerability of 105 mg SC etrolizumab every four weeks with regard to adverse events and laboratory abnormalities and to obtain long-term data on the efficacy and immunogenicity.

Patients receiving etrolizumab or placebo in Study GA29144 may be eligible to participate and will receive etrolizumab in Part 1 (OLE) of this study. Eligibility criteria and the timepoints for enrollment into the Part 1 (OLE) of this study are described in Section [4.1.1](#).

1.3.2 Study Rationale for Part 2 (Safety Monitoring or “SM”)

Part 2 (SM) of this study is designed to monitor for PML in patients who have stopped taking etrolizumab. Patients who exit Part 1 (OLE) of this study will then enter Part 2 (SM) of this study for monitoring for events of PML. In addition, all patients from Study GA29144 who do not enroll in Part 1 (OLE) of this study for continued etrolizumab treatment will be asked to enroll directly into Part 2 (SM) of this study for extended PML safety monitoring (following completion of the 12-week safety follow-up in Study GA29144).

1.3.3 Benefit-Risk Assessment

The current therapeutic options available for CD include corticosteroids, immunosuppressants, and biological agents. These treatments reduce symptoms and improve quality of life; however, patients often stop responding to treatments and the goals of maintaining clinical remission and healing mucosal inflammation are not achieved. Moreover, these therapies are associated with adverse effects including diabetes (reported with corticosteroid use; Peyrin-Boulet et al. 2010), systemic toxicities such as leucopenia and thrombocytopenia (reported with immunosuppressant use; Prefontaine et al. 2009), and an increased risk for lymphoma and serious and opportunistic infections (reported with immunosuppressant and anti-TNF use when given as monotherapy or in combination; Siegal and Melmed 2009).

The anti-integrins are another class of biologics approved for the treatment of CD. The reported efficacy of the recently licensed anti-integrin vedolizumab, an intravenously administered anti- $\alpha4\beta7$ mAb, in CD demonstrates a role for $\alpha4\beta7$ in the pathobiology of this disease (Sandborn et al. 2013). In addition to demonstrating efficacy compared with placebo, vedolizumab had an acceptable safety profile in two Phase III trials for CD (Sandborn et al. 2013; Sands et al. 2014). Although long-term safety data for vedolizumab are still being collected, to date no cases of PML *attributed to vedolizumab* have been reported.

Similar to vedolizumab, etrolizumab is a gut-selective anti-integrin, which blocks homing of leukocyte subpopulations to the intestinal mucosa by blocking $\alpha 4\beta 7$ integrin (see Etrolizumab Investigator's Brochure). In addition, etrolizumab may interfere with pathologic lymphocyte retention along the mucosa by blocking the interaction between $\alpha E\beta 7$ and E-cadherin. Etrolizumab showed significant rates of remission at 10 weeks in treating moderately to severely active UC when compared with placebo in the Phase II Study ABS4986g (EUCALYPTUS study; Vermeire et al. 2014) and was associated with ongoing high rates of clinical response among 108 of 124 patients from EUCALYPTUS who received open-label etrolizumab after roll-over into the Phase II OLE SPRUCE study (Study GA27927).

The most recent SPRUCE data cut (June 2014) demonstrates the median exposure to etrolizumab was 7.29 months, with 51% of patients experiencing at least 7–11 months of exposure and 11% experiencing at least 24 months. In most cases, this duration of exposure to etrolizumab is in addition to 10 weeks of treatment with etrolizumab in the EUCALYPTUS study. At the time of the data cut in this ongoing study, 80% of patients in SPRUCE experienced adverse events and 15% experienced at least one serious adverse event. The most common adverse events were nasopharyngitis (occurring in 25% of patients), UC flare (23.1%), headache (12%), arthralgia, gastroenteritis, and upper respiratory tract infection (11.1% each).

A potential safety risk associated with the use of anti-integrins includes the risk for infections related to gut-selective treatment blockade of lymphocyte trafficking and the potential for suppression of host defense against infectious pathogens. However, an analysis of the EUCALYPTUS study showed that infection rates were similar between etrolizumab and placebo in the subgroups of patients taking concomitant immunosuppressant therapy and the subgroups not taking this concomitant treatment (see Etrolizumab Investigator's Brochure). A slightly higher rate of infection was observed during long-term exposure to etrolizumab in SPRUCE compared with EUCALYPTUS, but only 3 patients have discontinued from SPRUCE to date because of infection-related adverse events (see Etrolizumab Investigator's Brochure).

Although the efficacy of etrolizumab has not been studied in patients with CD, preliminary expression studies of the pharmacological target for etrolizumab, the integrin $\beta 7$ receptor on gut CD4+ and CD8+ T cells isolated from resections of patients with UC and patients with CD, show that expression levels are similar between both diseases. In addition, because αE expression is reportedly elevated in patients with CD (Elewaut et al. 1998; Oshitani et al. 2003), with an observed increase in expression from distal to proximal bowel, etrolizumab may bring enhanced efficacy in CD. Given the preliminary evidence of efficacy in patients with UC and that elements of pathogenesis are shared across UC and CD, etrolizumab has the potential to be a novel, effective treatment for CD and will be assessed as a treatment for patients who are TNF-naive and patients who are non-responsive or refractory to anti-TNF therapy

(TNF-IR) with moderately to severely active CD in the combined Phase III, randomized, placebo-controlled induction and maintenance studies, Study GA29144.

Patients who experience disease worsening that is confirmed at Week 10 in the Induction Phase of Study GA29144 will have the option of enrolling in Part 1 (OLE) of Study GA29145 between and including Weeks 10 and 14 of the Induction Phase. Patients who are not eligible for the Maintenance Phase may also have the option to enroll in Part 1 (OLE) of Study GA29145, if eligible. During the Maintenance Phase in Study GA29144, patients will be able to withdraw and enter Part 1 (OLE) if they experience a clinical relapse (as defined in Section 4.1.1).

Study GA29144 patients who experience disease progression or lack of response while assigned to placebo during either the Induction or Maintenance Phase are expected to benefit most from participation in Part 1 (OLE) of Study GA29145. Patients who experienced disease progression or lack of response while assigned to etrolizumab in Study GA29144 may also experience treatment benefit by participating in Part 1 (OLE) depending on severity of disease and available treatment options, which include anticipated treatment benefit from rescue medication. Consequently, eligible patients from Study GA29144 are encouraged to enroll in Part 1 (OLE) to receive open-label etrolizumab with rescue medications at the discretion of the investigator, including the use of concomitant immunosuppressant therapy.

Patients may enter Part 1 (OLE) between Weeks 10 and 14 in Study GA29144, having received an induction regimen of either 210 mg or 105 mg etrolizumab. Data from the SPRUCE OLE study, in which patients received either 100 mg etrolizumab every 4 weeks (Q4W) or 300 mg etrolizumab Q4W (followed by a protocol-amendment driven reduction to 100 mg etrolizumab Q4W) after administration of placebo, 100 mg etrolizumab, or 300 mg etrolizumab (both are nominal doses) in the EUCALYPTUS Phase II study, showed that response and remission rates in SPRUCE were similar when the results were analyzed by treatment received in EUCALYPTUS. The clinical response rates in SPRUCE at Week 4, for patients previously treated with 100 mg etrolizumab, 300 mg etrolizumab, or placebo, were 48%, 49%, and 53%, respectively (n=31–38; see Etrolizumab Investigator's Brochure). Among TNF-IR patients, clinical response rates in SPRUCE at Week 4, for patients previously treated with 100 mg etrolizumab, 300 mg etrolizumab, or placebo, were 42%, 50%, and 44%, respectively (n=8–12). Given that both induction doses (105 mg and 210 mg) in Study GA29144 are expected to achieve full $\beta 7$ receptor occupancy and assuming that receptor occupancy is required for efficacy, these data suggest that patients who enter Part 1 (OLE) from the 210 mg arm of the Induction Phase of Study GA29144 may experience a treatment benefit with longer etrolizumab treatment. As described earlier, permitted use of corticosteroid and immunosuppressant therapy with etrolizumab in the OLE may benefit all patients escaping from Study GA29144 because of disease worsening. Safety events will be carefully and regularly monitored while patients are taking etrolizumab in Part 1 (OLE) and for 2 years after their last dose of etrolizumab (12-week

safety follow-up plus 92-week PML safety monitoring). The investigator will review patient safety in Part 1 (OLE) every month for the first 3 months and then every 3 months thereafter until a patient completes the study or withdraws. Safety assessments will include: assessment of vital signs, safety laboratory results, neurological exams, and continuous review of adverse events. Pregnancy, development of anaphylaxis, PML, malignancy, colonic mucosal dysplasia, or certain specific serious infections (see Section 5) will lead to permanent discontinuation from etrolizumab treatment. In addition, after treatment of etrolizumab has stopped, patients will be followed for 12 weeks for all safety events and then 92 weeks for any signs and symptoms of PML. Patients will be carefully monitored for symptoms of PML through regular neurological examinations and with the use of the PML subjective and objective checklists (Section 4.4.4.5)

In summary, there is a strong rationale and a positive benefit-risk assessment for studying etrolizumab in Crohn's Disease. Safety and efficacy results from the UC OLE SPRUCE study suggest that etrolizumab has an acceptable clinical safety profile and could benefit patients who are eligible to receive long-term treatment after exiting Study GA29144.

1.3.4 Rationale for Test Product Dosage

Patients enrolling in Part 1 (OLE) of this open-label extension–safety monitoring (OLE–SM) study from Study GA29144 will receive a dose of 105 mg of etrolizumab. A dosing regimen of 105 mg SC Q4W is specified in Part 1 (OLE) on the basis of the following considerations:

- The 105-mg SC Q4W dose planned for the Phase III study in CD is anticipated (by population modeling) to maintain full $\beta 7$ –receptor occupancy at all times in > 85% of patients. The nominal dose of 100 mg SC Q4W administered in the UC Phase II study demonstrated an acceptable safety profile.
- The in-class anti-integrin vedolizumab was successful in maintaining remission with an every 8-week regimen that provided an average steady-state trough serum concentration sufficient to maintain maximal receptor occupancy (Rosario et al. 2013; Sandborn et al. 2013).

Of note, no etrolizumab will be administered during Part 2 (SM) of this OLE–SM study.

2. OBJECTIVES

2.1 OBJECTIVES OF THE STUDY

The objectives of this OLE-SM study are as follows:

Part 1 (OLE)

- To assess the long-term safety and efficacy of etrolizumab in patients eligible for Part 1 (OLE)

Part 2 (SM)

- PML safety monitoring in patients who have stopped study treatment

2.2 OTHER SAFETY OBJECTIVES

The other safety objectives for this study are as follows:

Part 1 (OLE)

- To evaluate the incidence, rate per subject-year, and severity of infection-related adverse events
- To evaluate the incidence and rate per subject-year of malignancies
- To evaluate the incidence and severity of hypersensitivity reactions
- To evaluate the incidence and the clinical significance of anti-therapeutic antibodies (ATAs)

2.3 EXPLORATORY OBJECTIVE OF THE STUDY

The exploratory objective for this study is as follows:

Part 1 (OLE)

- To assess endoscopic appearance at Week 108

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This OLE-SM study is composed of two parts:

- Part 1 is the OLE for eligible patients, during which etrolizumab, 105 mg SC, will be administered Q4W followed by a 12-week safety follow-up post-treatment.
- Part 2 is the 92-week PML SM for all patients, during which no etrolizumab will be administered.

Patients who are enrolled in Part 1 (OLE) should participate in Part 2 (SM).

There may be patients from Study GA29144 who are ineligible for or choose not to participate in Part 1 (OLE) who will be asked to directly enroll in Part 2 (SM).

3.1.2 Overview of Part 1 (OLE)

Part 1 (OLE) of this study is an open-label, multicenter study to evaluate the long-term efficacy and safety of etrolizumab in patients with moderate to severe CD who were enrolled in Study GA29144 and who meet the eligibility criteria for enrollment into Part 1 (OLE; see Section 4.1.1).

All patients in Part 1 (OLE) will receive 105 mg etrolizumab Q4W by the SC route. All patients will be required to receive their first four doses (Weeks 0, 4, 8, and 12) of etrolizumab in the clinic setting as described in Section 4.2.2. Following the first four doses, etrolizumab may be administered in the home setting, and patients may self-administer the dose or have a caregiver administer the dose after being trained at the study clinic (see Section 4.2.2). If necessary, patients or their health care professional (HCP) may choose to continue administration of etrolizumab in the clinic.

Throughout Part 1 (OLE), patients will be monitored for safety by collection of safety parameters such as vital signs, laboratory tests, and adverse events (both serious and non-serious) and will be monitored for symptoms of PML with use of the PML subjective and objective checklists. Efficacy data will be evaluated by CDAI score, patient reported stool frequency (SF), and abdominal pain (AP) scores every 12 weeks until safety follow-up. In addition, patient's scoring on the abdominal pain questionnaire on an 11-point scale will be evaluated (see Appendix 6). Patients will have in-clinic visits at Weeks 0, 4, 8, and 12 and every 12 weeks thereafter (see Figure 1 and Appendix 1) and can continue to receive open-label etrolizumab in Part 1 (OLE) until commercial availability in their country or up to *approximately 10* years after the first patient is enrolled (see Section 3.2), whichever is earlier, or until the Sponsor's decision to terminate the study. Upon the completion of Part 1 (OLE) or early withdrawal from Part 1 (OLE), all patients will enter a 12-week safety follow-up, which consists of a telephone visit at Week 6 and an in-clinic visit at Week 12 (see Appendix 2).

During Part 1 (OLE), patients who have worsening CD may receive corticosteroid concomitantly (IV, oral, or topical) at the discretion of the investigator (see Section 4.3.1). Patients may continue immunosuppressant therapy (i.e., AZA, 6-MP, or MTX) with dose changes or initiate immunosuppressant therapy, at the discretion of the investigator (see Section 4.3.1). Any patient taking a prohibited therapy (described in Section 4.3.2) must withdraw from Part 1 (OLE), discontinue etrolizumab, and complete the 12-week safety follow-up, and then enter Part 2 (SM).

Upon completion of the 12-week safety follow-up, patients will enter Part 2 (SM) of the study, which will consist of 92 weeks of extended PML monitoring. See Figure 1 and Figure 2 for schemas of the study and see Section 3.1.3.

3.1.3 Overview of Part 2 (SM)

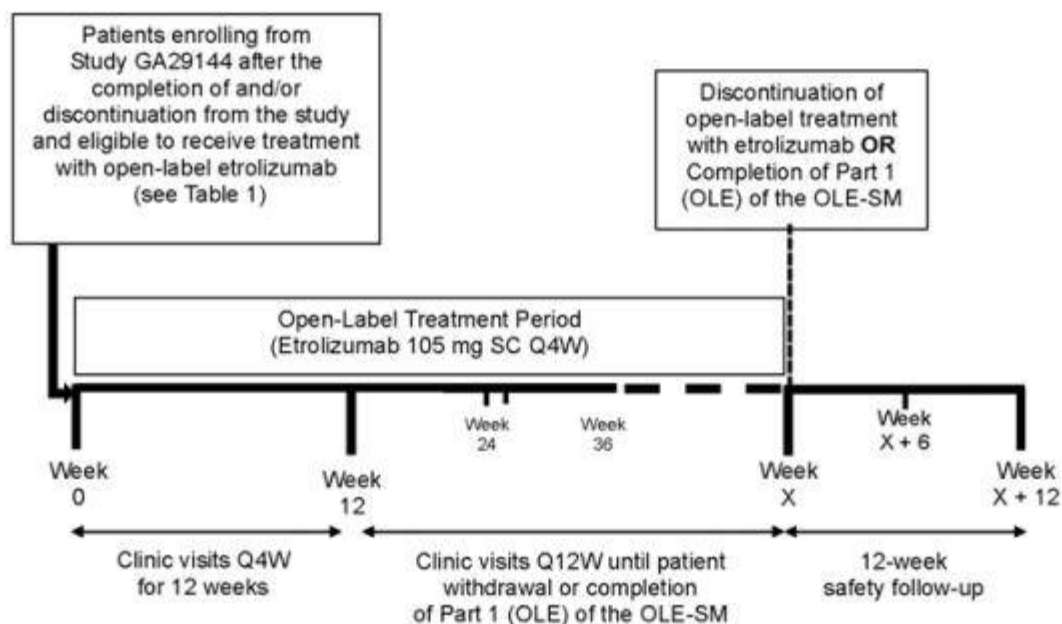
Patients may enroll into Part 2 (SM) of this study for 92 weeks of PML monitoring via two routes:

- Patients exiting Part 1 (OLE)
- Patients from Study GA29144 who are not eligible or choose not to receive etrolizumab in this study (e.g., due to receipt of prohibited medication)

Regardless of route of entry, patients will enroll following completion of the 12-week safety follow-up period within Part 1 of this study (OLE; for those entering from OLE) or within Study GA29144 (for those enrolling directly from Study GA29144).

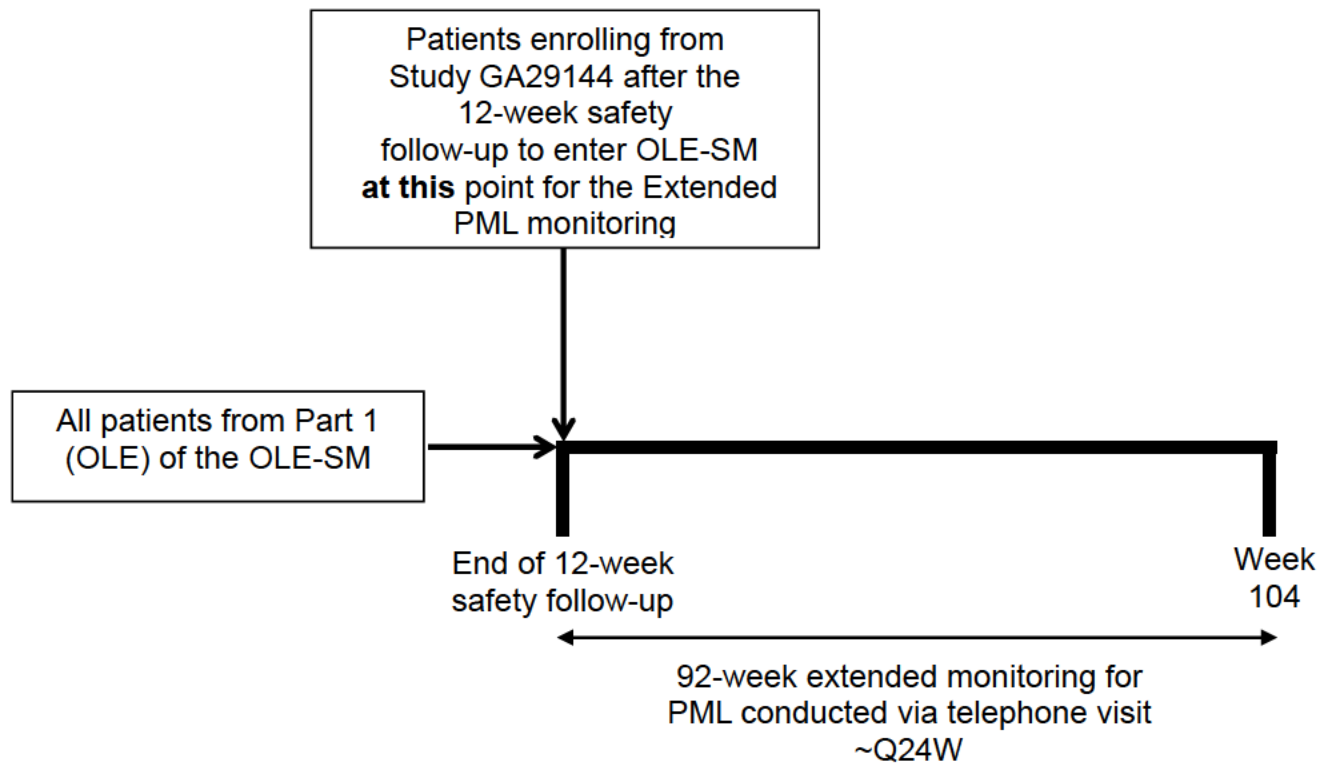
During Part 2 (SM), patients will be assessed for PML and safety events via telephone visits at Weeks 24, 48, 68, and 92 (see [Figure 2](#) and [Appendix 3](#)). If there are any signs or symptoms suggestive of PML during the telephone visit, the patient will be asked to come into the clinic for a neurologic examination (see Section [4.4.5](#)).

Figure 1 Study Schema for Part 1 (Open-Label Extension; OLE) of the OLE-SM Study



OLE = open-label extension; OLE-SM = open-label extension—safety monitoring; Q4W = every 4 weeks; Q12W = every 12 weeks; SC = subcutaneous.

Figure 2 Study Schema for Part 2 (Safety Monitoring; SM) of the OLE-SM Study



OLE=open-label extension; OLE-SM=open-label extension–safety monitoring; PML=progressive multifocal leukoencephalopathy; ~Q24W=approximately every 24 weeks.

3.1.4 Number of Patients

The OLE-SM study will be conducted in investigational sites that have participated in Study GA29144. The maximum number of patients potentially enrolling in this study will be all patients from Study GA29144, approximately 1150 patients.

3.2 STUDY DURATION

Part 1 (OLE)

Part 1 (OLE) of this study will continue for up to *approximately 10* years after the first patient is enrolled into the study, until commercial availability, or until the Sponsor's decision to terminate the study, *whichever is earlier*. Patients who withdraw from Part 1 (OLE) will complete the 12-week safety follow-up and then enter Part 2 (SM) for PML monitoring.

Part 2 (SM)

For patients who enter Part 2 (SM) of this study either from Part 1 (OLE) or enroll directly from Study GA29144, Part 2 (SM) of the study will last 92 weeks.

3.2.1 End of Study

The end of the study is defined as the date when the last patient completes the 92-week PML safety-monitoring period.

3.3 OUTCOME MEASURES

The efficacy outcome definitions are given in [Table 1](#).

3.3.1 Efficacy Outcome Measures (Part 1; OLE)

The efficacy outcome measures for this study are as follows:

- CDAI remission assessed at 12-week intervals during Part 1 (OLE)
- Clinical remission assessed at 12-week intervals during Part 1 (OLE), as defined by a SF mean daily score ≤ 3 and an AP mean daily score ≤ 1 with no worsening in either subscore compared to baseline, averaged over 7 days prior to visit
- Simple Endoscopic Score for Crohn's disease (SES-CD) score assessed at Week 108 or at early withdrawal, if prior to Week 108, during Part 1 (OLE)

Table 1 Efficacy Outcome Definitions

Outcome Term	Definition
CDAI	CDAI is a composite of eight assessments: number of liquid or soft stools, abdominal pain, general well-being, presence of complications, taking Lomotil® (diphenoxylate/atropine) or other opiates for diarrhea, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight
SES-CD	SES-CD is an endoscopic score derived from four variables (ulcers, ulcerated surface, inflamed surface, and presence of narrowing) that are scored in five ileocolonic segments.
CDAI Remission	CDAI score < 150
Clinical Remission	An SF mean daily score ≤3 and an AP mean daily score ≤1 with no worsening in either subscore compared to baseline, where the average is taken over 7 days prior to visit

AP = abdominal pain; CDAI = Crohn's Disease Activity Index; SES-CD = Simple Endoscopic Score for Crohn's disease; SF = liquid/soft stool frequency.

3.3.2 Safety Outcome Measures (Part 1; OLE)

The safety outcome measures for Part 1 (OLE) of this study are as follows:

- Incidence and severity of adverse events
- Incidence of serious adverse events
- Incidence, rate per subject-year, and severity of infection-related adverse events
- Incidence of serious infection-related adverse events
- Incidence and severity of injection-site reactions
- Incidence of adverse events leading to etrolizumab discontinuation
- Incidence of laboratory abnormalities
- Incidence and rate per subject-year of malignancies
- Incidence of ATAs to etrolizumab
- Incidence and severity of hypersensitivity reactions

3.3.3 Safety Outcome Measure (Part 2; SM)

The safety outcome measure for Part 2 (SM) of this study is as follows:

- Incidence of suspected or confirmed PML events

3.3.4 Exploratory Outcome Measures (Part 1; OLE)

The exploratory outcome measures for Part 1 (OLE) of this study are as follows:

- SES-CD ≤ 4 (≤ 2 for ileal patients), with no segment having a subcategory score (i.e., for ulceration size and extent, affected surface, or narrowing) that is >1 , at Week 108
- Change in SES-CD score between Week 0 (Study GA29144) and Week 108 or early withdrawal (Study GA29145, Part 1; OLE)

4. MATERIALS AND METHODS

4.1 PATIENTS

Part 1 (OLE)

The study population will consist of patients from Study GA29144 who meet all of the eligibility criteria for Part 1 (OLE) listed in Section 4.1.1.

Part 2 (SM)

The study population will consist of patients from Study GA29144 who either do not meet the eligibility criteria for Part 1 (OLE) or choose not to enroll in Part 1 (OLE) and patients from Study GA29145 who either completed or discontinued Part 1 (OLE), and who meet all the eligibility criteria for Part 2 (SM) listed in Section 4.1.1.

4.1.1 Inclusion Criteria

Part 1 (OLE)

- Patients who were previously enrolled in Study GA29144 and experienced any of the following:

Disease worsening in the Induction Phase of Study GA29144, defined as a CDAI score at Week 10 or later in the Induction Phase being greater than the patient's baseline (Week 0) score

Not eligible for the Maintenance Phase in Study GA29144

Completed the Week 14 visit in Study GA29144 and could not subsequently enter the Maintenance Phase, because the sample size for the Maintenance Phase has been achieved

A clinical relapse during the Maintenance Phase of Study GA29144, defined as meeting at least one of the following criteria on two consecutive visits (may include unscheduled visits), with at least one of the two consecutive CDAI scores ≥ 220 :

CDAI score \geq the baseline (Week 0) score

CDAI score ≥ 100 points higher than the Week 14 score

Completed the Maintenance Phase including the Week 66 or Week 74 clinic visit in Study GA29144

- Ability and willingness to provide written informed consent and comply with the requirements of the OLE-SM protocol.
- For women who are not postmenopausal (at least 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or to use a highly effective method of contraception (e.g., combined oral contraceptive pill or transdermal patch, spermicide and barrier [condoms], intrauterine device, implants for contraception, injections for contraception [with prolonged release], hormonal vaginal device, sterilization, or surgical tubal ligation) during the treatment period and for at least 24 weeks after the last dose of study drug (see [Appendix 4](#)).

Abstinence is acceptable only if it is in line with 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 or to use a condom, as well as not donate sperm, during the treatment period and for at least 24 weeks after the last dose of study drug

Abstinence is acceptable only if it is in line with 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.

PART 2 (SM)

- Patients who participated in Study GA29144 and are not eligible or chose not to enroll in Part 1 (OLE)
- Patients who participated in Part 1 (OLE) of this protocol
- Ability and willingness to provide written informed consent and comply with the requirements of Part 2 (SM) of the OLE-SM protocol

All patients must have completed the 12-week safety follow-up in either GA29144 or GA29145, Part 1 (OLE), as applicable, prior to entering Part 2 (SM).

4.1.2 Exclusion Criteria

Part 1 (OLE)

- Patients who leave Study GA29144 before Week 10
- Patients who discontinue study drug in the Induction Phase of Study GA29144, except for those escaping between and including Weeks 10 and 14 due to disease worsening
- Inability to comply with the study protocol, in the opinion of the investigator
- Pregnancy or lactation
- Patients who developed an anaphylactic/anaphylactoid or severe allergic reaction to study medication during Study GA29144

- Patients who have an untreated or unresolved serious infection event
- Patients who experienced a de novo or reactivated serious viral infection such as hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV during Study GA29144
- Patients who developed cytomegalovirus (CMV) colitis leading to early treatment discontinuation during Study GA29144
- Patients who developed life-threatening infections during Study GA29144
- Patients who developed a malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) or who develop adenocarcinoma in situ (AIS), high-grade squamous intraepithelial lesions (HSIL), or cervical intraepithelial neoplasia (CIN) of Grade > 1 on cervical Pap smear or who develop colonic dysplasia during Study GA29144
- Receipt of the following prohibited medications since commencement of Study GA29144:
 - Any investigational treatment, including investigational vaccines
 - Use of T or B cell depleting agents (e.g., rituximab, alemtuzumab, or visilizumab), with the exception of AZA and 6-MP (or equivalent)
 - Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF)
 - Use of natalizumab or vedolizumab
 - Use of TNF antagonists
 - Use of antagonists of IL-12 ± IL-23 (e.g., ustekinumab)*
 - Immunization with a live/attenuated vaccine
 - Use of anti-adhesion molecules (e.g., anti-MAdCAM-1)
- In the opinion of the investigator, any new (since enrolling in Study GA29144), significant, uncontrolled comorbidity, such as neurological, cardiac (e.g., moderate to severe heart failure New York Heart Association [NYHA] Class III/IV), pulmonary, renal, hepatic, endocrine, or gastrointestinal (GI) disorders (excluding CD)
- Any patient who developed PML in Study GA29144
- Any patient with neurological symptoms where suspected PML has not been ruled out

Part 2 (SM)

- No exclusion criteria

4.2 STUDY TREATMENT

4.2.1 Formulation, Packaging, and Handling

Part 1 (OLE)

Etrolizumab

Etrolizumab will be supplied by the Sponsor as a liquid formulation in prefilled syringes (PFSs) with needle safety device (hereafter referred to as PFS) and is administered as a SC injection. Each 1-mL PFS contains 105 mg etrolizumab (0.7 mL nominal volume of

150 mg/mL solution). Etolizumab is formulated as 150 mg/mL in 20 mM histidine, 0.2 M arginine succinate, and 0.04% polysorbate 20, pH 5.8. Each syringe is for single-dose SC administration and contains no preservatives.

Packaging

Study drug packaging will be overseen by the Sponsor's Clinical Trial Supplies Department and will be labelled with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labelling of the study medication will be in accordance with Sponsor's standards and local regulations.

Upon arrival of investigational products at the site, the pharmacist or medication nurse should check them for damage and verify proper identity, use by date, quantity, integrity of seals, and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

Handling

The study drug must be stored according to the details on the product label. PFSs of study medication should be refrigerated at 2°C–8°C and protected from light (i.e., remain in box). PFSs should not be frozen, shaken, or stored at room temperature.

The PFS containing study drug is stable for no longer than 8 hours at room temperature (should not exceed 30°C). If a syringe is left at room temperature for longer than this time, it should not be used. In the home-setting, patients should be instructed to contact the study site staff for a replacement.

Used PFS with study drug must be discarded in designated sharps containers and returned to the site for disposal per local schedule.

Under no circumstances is the investigator to allow study medication to be used other than as directed by the protocol.

Details about the packaging and labelling of the study drug will be provided in the protocol-supporting documents.

For further details, see the current Etolizumab Investigator's Brochure.

4.2.2 Dosage, Administration, and Compliance

Part 1 (OLE)

All patients will receive one 0.7-mL etolizumab injection with use of a PFS device once Q4W. The device is a 1-mL long glass syringe with a staked-in stainless steel needle prefilled with 0.7 mL (105 mg) of etolizumab. The needle is a 27G ½" thin-wall design. The needle-safety device is a standard design, and the device is fitted with a custom-designed plunger rod and an extended finger flange.

A part of the needle cap of the prefilled syringe may contain natural rubber latex that may cause allergic reactions in latex-sensitive individuals.

The recommended injection sites are the front of the middle thighs and the lower part of the abdomen below the navel except for the two inch area directly around the navel. Patients should place themselves in a comfortable position before self-administering study drug. Injections should never be given into areas where the skin is not intact or is tender, bruised, red, or hard. The injection sites will be inspected by the site personnel at each clinic visit. Any injection site reactions (see Section 5.1.1.4) should be documented on the appropriate Adverse Event electronic Case Report Form (eCRF) page. Patients administering at home should be taught to report any injection site reactions as adverse events (e.g., redness and swelling).

Patients must receive their first dose of etrolizumab in Part 1 (OLE) no more than 8 weeks after their last dose of study medication in Study GA29144. Whenever possible, patients should receive their first dose in this study within 4 weeks after their last dose in Study GA29144. Upon enrolling in Part 1 (OLE), the first four drug administrations of etrolizumab will be conducted in the clinic setting by the trained patient, the trained caregiver, or the HCP, in order to monitor for any possible hypersensitivity reactions. For those patients who choose to self-administer drug for the first time in this study, they will be trained how to use the device by a HCP and an “Information for Use” leaflet. In the event that a caregiver will ultimately administer study drug to the patient in the home setting, the caregiver is to be trained.

During the first four study treatment administrations, patients will be monitored for acute hypersensitivity reactions for at least 60 minutes after the end of the injection. Epinephrine and parenteral diphenhydramine must be readily available for immediate use if required to treat a hypersensitivity reaction; site personnel must be able to detect and treat such reactions. Patients with severe hypersensitivity reactions (e.g., stridor, angioedema, life-threatening change in vital signs) must be withdrawn from study treatment. These patients are to enter the 12-week safety follow-up in this study followed by PML monitoring in Part 2 (SM) of this study.

All adverse events of systemic hypersensitivity reactions or anaphylactoid or anaphylaxis reactions must be reported within 24 hours to the Sponsor and the Medical Monitor must be informed as soon as is practical (see the Study Manual for contact information).

Following the first four drug administrations (typically expected at 12 weeks), study drug administration will be continued in the home setting by the patient or a caregiver if considered appropriate by the investigator. If a caregiver is administering the injection, the outer area of the upper arm may be used in addition to the abdomen or thigh. If a patient is administering the injection to themselves, they are not allowed to administer the injection in their upper arm. Study medication will be administered in the patient’s home after return from the clinic visit on days when drug administration is to take place

on the same day as a clinic visit day. Patients and/or the caregiver will be provided with contact information for questions related to self-administration between visits. Competence of the patient or caregiver to administer at home will be documented in source documents. Compliance in the home setting is to be monitored by use of a patient diary to record drug administration and return of used and unused medication syringes. Patients and/or the caregiver will be provided with alert cards for themselves and a partner/caregiver, which they will be requested to carry at all times. These will include guidance on recognizing allergic/anaphylactic/anaphylactoid reactions and how to obtain emergency care in the event such a reaction occurs and information regarding recognition of symptoms of PML.

If the patient cannot administer study medication on the scheduled dosing day, study medication is to be administered within a window of ± 5 days from the scheduled dosing date. If the patient experiences a minor illness (e.g., minor infection), at the discretion of the investigator, study medication may be delayed for a maximum period of 2 weeks. Study medication dosing is to be resumed in accordance with the original dosing schedule.

If necessary, patients or their HCP may choose to continue administration of study medication in the clinic.

Guidelines for treatment interruption or discontinuation are provided in Section 4.5.

Part 2 (SM)

No study drug will be administered during Part 2 (SM) of this protocol.

4.2.3 Investigational Medicinal Product Accountability

Part 1 (OLE)

All investigational medicinal products (IMPs) required for completion of this study, namely, etrolizumab, will be provided by the Sponsor. The investigator is responsible for the control of the drugs under investigation. The investigational site will acknowledge receipt of IMP (e.g., drug receipt record) and disposition (e.g., drug dispensing log). Accountability will be assessed by maintaining adequate drug dispensing and return records. Interactive voice/Web-based response system (IxRS) will be used to confirm the shipment condition and content. Any damaged shipments will be replaced.

Accurate records must be kept for all study drug provided by the Sponsor.

These records must contain the following:

- Documentation of drug shipments received from the Sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to patients

- Drug Dispensing Log must be kept current and should contain the following information:
 - Identification of the patient to whom the study medication was dispensed
 - Date(s) and quantity of the study medication dispensed to the patient
 - Date(s) and quantity of the unused study medication returned by the patient

All records and drug supplies must be available for inspection by the study monitor.

4.2.4 Assessment of Compliance

Part 1 (OLE)

Patient compliance will be assessed by maintaining adequate drug dispensing logs, the patient diary, and return records.

Home-injection: A patient diary will be provided to patients to record home injections. Patients will be asked to return all unused PFSs in the provided boxes at each visit as a measure of drug accountability and patient compliance. Site personnel will monitor the medication records from the patient diary and patients should bring the patient diary to the clinic during each visit.

Sharps containers for any used PFSs will be provided to patients for home usage. After home injections, the used syringes must be placed into the sharps containers immediately. The sharps containers should be returned to sites. Sharps containers will be discarded by the site staff at the frequency per local schedule.

A Drug Dispensing Log must be kept as described in Section 4.2.3. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator. When the study is completed, the investigator will return all completed Drug Dispensing Logs to the Monitors.

Any unused study drug and Drug Return Records should be returned to the Monitor, unless alternate destruction has been authorized by Roche or required by local or institutional regulations (see Section 4.2.5). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Sponsor.

4.2.5 Destruction of the Investigational Medicinal Product

Part 1 (OLE)

Any used PFS will be placed into the sharps containers immediately after SC injections either at the site or at home. The sharps containers should be discarded at the study site by the site staff per local schedule. Written documentation of destruction of unused study drug must contain the following:

- Identity (batch numbers or subject numbers) of IMP(s) destroyed
- Quantity of IMP(s) destroyed

- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed investigational product(s).

In case of device failure or if there are any issues with the drug, the PFS should not be destroyed, and instead should be returned to the study site in the packaging provided for this purpose. The device is to be sent from the investigator site to the appropriate Roche Clinical Trial Supplies Department for further assessment (see Section 5.5.4).

4.2.6 Reporting of Prefilled Syringe Complaints/Events

Part 1 (OLE)

For reporting of PFS complaints or events, see Section 5.5.4.

4.3 CONCOMITANT THERAPY

4.3.1 Permitted Therapy

Part 1 (OLE)

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from the start of the study to completion/early withdrawal from treatment.

Patients who use oral contraceptives or maintenance therapy for comorbidities should continue their use.

At any time during the study, patients who have worsening CD may receive concomitant therapy with corticosteroids (IV, oral, or topical) at the discretion of the investigator.

All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. All concomitant medications ongoing in Study GA29144 must be recorded on the Concomitant Medications eCRF for this study.

Patients taking immunosuppressants in Study GA29144 may continue to receive immunosuppressants in the OLE-SM study or may initiate immunosuppressant treatment with dose adjustments at the discretion of the investigator. Generally accepted criteria for discontinuation of immunosuppressant due to toxicity include, but are not limited to, acute pancreatitis, severe leukopenia, severe thrombocytopenia, or clinically significant elevations of the liver-associated enzymes from baseline, especially in the presence of an elevated total bilirubin. The ultimate decision to discontinue or reduce dose of immunosuppressant remains at the discretion of the investigator.

Part 2 (SM)

During Part 2 (SM), investigators should follow standard practice and prescribe the local standard of care or treatments that in their opinion meet the needs of the patient.

ONLY concomitant medications used to treat event-related neurological abnormalities that are recorded and ongoing on the Adverse Event eCRF during Part 2 (SM) must be entered on the Concomitant Medication eCRF.

4.3.2 Prohibited Therapy

Part 1 (OLE)

Use of the following therapies is prohibited during Part 1 (OLE) of this study. Any patient taking the following therapies is to be withdrawn into Part 2 (SM) of this study following 12-week safety follow-up.

- Any investigational treatment, including investigational vaccines
- Use of T or B cell depleting agents (e.g., rituximab, alemtuzumab, or visilizumab), with the exception of AZA and 6-MP (or equivalent)
- Use of cyclosporine, tacrolimus, sirolimus, or MMF
- Use of anti-integrins (e.g., natalizumab or vedolizumab)
- Use of TNF antagonists
- *Use of antagonists of IL-12 ±IL-23 (e.g., ustekinumab)*
- Use of anti-adhesion molecules (e.g., anti-MAdCAM-1)

Part 2 (SM)

There are no prohibited therapies in Part 2 (SM).

4.4 STUDY ASSESSMENTS

The Schedules of Assessments are provided in the Study Flowcharts in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#). Study assessments are detailed below and will be undertaken at study visits as indicated in the Schedule of Assessments. Assessments will be performed only after informed consent has been obtained.

4.4.1 Assessments during the Study

Part 1 (OLE)

For patients enrolling into Part 1 (OLE) of this study, the informed consent for enrollment into Part 1(OLE) also includes informed consent for Part 2 (SM) of the study. Note that patients enrolling only in Part 2 (SM) from Study GA29144 will be required to sign a separate informed consent.

Eligibility criteria will be reviewed prior to the initial administration of etrolizumab in this study. Patients must meet all inclusion and exclusion criteria for study entry (see Sections [4.1.1](#) and [4.1.2](#)). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All assessments will be performed during the specified visit week, except where a time window is specified. Assessments scheduled on the day of etrolizumab administration should be performed prior to dosing, unless otherwise noted. When etrolizumab administration in the home is required on the same day as a clinic visit, drug is to be administered at home AFTER the clinic visit.

Patients enrolling in Part 1 (OLE) are to record their abdominal pain severity (using the abdominal pain questionnaire [APQ] and the 4-point ordinal pain scale provided in their study diary), loose stool frequency, and general well-being in the patient diary for 10 days prior to their clinic visit for Crohn's disease activity assessment (see [Appendix 6](#)). The Bristol Stool Scale will be provided to patients as a reference for determining loose stools (see [Appendix 7](#)). Patients will also be instructed to contact the site promptly if they have any questions about the use of the device at any time during the study.

See the Study Flowcharts provided in [Appendix 1](#) and [Appendix 2](#) for the schedule of assessments to be performed during the treatment period.

Part 2 (SM)

For patients enrolling directly into Part 2 (SM) of this study, written informed consent for participation in Part 2 (SM) of the study must be obtained prior to entry. Note that for patients enrolling only into Part 2 (SM), a separate informed consent form detailing only Part 2 (SM) assessments will be available.

See the Study Flowchart provided in [Appendix 3](#) for the assessments to be performed during the safety monitoring period.

4.4.2 Assessments at Unscheduled Visits in OLE (Part 1) and in 12-Week Safety Follow-Up

An unscheduled visit may occur at any time during the treatment period in Part 1 (OLE), including during the 12-week safety follow-up period (e.g., due to relapse of disease, disease worsening, or an adverse event). Patients who are seen by the investigator or site staff at a timepoint not required by the protocol due to assessment of potential relapse or disease worsening will undergo assessments consistent with the purpose of the unscheduled visit. Such assessments may include:

- Review of patient diary
- Recording of concomitant medications and procedures
- Collection of adverse events and serious adverse events
- Clinical chemistry and hematology, and C-reactive protein, if indicated
- Collection of ATA sample, if indicated

For unscheduled visits for reasons other than possible disease worsening or an adverse event, assessments will be done at the discretion of the investigator.

4.4.3 Assessments at Early Withdrawal

Part 1 (OLE)

Discontinuation during the OLE

Patients who discontinue treatment for any reason will be asked to complete the early withdrawal from treatment visit for Part 1 (OLE; see [Appendix 1](#)). The early withdrawal from treatment visit will be followed by a 12-week safety follow-up consisting of one telephone visit at Week 6 and one clinic visit at Week 12 (see [Appendix 2](#)). The patient should then enter the extended PML monitoring in Part 2 (SM; see [Appendix 3](#)).

Discontinuation during the 12-Week Safety Follow-Up Period after OLE

Patients who discontinue the study during the 12-week safety follow-up will be asked to complete the early withdrawal visit from the 12-week safety follow-up (see [Appendix 2](#)) and then enter the extended PML monitoring in Part 2 (SM).

Part 2 (SM)

Discontinuation during the Extended PML Monitoring Period of SM

Patients who discontinue from Part 2 (SM) of this study prior to completion of the extended PML monitoring period will be asked to complete the early termination visit from the extended PML monitoring period (see [Appendix 3](#)).

After the study completion/early termination visit, adverse events should be followed as outlined in Section [5.7](#).

See [Appendix 3](#) for specified follow-up assessments.

4.4.4 Description of Study Assessments in Part 1 (OLE)

Data from the final visit of Study GA29144 will be used for analysis and data sets for the first visit of the OLE-SM study. If any procedure and assessment was missed at the time of the final visit, it should be performed for the first visit of the OLE-SM study.

4.4.4.1 Physical Examinations

A partial physical examination will be performed at Weeks 0, 4, and 12, every 12 weeks thereafter, and at Study Completion (or Early Withdrawal visit) and the partial physical examination is to be recorded as “normal” or “abnormal.” New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF. Past resolved adverse events will be recorded in the medical history according to their medical relevance. Adverse events reported as ongoing at the end of Study GA29144 will be stated unresolved in that study and also reported in Study GA29145. The adverse event will be reported with the start date and adverse event term identical to those in Study GA29144. The initial intensity should be evaluated by the investigator at Part I (OLE) study start with the current intensity entered into the event in the eCRF.

4.4.4.2 Vital Signs

Vital signs will include measurements of heart rate and systolic and diastolic blood pressure, after the patient has been in a seated position for 5 minutes, and are to be recorded before study drug administration at clinic visit only.

Vital signs will be collected at Weeks 0 and 12, every 12 weeks thereafter, and at Study Completion (or Early Withdrawal visit).

4.4.4.3 Crohn's Disease Activity Assessments

Disease severity will be evaluated using the CDAI, SF, AP, and SES-CD, which are described below.

Crohn's Disease Activity Index

The CDAI quantifies the signs and symptoms of patients with CD (see [Appendix 5](#)). 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, abdominal pain, general well-being, presence of complications, use of Lomotil[®] (diphenoxylate/atropine) or other opiates for diarrhea, presence of an abdominal mass, hematocrit, and percentage deviation from standard weight. Of the eight factors of the CDAI, three are patient reported (number of liquid or soft stools, abdominal pain, and general well-being), four are based on physician assessment (presence of complications, use of Lomotil[®] or other opiates for diarrhea, presence of abdominal mass, and percentage of deviation from standard weight, which is based on the patient's weight at the visit), and one factor is based on a blood test (hematocrit). Patients are to report their abdominal pain severity, loose-stool frequency, and general well-being for 10 days prior to each study visit on a patient diary. The weighted sum of the average scores over 7 days is calculated for the PRO component of the CDAI score. The Bristol Stool Scale is provided to patients as a reference for determining loose stools (see [Appendix 7](#)).

Stool Frequency and Abdominal Pain

Two patient reported factors will be evaluated: the frequency of liquid or soft stools and abdominal pain. A mean daily score will be calculated for each factor, where the average will be taken over 7 days prior to the assessment visit. Patients are to report their loose-stool frequency (the Bristol Stool Scale will be provided) and abdominal pain severity for 10 days prior to each study visit on a patient diary.

Simple Endoscopic Score for Crohn's Disease (SES-CD)

The SES-CD is assessed by the investigator through endoscopy and is a composite of four factors (ulcer size, percentage of ulcerated surface, percentage of surface affected by other lesions, and extent of stenosis) in up to five ileocolonic segments (see [Appendix 11](#) for further details) and will be entered into the RAVE eCRF. Unlike the parent study, GA29144, there will be no central adjudication performed; only the investigator's evaluation of SES-CD will be used.

Abdominal Pain Questionnaire

The 0-10 point Abdominal Pain Questionnaire (APQ) is an 11-point numeric rating scale to assess the worst abdominal pain on a daily basis. A higher score indicates a greater severity of abdominal pain. The APQ has a recall specification of 24 hours. As with the CDAI, SF and AP, patients are to report their abdominal pain severity using the APQ for 10 days prior to each study visit on a patient diary.

The CDAI, SF and AP scores will be calculated, and the APQ will be completed every 12 weeks and at Study Completion (or Early Withdrawal visit if the patient completed the patient diary); SES-CD assessment will take place at the Week 108 visit or early withdrawal visit.

4.4.4.4 Ileocolonoscopy with Biopsies

An ileocolonoscopy will be performed at the Week 108 visit or Early Withdrawal visit if prior to Week 108. If the early withdrawal visit occurs after the Week 108 visit, then the ileocolonoscopy with biopsies should be conducted only at Week 108. The ileocolonoscopy should take place on the day of the Week 108 or Early Withdrawal visit or no later than 10 days after the visit. The ileocolonoscopy is being performed to assess the endoscopic change in response to prolonged continuous treatment with etrolizumab.

Patients are to prepare their bowel prior to the ileocolonoscopy procedures with a polyethylene glycol (PEG)-based preparation. Medications used for bowel preparation should be reported on the concomitant medications pages of eCRF.

Each patient entered into the study will have the opportunity to donate a single paired biopsy sample from the ileocolonoscopy procedure. The paired biopsy sample will be stored in the Roche Clinical Repository (RCR) and used in future research for Crohn's disease. Sample donation is optional and requires separate informed consent from the patient.

In consenting patients, the paired biopsy sample should be taken from the terminal ileum during the ileocolonoscopy. Necrotic areas of ulcerated mucosa should be avoided during biopsy sample collection. The paired biopsy sample should be placed in formalin and sent to the central laboratory where it will be paraffin embedded and distributed to the RCR.

4.4.4.5 Progressive Multifocal Leukoencephalopathy Assessment

Study site personnel and patients will be educated regarding the signs and symptoms of PML. New symptoms or signs suggestive of PML will be evaluated by a qualified HCP (e.g., investigator, physician assistant, nurse, nurse practitioner; a neurology consult is not required) with use of the PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation; see [Appendix 8](#)) during Part 1 (OLE), 12-week safety follow-up, and Part 2 (SM) (see [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#), respectively).

During Part 1 (OLE), the PML monitoring assessments will take place at Weeks 0 and 12 and every 12 weeks thereafter and at Study Completion (or Early Withdrawal visit).

If a patient has a positive finding on the PML Subjective Checklist that is accompanied by a positive finding on the PML Objective Checklist or if there is strong clinical suspicion for PML, the neurologic symptom or sign should be expeditiously reported to the Sponsor as adverse events of special interest or serious adverse events, as appropriate, within 24 hours (see Section [5.5.2](#) and [Appendix 9](#) for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy). If PML is suspected, dosing with etrolizumab for that patient will be suspended and the patient should be promptly referred to a neurologist.

Following formal evaluation by a neurologist, if PML cannot be ruled out, the case will be referred to an expert PML adjudication committee for further work-up, which may include brain magnetic resonance imaging (MRI) with and without contrast. If there remains any suspicion for PML, the PML adjudication committee may recommend performing a lumbar puncture with cerebrospinal fluid (CSF) analysis for JCV by polymerase chain reaction (PCR). If JCV is detected, the patient should be treated as a PML case, and the patient should permanently discontinue study drug and enter safety follow-up.

Dosing with study treatments can only be resumed in patients where PML has been ruled out. Refer to [Appendix 9](#) for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy.

After completing Part 1 (OLE), patients will enter the 12-week safety follow-up (see [Appendix 2](#)). The PML monitoring assessment is to be performed at Week 12 of this safety follow-up.

Following the 12-week safety follow-up, all patients (i.e., patients entering from Part 1 [OLE] and those enrolling directly from Study GA29144) will be requested to continue to be monitored for PML for an additional 92 weeks by enrolling in Part 2 (SM) of this study, for a total of 2 years PML follow-up after the last dose of study medication (see Section [4.4.5](#) for details of assessments in Part 2 [SM]).

4.4.4.6 Pregnancy Testing

All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test performed prior to each drug administration (Q4W).

Pregnancy tests are to be conducted at home when drug administration is in the home setting and the outcome of the pregnancy test should be recorded on a patient diary.

If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

4.4.4.7 Laboratory Assessments

Laboratory assessments will be performed as indicated on the Schedule of Assessments (see [Appendix 1](#) and [Appendix 2](#)).

General guidelines:

- Week 0 laboratory assessments that have been performed as part of the final visit for Study GA29144 do not need to be repeated, with the exception of ATAs, which must be recollected at Week 0 if the Week 0 visit occurs >7 days after the final visit for Study GA29144.
- With the exception of urine pregnancy tests, all laboratory investigations will be performed by a central laboratory.
- On days of etrolizumab administration, indicated laboratory samples should be drawn prior to study drug administration.

Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute count [neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells], mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red cell distribution width)
Collected at Weeks 0 and 12 and every 12 weeks thereafter and at Study Completion (or Early Withdrawal visit)
- Serum chemistries including liver function test (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid)
Collected at Weeks 0 and 12, every 12 weeks thereafter, and at Study Completion (or Early Withdrawal visit)
- C-reactive protein (CRP)
Collected at Week 0, every 48 weeks thereafter, and at Study Completion (or Early Withdrawal visit)

- Anti-therapeutic antibody (ATA)
Collected at Week 0 (if Week 0 visit is > 7 days from final visit in Study GA29144), Week 12, every 48 weeks thereafter, and at Study Completion (or Early Withdrawal visit)
- Hepatitis B DNA (only for those patients who are Hepatitis B core antibody positive)
Collected at Weeks 0 and 12 and every 12 weeks thereafter

4.4.4.8 Electrocardiograms

A 12-lead electrocardiogram (ECG) with formal readings will be taken every 48 weeks as well as at Study Completion (or Early Withdrawal visit) as indicated on the Schedule of Assessments. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important patients be in a resting position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. Perform ECGs prior to any scheduled vital sign measurements and blood draws.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper copies are kept as part of the patient's permanent study file at the site. ECG outputs are stored at the site.

4.4.4.9 Concomitant Medications

Concomitant medications will be monitored and reviewed at each study visit, including any unscheduled visit(s).

4.4.4.10 Adverse Events

Adverse events will be monitored and reviewed at each study visit, including any unscheduled visit(s). See Section 5 for more details about adverse events and safety reporting.

4.4.5 Description of Study Assessments in Part 2 (SM)

During the SM portion of the OLE-SM study, patients will not be administered study drug.

The PML safety monitoring portion of the OLE-SM study will consist of a telephone visit approximately every 6 months (see [Appendix 3](#)), with administration of the PML Subjective Checklist. If there are any signs or symptoms suggestive of PML identified on this subjective checklist during the telephone visit, the patient will be asked to come into the clinic for a neurologic examination, including administration of the PML Objective Checklist (see [Appendix 8](#)). The PML Algorithm (see [Appendix 9](#)) will be followed for any suspected case of PML, and any confirmed case of PML will be reported as a serious adverse event (see Section [5.1.1.1](#)).

4.5 PATIENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Patient Discontinuation

Part 1 (OLE) and Part 2 (SM)

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, specifically defined as missing scheduled visits

4.5.1.1 Withdrawal from Study

Part 1 (OLE) and Part 2 (SM)

Every effort should be made to obtain information about patients who withdraw consent or are withdrawn from the study. The primary reason for withdrawal from the study should be documented on the Study Completion/Early Discontinuation eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.2 Discontinuation from Study Drug

Part 1 (OLE)

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

- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- Confirmed PML
- Develop colonic mucosal dysplasia
- Malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin), or who develop AIS, HSIL, or CIN of Grade > 1 on cervical Pap smear.
- Any patient who experiences a de novo or reactivated serious viral infection, such as HBV, HCV, HIV
- Develop life-threatening infections during the study
- Use of any prohibited medication as a concomitant therapy (see Section [4.3.2](#))

Every effort should be made to obtain information about patients who discontinue early from the study. Patients who discontinue study drug prematurely for the reasons listed above will be asked to return to the clinic for an early withdrawal from treatment visit (see Section [4.4.3](#)) and will undergo follow-up assessments for 12 weeks within Part 1

(OLE) of this study. Patients should then enter Part 2 (SM) for 92 weeks of monitoring for PML (see Section 4.4.5). The primary reason for premature study drug discontinuation should be documented on the Study Completion/Early Discontinuation eCRF.

4.5.3 Study and Site Discontinuation

Part 1 (OLE)

The Sponsor has the right to terminate this study at any time. 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.

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study or development program.

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

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

Part 2 (SM)

- In the event of discontinuation of Part 1 (OLE), Part 2 (SM) may continue depending on the reason for study or site discontinuation.

5. ASSESSMENT OF SAFETY

The safety plan for Part 1 (OLE) and the 12-week safety follow-up is provided first, followed by the safety plan for Part 2 (SM), which focuses on PML safety monitoring in patients off etrolizumab.

5.1 SAFETY PLAN (PART 1, OLE)

The safety plan for this study is designed to ensure patient safety and mitigate potential risks. The principles of the safety plan include education of investigators and patients regarding all identified and potential safety risks, specific eligibility criteria to screen out at-risk patients, monitoring to ensure timely identification and management of a safety event, and management strategy such as guidelines for treating an event and for withholding or discontinuing of study treatment, as appropriate. These principles are to be applied for all safety risks in the clinical program.

5.1.1 Potential Risks for Etrolizumab

CD and UC share a common pathogenesis in which inflammation is caused by immune dysregulation in the gut leading to overproduction of inflammatory cytokines and

trafficking of effector leukocytes into the bowel. Although no clinical trials of etrolizumab have been conducted to date in patients with CD, etrolizumab has shown a favorable safety profile in a Phase II clinical trial in patients with moderately to severely active UC. In addition, preliminary expression studies of the pharmacological target for etrolizumab, the integrin $\beta 7$ receptor, on gut CD4+ and CD8+ T cells isolated from resections of both UC and CD patients suggest that expression levels are similar between both diseases. Given the clinical results in patients with UC and the common mechanism underlying both diseases, the safety profile for etrolizumab for CD is likely to be similar to UC.

The potential and/or hypothetical risks for etrolizumab are based on its mechanism of action, available nonclinical and clinical data, data from other anti-integrin drugs, and general risks associated with biologic agents.

Investigators should always refer to the Etrolizumab Investigator's Brochure (Section 6) for a complete summary of safety information.

Important potential risks for etrolizumab include:

- Infections, in particular, serious or life-threatening infections, such as:
 - PML
 - Other serious infections (e.g., gastrointestinal, opportunistic)
- Hypersensitivity reactions, in particular:
 - Anaphylactic, anaphylactoid reactions
 - Other systemic hypersensitivity reactions
- Hepatic effects
- Local injection-site reactions
- Malignancies
- Immunogenicity
- Decreased effectiveness of immunization

5.1.1.1 Serious Infections

5.1.1.1.1 Progressive Multifocal Leukoencephalopathy

Background

PML is a potentially fatal neurological condition linked to reactivation of a polyomavirus (JCV) and active viral replication in the brain. Cases of PML have been reported in patients with CD and multiple sclerosis who received concomitant treatment with the anti- $\alpha 4$ integrin natalizumab and immunosuppressives. Integrin $\alpha 4\beta 1$, which is inhibited by natalizumab, is a pleiotropic integrin that is believed to facilitate T cell migration into the CNS. Inhibition of integrin $\alpha 4\beta 1$ is thought to reduce (CNS) immune surveillance and facilitate development of PML.

On the other hand, extensive treatment exposure with vedolizumab, which selectively impedes lymphocyte trafficking into gut tissue by specifically blocking only the $\alpha 4\beta 7$ integrin and not the $\alpha 4\beta 1$ integrin, has not been associated with PML (Dotan 2017).

Etrolizumab targets cells expressing the $\beta 7$ integrin ($\alpha 4\beta 7$ and $\alpha E\beta 7$ cells) and not $\alpha 4\beta 1$ cells. Despite the lack of theoretical or experimental evidence for a specific role of $\beta 7$ integrins in leukocyte homing to the CNS and given the observation of PML risk with natalizumab, the Sponsor will continue to conduct extensive risk-monitoring procedures during this study. To date, there have been no cases of PML in patients treated with etrolizumab.

Screening, Patient Selection, and PML Education

No known interventions can reliably prevent or treat PML if it occurs; therefore, it is important to exclude patients with a perceived higher baseline risk for PML, such as patients who have received natalizumab, rituximab, B or T cell depleting agents (e.g., alemtuzumab or visilizumab [with the exception of AZA and 6-MP, or equivalent), cyclosporine, tacrolimus, sirolimus, or MMF. Patients with a history of PML or neurological symptoms where suspected PML has not been ruled out should also be excluded.

Study site personnel and patient participants should be educated regarding the signs and symptoms of PML. Patients and partners/caregivers should be issued with alert cards to remind them of these and to advise them to contact the investigator right away if they notice any new or worsening neurological abnormalities.

See [Appendix 1](#) for details of assessments regarding PML.

PML Monitoring

During the etrolizumab treatment, patients should be closely monitored for any signs and symptoms of PML via regular (approximately once every 12 weeks) subjective and objective tests employing the use of checklists to assess the patient's mental and neurological status. These will comprise regular neurologic examinations (including evaluation of cranial nerves, motor and sensory function, coordination, and mental status) as per the Schedule of Assessments (see [Appendix 1](#)). The PML Subjective Checklist (symptom assessment) and the PML Objective Checklist (neurologic evaluation) will be administered ([Appendix 8](#); Worksheet for the PML Neurologic Examination) by a qualified HCP and will be performed as indicated on the Schedule of Assessments (see [Appendix 1](#)).

During the in-clinic visits, patients will undergo PML monitoring assessments.

If a patient has a positive finding on the PML Subjective Checklist that is accompanied by a positive finding on the PML Objective Checklist or if there is strong clinical suspicion for PML, the neurologic symptom or sign should be expeditiously reported to the

Sponsor as adverse events of special interest or serious adverse events, as appropriate, within 24 hours (see Section 5.5.2 and [Appendix 9](#) for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy).

If PML is suspected, dosing with study treatment for that patient will be suspended and the patient should be promptly referred to a neurologist. Following formal evaluation by a neurologist, if PML cannot be ruled out, the case will be referred to an expert PML adjudication committee for further work-up, which may include brain MRI with and without contrast. If there remains any suspicion for PML, the PML adjudication committee may recommend performing a lumbar puncture with CSF analysis for JCV DNA by PCR. If JCV DNA is detected, the patient should be treated as a PML case and the patient should permanently discontinue study drug and enter safety follow-up. Dosing with study treatments can only be resumed in patients where PML has been ruled out. Refer to [Appendix 9](#) for the Algorithm for Evaluation of Progressive Multifocal Leukoencephalopathy.

PML Treatment

There is no known effective treatment for PML. Plasmapheresis has been employed in some patients where the event has been thought to be due to administration of a drug (Tan et al. 2011). If an event of PML occurs, subsequent management of PML will be at the direction of the consulting neurologist.

Additional information for the management of this potential risk is provided in [Appendix 8](#) (Worksheet for the PML Neurologic Examination) and [Appendix 9](#) (Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy).

5.1.1.1.2 Other Serious Infections Background

Clinical data to date have not shown an increased risk of serious infections with etrolizumab. In the Phase II EUCALYPTUS study, serious infections were reported in 2.3% of patients who received placebo versus none in the etrolizumab-treated patients. Nonetheless, serious infections are a potential risk due to the mechanism of action of etrolizumab, which blocks trafficking of gut-selective lymphocytes.

Patient Selection

Patients who experienced a life-threatening infection or a de novo or reactivated serious viral infection, such as HBV, HCV, or HIV, during Study GA29144 should not be enrolled in Part 1 (OLE) of this study. Similarly, patients who developed CMV colitis leading to early treatment discontinuation in Study GA29144 should be excluded

Patients who have an ongoing serious infection event should not receive study drug until the event has completely resolved and treatment with anti-infective medications has been completed. Patients with hepatitis B infection who test positive only for core

antibody (anti-HBc+) and test negative for HBV DNA test are eligible for the study; however, these patients must undergo periodic monitoring for HBV DNA during the study.

Education, Monitoring, and Management

Patients should be monitored closely for serious infections during the study. Patients and study staff should be informed of the possibility of increased susceptibility to infectious pathogens. Investigators will be encouraged to promptly evaluate and aggressively treat any signs and symptoms consistent with an infection.

Patients who experience a serious infection event should not receive further study drug until the event has completely resolved and treatment with anti-infective medications has been completed. All efforts should be made to identify the infectious agent. For those patients who recover from a serious infection, study medication may be restarted following consultation with the Medical Monitor.

Patients who develop life-threatening infections, including de novo or reactivated serious viral infection, such as HBV, HCV, HIV, during the study should discontinue study drug. Any patient who develops CMV colitis should not receive further study drug until the event has resolved and treatment with appropriate anti-viral medication has been completed. Re-initiation of study treatment requires consultation with the Medical Monitor.

5.1.1.2 Hypersensitivity Reactions Background

In completed Phase I/II clinical trials of etrolizumab in UC, one serious adverse event of hypersensitivity (Grade 2) has been reported. No anaphylactic, anaphylactoid, or severe hypersensitivity reactions were observed; however, anaphylaxis, anaphylactoid, and hypersensitivity reactions will be closely monitored during the study.

Patient Selection

Patients who developed an anaphylactic/anaphylactoid or severe allergic reaction to study medication during Study GA29144 will be excluded from participation in Part 1 (OLE) of this study.

Education, Monitoring, and Management

The first four injections should be administered in the clinic in order to monitor for any possible hypersensitivity reactions, given that patients who received blinded placebo in Study GA29144 may receive their first etrolizumab dose upon enrolling in the OLE-SM study. After each of these four injections, the patient must be monitored for 60 minutes. Medicinal products for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, and glucocorticoids) must be available for immediate use in the clinic for the event of an allergic reaction during administration of the study drug. Resuscitation equipment should also be available.

Patients should be instructed to recognize the symptoms of any anaphylactic, anaphylactoid, or hypersensitivity reaction and to contact a HCP 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 the above.

If the patient develops any systemic hypersensitivity, anaphylactic, or anaphylactoid reaction, the event should be expeditiously reported to the Sponsor as an adverse event of special interest or serious adverse event, as appropriate, within 24 hours.

If a patient has symptoms of anaphylaxis or severe hypersensitivity, the administration of etrolizumab must be discontinued permanently.

Refer to [Appendix 10](#) (Clinical Criteria for Diagnosing Anaphylaxis).

5.1.1.3 Hepatic Effects

Background

Liver toxicity has been reported with other class drugs that target $\alpha 4$ integrins (natalizumab) and $\alpha 4\beta 7$ integrins (vedolizumab). Therefore, this potential risk is being monitored in all etrolizumab studies. In nonclinical chronic toxicology studies, no abnormalities indicating liver toxicity with etrolizumab were observed. The risk in humans is currently unknown.

Education, Monitoring, and Management

Patients should receive guidance on reporting liver problems if they occur. Liver function tests should continue to be monitored according to the schedule of assessments and as clinically indicated. Significant hepatic events should be evaluated promptly and managed accordingly.

5.1.1.4 Local Injection-Site Reactions

Background

A local injection-site reaction is any local reaction occurring at the site of injection following study drug administration. In completed Phase I/II trials, injection-site reactions were reported at a rate of $\leq 10\%$, all of which were of mild intensity.

Monitoring

In the clinic setting, patients should be monitored for signs of injection-site reactions in the period immediately following injections. Patients should be given guidance on reporting injection-site reactions when administering drug at home or after the patient leaves the clinic.

5.1.1.5 Malignancies

Background

There has been no evidence for increased incidence of malignancy in completed Phase I/II trials and nonclinical studies to date. Nonetheless, given the elevated risk of

malignancy in this patient population a priori, the study includes selection criteria and additional information to minimize any hypothetical risk.

Patient Selection

Patients who developed a malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) during Study GA29144, including AIS, HSIL, or CIN of Grade > 1 or colonic dysplasia, are to be excluded from this study.

Monitoring and Management

Investigators should remain vigilant for signs or symptoms of malignancy in scheduled study assessments, including those of potential lymphoma.

Any signs or symptoms that could be suggestive of malignancy should be promptly and aggressively evaluated and reported to the Sponsor. Incident hematologic abnormalities (e.g., new or worsening neutropenia, anemia, thrombocytopenia, macrocytosis, or atypical cells in the WBC differential) should be carefully evaluated.

Patients who develop a malignancy (with the exception of local and resected basal or squamous cell carcinoma of the skin) or who develop AIS, HSIL, or CIN of Grade > 1 on cervical Pap smear or who develop colonic dysplasia during the study should be withdrawn from study drug and must not receive additional doses of study drug.

5.1.1.6 Immunogenicity Background

As with administration of any exogenous protein, a potential exists for the development of ATAs. Such antibodies can be neutralizing with potential for reducing therapeutic effect of the drug and/or sensitizing, with potential for allergic reactions. On the basis of the clinical experience to date, approximately 5% of patients develop ATAs to etrolizumab; however, this has not been correlated with any efficacy or safety sequelae.

Monitoring

To assess for the potential development of immunogenicity, antibody samples will be obtained at baseline, at regular intervals during treatment, and during the Safety Follow-Up Period (see [Appendix 1](#) and [Appendix 2](#)), and stored appropriately for further evaluation as needed.

5.1.1.7 Decreased Effectiveness of Immunizations Background

The effect of etrolizumab upon the efficacy of vaccinations is unknown.

Patient Selection and Risk Mitigation

Patients who received a live attenuated vaccine during Study GA29144 or within 4 weeks prior to enrollment in the OLE are excluded from the study. Patients should not receive live attenuated vaccines during the study and for at least 5 half-lives (approximately 12 weeks) after final study drug administration.

5.1.2 Risks Associated with Worsening of Crohn's Disease

The worsening of CD may result in the use of rescue medications. In severe cases, worsening of CD may lead to hospitalization or require surgery.

At any time during the study, patients who have worsening of their CD will be permitted to receive additional therapy with corticosteroids (IV, oral, or topical). Addition of or increases in doses of immunosuppressants (i.e., AZA, 6-MP, or MTX) will also be allowed if clinically indicated by the Principal Investigator.

Rescue therapy with anti-TNF agents (including TNF inhibitor biosimilars), cyclosporine, tacrolimus, sirolimus, MMF, natalizumab, vedolizumab, anti-adhesion agents, rituximab, other lymphocyte depleting agents (except AZA and 6-MP, or equivalent), or other biological or investigational therapeutics will not be allowed in conjunction with etrolizumab because of the level of immunosuppression anticipated with the use of these agents. Patients who receive any of these prohibited rescue medications are not to receive further treatment with etrolizumab, are to complete the 12-week safety follow-up, and should then enter into Part 2 (SM) of the study.

See Section 4.4.2 and Appendix 1 for the schedule of assessments to be performed in the event of worsening of CD, which may lead to an unscheduled visit.

5.1.3 Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will monitor safety and study conduct for Study GA29144 on an ongoing basis until the study is unblinded to the Sponsor. Safety data from Study GA29145 will also be available for review by the iDMC on an ongoing basis to inform their assessment of the overall safety of etrolizumab in CD.

Members of the iDMC will be external to the Sponsor and will follow a charter that outlines the iDMC roles and responsibilities. The iDMC will meet approximately every 6 months (frequency adjustable as required) to review data prepared by an independent data coordinating center. The iDMC may recommend stopping the study early for safety reasons.

Because of the open-label design of the OLE-SM study, the Sponsor will retain the primary responsibility for monitoring its safety and study conduct.

5.2 SAFETY PLAN (PART 2, SM)

PML Monitoring Part 2 (SM)

Following the 12-week safety follow-up period in Study GA29144 or in Part 1 (OLE) of the OLE-SM study, all patients are to continue to be monitored for PML for an additional 92 weeks (extended PML monitoring) in Part 2 (SM) of this study, providing a total of 2 years PML follow-up after the last dose of study drug. No etrolizumab will be administered during this time.

PML monitoring during this period will consist of the PML assessment interview conducted by telephone at intervals of approximately 6 months (see [Appendix 3](#)). Any signs or symptoms suggestive of PML or cases of suspected PML (see [Appendix 8](#)) should be documented and handled and expeditiously reported to the Sponsor as adverse events of special interest or serious adverse events, as appropriate, within 24 hours, as described in Section [5.1.1.1.1](#) and [Appendix 9](#) (Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy). Study site personnel and patient participants will be educated regarding the signs and symptoms of PML and suspected cases of PML will be managed as in Section [5.1.1.1.1](#). Patients are to be instructed to contact the investigator immediately if they experience signs and/or symptoms suspected to be PML between the 6-month telephone intervals.

5.3 SAFETY PARAMETERS AND DEFINITIONS

Safety Assessments during Part 1 (OLE)

Safety assessments in Part 1 (OLE) will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and 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 [5.5](#).

Safety Assessments during Part 2 (SM)

Safety assessment in Part 2 (SM) will consist of only PML monitoring with use of the PML Subjective Checklist conducted by telephone at intervals of approximately 6 months (see [Appendix 3](#)) during which any signs or symptoms suggestive of PML (see [Appendix 8](#)) will be documented and handled as described in Section [5.1.1.1](#) and [Appendix 9](#) (Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy).

5.3.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation patient 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), except as described in Sections [5.4.6.9](#) and [5.4.6.10](#)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.3.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Fatal (i.e., the adverse event actually causes or leads to death)
- 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 [5.4.6.11](#))
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- 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 (rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section [5.4.4](#)); 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 [5.5.2](#) for reporting instructions).

5.3.3 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 5.5.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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 (Section 5.4.6.7)
- Suspected transmission of an infectious agent by etrolizumab, 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.
- Adverse events of special interest specific to etrolizumab:

Systemic hypersensitivity reactions and anaphylactic and anaphylactoid reactions (see Section 5.1.1.2 and Clinical Criteria for Diagnosing Anaphylaxis in Appendix 10)

Neurological signs, symptoms, and adverse events that may suggest possible PML, on the basis of a positive finding on the PML Subjective Checklist that is accompanied by a positive finding on the PML Objective Checklist, or if there is strong clinical suspicion for PML (see Appendix 9 Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy and Section 5.1.1.1)

5.4 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

5.4.1 Adverse Event Reporting Period for Part 1 (OLE)

After informed consent has been obtained, all adverse events, regardless of relationship to study drug, will be reported until the patient completes Part 1 (OLE).

During Part 1 (OLE), the investigator is responsible for ensuring that all adverse events (see Section 5.3.1 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 5.5, 5.6, and 5.7. The investigator is also responsible for reporting medical device complaints (see Section 5.5.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.3.2 for seriousness criteria), severity (see Section 5.4.4), and causality (see Section 5.4.5).

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. Past resolved adverse events will be recorded in the medical history according to their medical relevance. Adverse events reported ongoing at the end of Study GA29144 will be stated unresolved in that study and also reopened in Study GA29145. The adverse event will be reported with the start date and adverse event term identical to those in Study GA29144. Intensity should be evaluated by the investigator at the start of Part 1 (OLE) with the intensity entered into the initial intensity field for the event in the eCRF for Study GA29145. Additionally, the most extreme NCI CTCAE grade for the event that occurs during Study GA29145 should also be recorded in the eCRF for Study GA29145.

All adverse events following patient informed consent to the study, regardless of relationship to study drug, will be reported until the patient completes Part 1 (OLE).

Some patients may not enroll into Part 2 (SM), although all patients will be strongly encouraged to enter. For those patients who do not enroll into Part 2 (SM) (i.e., withdraw consent from the study), the Sponsor should be notified if post-study the investigators becomes aware of any serious adverse events that are believed to be related to prior study drug treatment (see Sections 5.7.1). In addition, the Sponsor should be notified if the investigator becomes aware of any post-study events of confirmed or suspected PML, regardless of relationship to study drug, for up to 2 years after the patient's last dose of study drug.

5.4.2 Adverse Event Reporting Period for Part 2 (SM)

Part 2 (SM) of the OLE-SM study is focused on extended follow-up for PML. During Part 2 (SM), the investigator will use the PML assessment interview to monitor for signs and symptoms of PML. All adverse events suggestive of PML, regardless of relationship to study drug, should be expeditiously reported to the Sponsor as adverse events of special interest or serious adverse events, as appropriate, within 24 hours.

The eCRF will be available during Part 2 (SM) to only report any adverse events of special interest or serious adverse events that may suggest possible PML or confirmed PML. Refer to the eCRF help instructions for more details. If the eCRF system is not available, then the process for submitting non-PML events (see below) should be followed.

The investigator is not required to actively monitor patients for other non-PML adverse events during Part 2 (SM); however, the investigator should notify the Sponsor if they become aware of any other non-PML serious adverse events that are believed to be related to prior study drug treatment. The investigator should report such events directly to Roche or its designee either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators

5.4.3 Eliciting Adverse Event Information in Part 1 (OLE)

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?”

5.4.4 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 2](#) will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2 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 one's self, 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 5.5.2 for reporting instructions), per the definition of serious adverse event in Section 5.3.2.
- ^d Grade 4 and 5 events must be reported as serious adverse events (see Section 5.5.2 or reporting instructions), per the definition of serious adverse event in Section 5.3.2.

5.4.5 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 (see [Table 3](#)). The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where 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 3 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	<u>Adverse events will be considered related, unless they fulfill the criteria as specified below.</u> 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 two days after first dose of study drug).

5.4.6 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.

PART 1 (OLE)

All ongoing adverse events from Study GA29144 should be entered on the Adverse Event eCRF.

All new adverse events that occur during Part 1 (OLE) should be entered on the Adverse Event eCRF.

PART 2 (SM)

Record on the Adverse Event eCRF ONLY event-related neurological abnormalities (signs/symptoms that may suggest possible PML) identified on both the PML Subjective AND PML Objective Checklist or if there is a strong clinical suspicion for PML as an adverse event of special interest or serious adverse event, as appropriate. Each abnormality should be reported as a separate adverse event of special interest. Do NOT report events as "Suspected PML" or "Rule out PML." If there is a confirmed diagnosis of PML, report this diagnosis as a serious adverse event.

In Part 2 of the study, all events that may suggest possible PML should be entered on the Adverse Event eCRF. All other non-PML serious adverse events that the investigator becomes aware of and believes to be related to prior study drug treatment should be reported to the Sponsor via faxing/e-mailing the paper serious adverse event reporting form.

5.4.6.1 Injection-Site Reactions

Local cutaneous adverse events that occur at or around the injection site during or within 24 hours after study drug injection should be captured as individual signs (e.g., erythema, induration/swelling at injection site) and symptoms (e.g., pain, pruritus at injection site) rather than a diagnosis of allergic reaction or injection site reaction.

5.4.6.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection-site reactions (see Section 5.3.1), 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.

5.4.6.3 Adverse Events Occurring Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent 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.

5.4.6.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported in this study. For adverse events ongoing from the parent study, the current intensity of the event at this study start will be recorded as the initial intensity for the event in this study. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event 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 5.5.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.4.6.5 Abnormal Laboratory Values

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

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

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× upper limit of normal [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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.4.6.4 for more details).

5.4.6.6 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.4.6.4 for more details).

5.4.6.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) 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 $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ 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 5.4.6.5) 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 5.5.2).

5.4.6.8 Deaths

Part 1 OLE (including the 12-week safety follow-up period)

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.4.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.5.2). This includes death attributed to progression of 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 CD, "Crohn's disease progression" should be recorded on the Adverse Event eCRF.

Part 2 (SM)

During the 92-week safety monitoring for PML, all deaths due to PML, regardless of relationship to study drug, must be reported to the sponsor as a serious adverse event on the Adverse Event eCRF (see Section 5.4.6).

If the investigator is made aware of a non-PML event of death, then it should be reported directly to Roche or its designee either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

5.4.6.9 Preexisting Medical Conditions

Past resolved adverse events will be recorded in the medical history according to their medical relevance. Adverse events reported ongoing at the end of Study GA29144 will be stated unresolved in those studies and also reported in Study GA29145.

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").

5.4.6.10 Lack of Efficacy or Worsening of Crohn's Disease

Medical occurrences or symptoms of deterioration that are anticipated as part of CD should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening CD on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated Crohn's disease" or "worsening of Crohn's disease").

5.4.6.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient 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 5.3.2), except as outlined below. The duration of hospitalization should also be noted on the eCRF.

The following hospitalization scenarios are not considered to be adverse events or serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- 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 suffered an adverse event.

The following hospitalization scenario 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

5.4.6.12 *Adverse Events Associated with an Overdose or Error in Drug Administration*

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not itself an adverse event, but it may result in an adverse event.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

5.4.6.13 **Patient-Reported Outcome Data**

Adverse event reports will not be derived from patient-reported outcome (PRO) data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.5 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR DURING PART 1 (OLE) AND PART 2 (SM)

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. See Section 5.5.2 for reporting requirements in Part 1 (OLE) and Part 2 (SM).

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 (see Section 5.5.2 for more details)
- Adverse events of special interest (see Section 5.5.2 for more details)
- Pregnancies (see Section 5.5.3 for more details)

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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.5.1 Emergency Medical Contacts

Medical Monitor Contact Information

Primary Contact

Medical Monitor: [REDACTED], M.B., Ch.B.

Primary: +1 973 659 6677

Secondary: +1 570 819 8565

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Quintiles Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Quintiles Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. A primary global contact number and additional back up number for the Help Desk and Medical Monitor contact information

will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

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

Part 1 (OLE)

For reports of serious adverse events and adverse events of special interest, 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 the Sponsor by the EDC system.

In the event that the EDC system is unavailable, a paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form and fax cover sheet should be completed and faxed to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Part 2 (SM)

Reports of all PML-related serious adverse events and adverse events of special interest (regardless of relationship) should be entered into the Adverse Event eCRF. Events of related non-PML serious adverse events and pregnancies will be reported via faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

5.5.3 Reporting Requirements for Pregnancies

5.5.3.1 Pregnancies in Female Patients

Part 1 (OLE)

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 24 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In addition, the investigator will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Part 2 (SM)

The same approach (e.g., immediate reporting) as described below applies; however, pregnancies should be reported directly to the Sponsor by completion of the Clinical Trial Pregnancy Reporting Form and either by faxing or by scanning and e-mailing the form using the fax number or e-mail address provided to investigators. Abortions or congenital anomalies/birth defects should be reported directly to the Sponsor with use of the Serious Adverse Event/Adverse Event of Special Interest Reporting Form as indicated in Section [5.5.2](#).

5.5.3.2 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 24 weeks after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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 paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy 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.

5.5.3.3 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant events), 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 [5.5.2](#)).

5.5.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or 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 [5.5.2](#)).

5.5.4 Reporting Requirements for Prefilled Syringe Complaints/Events

The investigator should report all medical device complaints to the Sponsor. The investigator must document as much information as possible on the PD103 IMP Deviation Form, including product batch number and expiration date, and forward the complaint form to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event). The PD103 IMP Deviation Form, together with pictures of the defective PFS, should be sent to kaiseraugst.global_impcomplaint_management@roche.com.

Where possible, the investigator will retrieve the PFS unit(s) involved in the complaint and attempt to return it to the Sponsor for further assessment, if necessary.

If the medical device complaint results in an adverse event, an Adverse Event eCRF must be completed and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed and submitted through the EDC immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.5.2. If the medical device complaint results in an adverse event to an individual other than the study patient, the device complaint must be reported on the PD103 IMP Deviation Form and the adverse event must be reported as a spontaneous adverse event to the Sponsor.

5.6 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.6.1 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 study-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.

5.6.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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.

5.7 POST-STUDY ADVERSE EVENTS

5.7.1 Post-Study Adverse Events Part 1 (OLE)

Patients Who Exit Part 1 (OLE) and Do Not Enter Part 2 (SM)

All patients should be encouraged to enter Part 2 (SM) of this study to allow for long-term PML monitoring and timely assessment of any symptoms that could be related to PML.

For those patients who do not enter Part 2 (SM) of this study, if investigators become aware of any serious adverse event after the end of the 12-week safety follow-up period that is believed to be related to prior study drug treatment, this should be reported to the Sponsor. In addition, the Sponsor should be notified if the investigator becomes aware of any post-study events of confirmed or suspected PML, regardless of relationship to study drug, for up to 2 years after the patient's last dose of study drug.

The investigator should report these events directly to Roche or its designee either by faxing or by scanning and e-mailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

Patients Who Exit Part 1 (OLE) and Enter Part 2 (SM)

Investigators should continue to provide follow-up data, if they receive it, to the Sponsor on unresolved adverse events.

5.7.2 Post-Study Adverse Events Part 2 (SM)

The Sponsor should be notified if the investigator becomes aware of any post-study serious adverse events that are believed to be related to prior study drug treatment.

For patients who withdraw from the study, the Sponsor should also be notified if the investigator becomes aware of any post-study events of confirmed or suspected PML, regardless of relationship to study drug, for up to 2 years after the patient's last dose of study drug.

The investigator should report these events directly to Roche or its designee either by faxing or by scanning and e-mailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or e-mail address provided to investigators.

5.8 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 for etrolizumab using the following reference document:

- Etrolizumab Investigator's Brochure

Within the Investigator's Brochure, the reference safety information is provided in Section 6.4 Identified Risks and Adverse Drug Reactions (Reference Safety Information).

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.

All serious related (as assessed by the investigator and/or Sponsor) adverse events occurring in a patient administered etrolizumab at any time during the trial and assessed as unexpected per the reference safety information will be considered Suspected Unexpected Serious Adverse Reactions (SUSARs) for the purpose of regulatory reporting to all health authorities, with the exception of the U.S. Food and Drug Administration (FDA). For the FDA, SUSARs will be submitted as IND Safety Reports, in line with the FDA guidance "Safety Reporting Requirements for INDs and BA/BE Studies" dated December 2012.

The Sponsor will report all SUSARs into the EudraVigilance database in accordance with the "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')."

To maintain the blind, investigators will be informed of all unexpected serious adverse events satisfying local regulatory reporting criteria but regardless of study drug assignment (i.e., they may also receive reports of patients on placebo).

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Because of the non-comparative character of the study, no statistical tests are planned; all efficacy parameters will be summarized descriptively. Efficacy in Part 1 (OLE) will be assessed across visits using absolute values and change from baseline for continuous outcomes, and dichotomous data (e.g., CDAI remission, clinical remission) will be evaluated using frequency counts and proportions. Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants, duration of disease, and CDAI, SF and AP scores will be summarized by use of descriptive statistics.

6.1 NUMBER OF PATIENTS

The maximum number of patients enrolled in the OLE-SM study is approximately 1150 (i.e., all patients enrolled in Study GA29144). No formal sample size calculations were performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enrolled in Part 1 (OLE) and Part 2 (SM) will be tabulated by country and study site. The number of patients who discontinued early (early discontinuation of OLE treatment or early termination from the study) or completed the study will be tabulated. Reasons for early discontinuation of treatment or early termination from the study will be listed and summarized. Any eligibility criteria exceptions and other major protocol deviations will also be summarized.

6.3 SAFETY ANALYSES FOR PART 1 (OLE)

The safety analyses will include all patients who received at least one dose of etrolizumab.

Safety will be assessed through descriptive summaries of adverse events, laboratory test results (serum chemistry, hematology including complete blood count with differential and platelet counts), and antibodies to etrolizumab.

6.3.1 Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded and their incidence and observation time-adjusted rate will be summarized, as appropriate. A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug. In addition, separate summaries will be generated for serious adverse events, deaths, and adverse events leading to discontinuation of etrolizumab.

Analyses will also be performed for:

- Systemic hypersensitivity events

Specific analyses will be performed for anaphylactic reactions using both the anaphylactic reaction MedDRA SMQ and Sampson's criteria (see [Appendix 10 Clinical Criteria for Diagnosing Anaphylaxis](#)).

- Serious infections, in particular GI infections
- Opportunistic infections
- Malignancies
- Injection-site reactions

6.3.2 Laboratory Tests

Descriptive summaries of laboratory values at baseline and throughout the study will be tabulated. For selected parameters, changes from baseline and the proportion of patients experiencing clinically significant changes relative to baseline will be summarized.

The number and percentage of patients with positive serum antibodies to etrolizumab at baseline and during the study will be tabulated.

6.4 SAFETY ANALYSES FOR PART 2 (SM)

In Part 2 (SM), any suspected or confirmed PML events will be listed and described by means of safety narratives.

Serious adverse events (including serious infections) and deaths will also be described as narratives.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Sponsor, contract research organization (CRO), and Data Management vendor will be responsible for the data management of this study, including quality checking of the data. Sites will be responsible for data entry into the eCRF via the EDC system. In the event of discrepant data, data queries will be issued to the sites and resolved by the sites via the EDC system. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. In addition, eCRF Help Text will be provided to the sites through the EDC system. eCRFs and correction documentation will be maintained in the EDC system's audit trail.

Central laboratory data will be transferred directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to Help Text Medidata RAVE 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 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Patient-reported data may be collected electronically through use of electronic devices provided by an electronic patient-reported outcome (ePRO) vendor. If an electronic device, such as an electronic diary (e-diary), is used, the electronic device will be designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 Code of Federal Regulations, Part 11). The data will be transmitted to a centralized database at the ePRO vendor. The data from the e-devices are available for view access only via secure access to a Web portal provided by the ePRO vendor. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. Regular data transfers will occur from the centralized database at the vendor to the database at the Sponsor.

Once the study is complete, the ePRO data, audit trail, and trial and system documentation will be archived. The Sponsor will receive all data entered by patient on the e-diary and tablet device and all the study documentation.

Details regarding patient reported data and the electronic device is available in the Study Reference Manual. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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, 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, MRIs, ECGs, 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 into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section [7.6](#).

To facilitate source data verification, 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 investigational site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

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

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, patient data (including PROs), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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 EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms, 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.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens 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 allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative 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 or the patient's legally authorized representative. 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 of 1996 (HIPAA). 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 only be disclosed to third parties 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.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other 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 (i.e., last patient last visit in PML monitoring).

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, which includes 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 trial is sponsored by F. Hoffmann–La Roche Ltd.

A CRO will be contracted to manage the study and perform monitoring activities.

Centralized facilities (vendors) will be used to collect patient reported outcome symptom data.

A central laboratory will be used for most laboratory assessments. A selected group of assessments will be performed on site or by a local laboratory.

The eCRF data will be recorded via a Sponsor-designated EDC system. An IxRS will be used for study drug inventory management.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. 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.

The Sponsor will comply with the requirements for publication of study results. 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 Open-Label Extension (OLE, Part 1) Schedule of Assessments

Assessment Category	Part 1 (OLE)	In-Clinic Etrolizumab Administration Every 4 Weeks				At-Home Etrolizumab Administration Every 4 Weeks (or in-clinic administration if unable to perform at home)				
		Clinic Visit at Every 4-Week Interval (± 3 days)				Clinic Visit at Every 12-Week Interval (starting at Week 24) (± 7 days)	Clinic Visit at Every 48-Week Interval ^c (± 7 days)	Clinic Visit at Week 108 ^d (± 7 days)	Unscheduled Visit ^e	Study Completion or Early Withdrawal Visit ^f
		0 ^{a, b}	4	8	12					
Prior to entry into Part 1 (OLE)	Informed consent	x								
	Review eligibility criteria	x								
Study Drug	Etrolizumab administration	x	x	x	x	x				
Assessments during Part 1 (OLE)	Concomitant medications	x	x	x	x	x			x	x
	Adverse events ^g	x	x	x	x	x			x	x
	Patient diary check	x			x	x				x ^h
	Pregnancy test ⁱ	x	x	x	x	x				x
	CDAI assessment	x ^j			x ^k	x ^k			x	x ^h
	Weight	x			x	x				x ^h
	PML neurologic examination ^l	x			x	x			x	x
	Vital signs (BP, pulse rate)	x			x	x				x
	Limited/symptom-driven physical examination, including GI	x	x		x	x			x	x

Appendix 1
Open-Label Extension (OLE, Part 1) Schedule of Assessments (cont.)

Assessment Category	Part 1 (OLE)	In-Clinic Etrolizumab Administration Every 4 Weeks				At-Home Etrolizumab Administration Every 4 Weeks (or in-clinic administration if unable to perform at home)				
		Clinic Visit at Every 4-Week Interval (± 3 days)				Clinic Visit at Every 12-Week Interval (starting at Week 24) (± 7 days)	Clinic Visit at Every 48-Week Interval ^c (± 7 days)	Clinic Visit at Week 108 ^d (± 7 days)	Unscheduled Visit ^e	Study Completion or Early Withdrawal Visit ^f
		0 ^{a, b}	4	8	12					
	ECG	x					x			x
	Ileocolonoscopy							x ^m	x	x ⁿ
	Paired biopsy collection (optional; requires RCR consent)							x		x
Laboratory Assessments	Hematology ^o	x			x	x			x	x ^p
	Chemistry (including LFTs) ^q	x			x	x			x	x ^p
	Serum (CRP)	x					x		x	x ^p
	Hepatitis B DNA ^r	x			x	x				
	Anti-therapeutic antibody sample (serum) ^s	x ^b			x		x		x	x ^p

AP=abdominal pain; ATA=anti-therapeutic antibody; BP=blood pressure; CDAI=Crohn's Disease Activity Index; CRP=C-reactive protein; ECG=electrocardiogram; eCRF=electronic case report form; GI=gastrointestinal; JCV=John Cunningham virus; LFT=liver function test; OLE=open-label extension; PML=progressive multifocal leukoencephalopathy; RCR=Roche Clinical Repository; SF=stool frequency.

Note: All assessments and blood draws are to be conducted prior to study medication administration.

^a Day 1 of Week 0.

^b Week 0 procedures and laboratory assessments that have been performed as part of the final visit for Study GA29144 do not need to be repeated, with the exception of ATAs, which must be recollected at Week 0 if the Week 0 visit occurs >7 days after the final visit for Study GA29144.

Appendix 1

Open-Label Extension (OLE, Part 1) Schedule of Assessments (cont.)

- ^c Assessments in this column should be conducted in addition to the assessments conducted every 12 weeks.
- ^d Assessments in this column should be conducted in addition to the assessments conducted every 12 weeks and every 48 weeks.
- ^e Unscheduled visit represents a visit that is not as per Schedule of Assessments and is required for an adverse event or for potential relapse assessment. All indicated assessments are NOT performed at each unscheduled visit. Assessments would be symptom driven (e.g., only perform PML neurologic examination if patient reports symptoms suspected to indicate PML). Assessments corresponding to items noted in this column should be recorded on the eCRF.
- ^f Denotes the early withdrawal from treatment visit for the open-label treatment period. To be performed within 30 days of last dose of study drug. Study drug is not administered at the Early Withdrawal from Treatment visit.
- ^g Patients will be given patient alert cards that provide information regarding the signs and symptoms of PML. Patients will be instructed to contact the study site at any time if they develop any new neurological signs or symptoms suggestive of PML.
- ^h Patient diary check (including completion of abdominal pain questionnaire), CDAI assessment, and recording patient's weight are required at study completion. Conduct CDAI assessment and record patient's weight at early withdrawal visit if diary-data captured prior to the early withdrawal visit are available.
- ⁱ For women of childbearing potential, including those who have had a tubal ligation. Perform a urine pregnancy test; if the urine pregnancy test result is positive, perform a confirmatory serum pregnancy test. Pregnancy test will be carried out at home once the patient starts etrolizumab administration at home. Pregnancy test must be completed prior to etrolizumab administration. Patient is to report the pregnancy test result in the patient diary. Patients must be instructed at screening and reminded throughout the study that in case of a positive pregnancy test, they should stop self-administration of study drug and call the site immediately. Do not administer etrolizumab unless the serum pregnancy test result is negative.
- ^j CDAI, SF, and AP scores will not be recalculated at the Week 0 visit; however, scores from the most recent visit in Study GA29144 (Week 10, Week 14, Week 74, or Early Withdrawal visit) should be entered into the database along with date of assessment.
- ^k Patients are to complete the patient diary for stool frequency, abdominal pain, and general well-being for 10 days prior to the clinic visits when CDAI assessments are scheduled (every 12 weeks).
- ^l PML neurologic examination consists of the PML Subjective Checklist and the PML Objective Checklist. Administered by a qualified HCP before other assessments, as per [Appendix 8](#).
- ^m The ileocolonoscopy should be conducted on the day of the clinic visit or within 10 days after the clinic visit was completed.
- ⁿ An ileocolonoscopy will be performed at the Week 108 visit or early withdrawal visit if prior to Week 108. If early withdrawal visit occurs after the Week 108 visit, then the ileocolonoscopy with biopsies should be conducted only at Week 108.
- ^o Includes hemoglobin, hematocrit, platelet count, RBC count, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, red cell distribution width, WBC count, and differential.
- ^p Not required if unscheduled visit leads to withdrawal and assessment previously conducted at unscheduled visit.

Appendix 1
Open-Label Extension (OLE, Part 1) Schedule of Assessments (cont.)

- ^q Includes sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine phosphokinase, and uric acid.
- ^r Only enrolled patients who were hepatitis B core antibody positive in Study GA29144 should have hepatitis B DNA measured at these timepoints.
- ^s Samples are to be collected prior to dose administration at all timepoints indicated and whenever serum sickness is suspected. If serum sickness or a clinically significant allergic drug reaction is suspected, the Sponsor should be notified, and serum for ATA analysis should be drawn and sent to the central laboratory. ATA samples may also be utilized for assessment of etrolizumab serum concentrations.

Appendix 2 12-Week Safety Follow-Up (OLE, Part 1) Schedule of Assessments

Part 1 (OLE)	Week (± 7 days)		Unscheduled Visit ^c
	6 ^a	12/Early Withdrawal Visit ^b	
Concomitant medications	x	x	x
Adverse events	x	x	x
Urine pregnancy test ^d		x	
Anti-therapeutic antibody sample (serum) ^e		x	
PML assessment interview ^f		x	x ^g
Neurological examination ^{f, h}		x	x ^g

ATA = anti-therapeutic antibody; JCV = John Cunningham virus; OLE = open-label extension; PML = progressive multifocal leukoencephalopathy.

- ^a Week 6 study assessments are to be made by telephone visit and not by clinic visit.
- ^b If the patient discontinues prior to completion of the 12-week safety follow-up, the indicated assessments for the 12-week safety follow-up clinic visit should be performed as the Early Withdrawal visit of the safety follow-up period.
- ^c Unscheduled visit for safety monitoring.
- ^d For women of childbearing potential, including those who have had a tubal ligation, perform a urine pregnancy test; if the urine pregnancy test result is positive, confirm with a serum pregnancy test.
- ^e If serum sickness or a clinically significant allergic drug reaction is suspected, Sponsor should be notified and serum for ATAs should be drawn and sent to the central laboratory. ATA samples may be used for assessment of etrolizumab serum concentration.
- ^f Administer before other assessments.
- ^g If clinically indicated.
- ^h Neurologic examination consists of the PML Subjective Checklist and the PML Objective Checklist, as per [Appendix 8](#).

Appendix 3 Extended Progressive Multifocal Leukoencephalopathy Safety Monitoring (SM, Part 2) Schedule of Assessments

Part 2 (SM)	92-week Extended PML Monitoring Period ^a
	24, 48, 68, and 92 Weeks after Patient Discontinuation from Study OR Early Termination ^b
PML Subjective Checklist (Telephone Only) ^c	X
Adverse Event Reporting to Roche Safety Risk Management ^d	X

OLE-SM=open-label extension–safety monitoring; PML=progressive multifocal leukoencephalopathy; SM=safety monitoring.

Note: The extended PML monitoring period is to be conducted for patients completing or discontinuing from Part 1 (OLE) of the OLE-SM study AND for patients entering OLE-SM Part 2 (SM) from Study GA29144 after completion of 12-week safety follow-up in Study GA29144.

- ^a The total length of the PML monitoring period is 104 weeks after the patient discontinues from the study (12-week safety follow-up plus 92-week extended PML monitoring period). During the extended PML monitoring period telephone visits will occur at the indicated timepoints for the 92-week extended PML monitoring period. The extended PML monitoring will be conducted using a PML Subjective Checklist over the telephone. PML monitoring should occur within 7 days of the specified day.
- ^b If the patient discontinues after the 12-week safety follow-up visit but prior to study completion (end of extended PML monitoring period), the early termination visit from the extended PML monitoring period should be performed (a subjective checklist by telephone).
- ^c If there are any signs or symptoms suggestive of PML during the telephone visit, the patient will be asked to come into the clinic for a neurologic examination (see Section 4.4.5).
- ^d Investigators are not required to actively monitor patients for adverse events; however, if they become aware of any deaths, serious adverse events, or non-serious adverse events of special interest, these should be reported directly to the Sponsor via telephone or via fax machine using the Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

Appendix 4

Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening and a urine pregnancy test prior to administration of study drug at subsequent visits. If a urine pregnancy test result is positive, study drug will not be administered that day. The result must be confirmed by a serum pregnancy test (conducted by the central laboratory). Refer to Section 5.5.3 of the protocol for management of a patient with a confirmed pregnancy.

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

For women: patients are considered to be of childbearing potential unless they meet one of the following criteria:

- The patient has been postmenopausal (non–therapy-induced amenorrhea) for at least 12 months
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to enrollment
- The patient had a hysterectomy

Female patients of reproductive or childbearing potential who are unwilling to use a highly effective method of contraception or remain abstinent during the treatment period and for at least 24 weeks after the last dose of study drug will be excluded from study participation.

Abstinence is acceptable only if it is in line with 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.

Examples of highly effective contraception include the following:

- Combined oral contraception pill
- Contraceptive transdermal patch
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate postsurgical verification of the absence of spermatozoa in the ejaculate

Appendix 4

Childbearing Potential, Pregnancy Testing, and Contraception (cont.)

- Double-barrier methods: condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (Note: a female condom and male condom should not be used together as friction between the two can result in either product failing)

Patients may provide verbal confirmation that the partner completed appropriate follow-up after vasectomy. Sites are not required to obtain partner medical records.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures 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 at least 24 weeks after the last dose of study drug. Men must refrain from donating sperm during this same period.

For men and women: 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.

Appendix 5 Crohn's Disease Activity Index

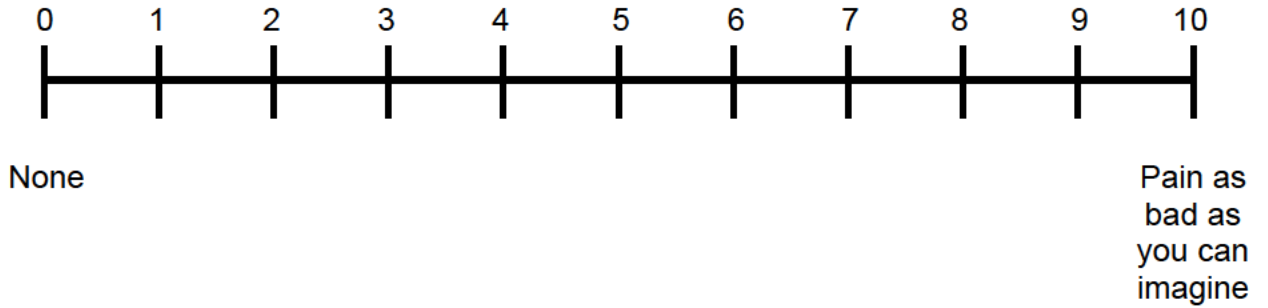
Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		x 2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0=none, 1=mild, 2=moderate, 3=severe (reported on the 7 days immediately prior to the study visit)		x 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)		x 7	
Extra-intestinal manifestations of Crohn's Disease	Total number of checked boxes (check all that apply): <input type="checkbox"/> Arthritis/arthralgia <input type="checkbox"/> Iritis/uveitis <input type="checkbox"/> Erythema nodosum/pyoderma gangrenosum/apthous stomatitis <input type="checkbox"/> Anal fissure, fistula, or abscess <input type="checkbox"/> Other fistula <input type="checkbox"/> Fever over 37.8°C during past week		x 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		x 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		x 10	
Hematocrit (%) ^a	Males: subtract value from 47 Females: subtract value from 42		x 6	
Body Weight ^b	(1- (Body weight/Standard Weight)) x 100		x 1	
Final Score			Add totals:	

^a If hematocrit subtotal <0, enter 0.
^b If body weight subtotal < -10, enter -10.

Adapted from: Best WR, Beckett JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70(3):439-44.








Appendix 6
Abdominal Pain Questionnaire (APQ)

Please rate your worst abdominal pain over the past 24 hours:



Appendix 7 Bristol Stool Form Scale

THE BRISTOL STOOL FORM SCALE

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

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Appendix 8 Worksheet for the PML Neurologic Examination

PML Subjective and Objective Checklists of neurologic assessments to monitor for progressive multifocal leukoencephalopathy (PML) in the Etralizumab Phase III Studies

PML usually manifests with subacute, progressive neurologic deficits including:

Neurologic Domain	Signs/Symptoms	Relevant PML Subjective/Objective Checklist Question
Altered mental status	Can encompass a variety of presenting signs and symptoms including cognitive changes (confusion, difficulty concentrating, memory loss) and altered behavior (including personality changes)	Q2, Q5, Q6
Higher cortical dysfunction	Impaired comprehension and/or formulation of language (aphasia), loss of ability to recognize objects, persons, sounds, shapes, or smells (agnosia)	Q2, Q5, Q6
Visual changes	Loss of visual fields (homonymous hemianopsia), double vision (diplopia)	Q1
Motor deficits	Weakness (hemiparesis or monoparesis), seizures (generalized or partial), difficulties with speech (dysarthria) or swallowing (dysphagia)	Q2, Q3
Sensory deficits	Sensory loss (i.e. paresthesia)	Q7
Coordination	Difficulty walking and maintaining balance (ataxia), lack of voluntary coordination of limb movement (limb ataxia)	Q4

In order to monitor patients for PML, a neurologic exam (including evaluation of cranial nerves, motor and sensory function, coordination, and mental status) will be performed as per the Schedules of Assessments (see [Appendix 1](#)). This neurologic exam will consist of administration of the PML Subjective Checklist and the PML Objective Checklist.

At screening, the PML Subjective Checklist and the PML Objective Checklist (including the components listed as optional, e.g. muscle group strength testing, recall of 3 objects in 1 minute, and sensory testing) should be performed.

At all other visits, the PML Subjective Checklist and the PML Objective Checklist (bolded items) should be performed, and the optional items should only be performed when there is an abnormal finding on the corresponding PML Subjective Checklist (i.e., complaints of focal weakness or focal sensory change would prompt a more detailed objective neurologic evaluation).

Appendix 8 Worksheet for the PML Neurologic Examination (cont.)

PML Subjective Checklist

Symptoms	“Compared to how you usually feel, have you had a significant change in any of the following?”		If the answer is “Yes”, obtain a description of the symptom(s) with examples	Applicable Objective Test(s): Document result on PML Objective Checklist Worksheet
	YES	NO		
1. Have you been experiencing any persistent difficulty with your vision such as loss of vision or double vision? Have you been having trouble with reading?				<ul style="list-style-type: none"> • Test visual fields and ocular motility
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				<ul style="list-style-type: none"> • Casual observation of speech output for dysarthria or aphasia.
3. Have you been experiencing any persistent weakness in an arm or a leg?				<ul style="list-style-type: none"> • Test for pronator drift (Barre maneuver). • Assess gait. • Test muscle
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				<ul style="list-style-type: none"> • Observe tandem gait and finger to nose.
5. Have you regularly been experiencing difficulty understanding others?				<ul style="list-style-type: none"> • Test ability to follow serial commands.
6. Have you had persistent problems with your memory or thinking?				<ul style="list-style-type: none"> • Recall of 3 objects over 1 minute with distraction (only if
7. Have you been experiencing any persistent numbness or other loss of sensation?				<ul style="list-style-type: none"> • Test sensation side to side with either pinprick or cold (only if

Appendix 8 Worksheet for the PML Neurologic Examination (cont.)

PML Objective Checklist

Neurologic function being assessed	Instructions (bold text indicates parts of exam required at each visit, as specified in Schedule of Assessments)	Abnormal exam?		If the answer is "Yes", describe the abnormal objective exam
		YES	NO	
1. Visual fields and ocular motility	<ul style="list-style-type: none"> Visual Field Testing Ocular Motility Testing 			
2. Speech	<ul style="list-style-type: none"> Observe the patient's speech output for dysarthria or aphasia. 			
3. Strength	<ul style="list-style-type: none"> Pronator drift test (Barre maneuver) Gait testing (normal, heel and toe walk) ONLY if the patient has any subjective complaints of weakness, test muscle strength of the relevant muscle groups 			
4. Coordination	<ul style="list-style-type: none"> Observe tandem gait and finger to nose 			
5. Comprehension	<ul style="list-style-type: none"> Test ability to follow serial commands "Take a piece of paper in your hand, fold it in half, and put it on the floor." 			
6. Memory and thinking	<ul style="list-style-type: none"> ONLY if the patient has subjective complaints about their memory or thinking, test the ability of the patient to recall 3 objects over 1 minute with distraction 			
7. Sensation	<ul style="list-style-type: none"> ONLY if the patient has subjective sensory complaints, evaluate relevant areas based on patient's subjective complaints by comparing left vs. right side sensation to cold (e.g. alcohol swab or cold stethoscope) or pinprick (e.g. broken Q-tip) 			

Please refer to the PML Algorithm in the Protocol Appendix for details.

- If there is an abnormal finding on the PML Subjective Checklist, this should be appropriately documented on the worksheet and in the eCRF.

Appendix 8

Worksheet for the PML Neurologic Examination (cont.)

- If there is an abnormal finding on the PML Objective Checklist, this should be appropriately documented on the worksheet and in the eCRF.
- If there are any abnormalities found on the PML Subjective Checklist that are accompanied by the corresponding abnormality on the PML Objective Checklist, or if there is high clinical suspicion for PML (in the opinion of the investigator):
 - This must be reported as an adverse event of special interest (AESI) within 24 hours
 - An urgent referral to a neurologist should be made.
 - Dosing with study drug will be suspended until PML can be ruled out.
 - Further evaluation will proceed according to the PML Algorithm in the Protocol Appendix.
 - Any confirmed diagnosis of PML should be reported as a serious adverse event (SAE).

Please complete the PML eCRF.

Was the PML Subjective Checklist administered? (Yes/No)

If yes, date of administration of PML Subjective Checklist (Date)

If yes, were there any abnormalities on the PML Subjective Checklist? (Yes/No)

Was the PML Objective Checklist administered? (Yes/No)

If yes, were there any abnormalities on the PML Objective Checklist? (Yes/No)

Is PML suspected? (Yes/No)

More detailed instructions for the PML Objective Checklist Neurologic Evaluations (please refer to the PML Neurologic Exam Video for more information):

1. Visual fields and ocular motility

Visual Field Testing:

- Position yourself approximately 3 feet away from the patient, with eyes at the same level.
- Keeping both eyes open, ask the patient to cover one eye and ask if all parts of your face and head are clear to them. Ask them to repeat, covering the other eye.

Appendix 8

Worksheet for the PML Neurologic Examination (cont.)

- Have the patient cover one eye and stare at your nose, and then ask them how many fingers you are holding up, testing each of the 4 visual quadrants. Repeat with the other eye covered.

Ocular Motility Testing:

- Evaluate the patient for conjugate eye movement.
- Starting about 3 feet from center, move in a big “H”, pausing at the center and at lateral gaze, and finishing with convergence (finger to their nose). Watch for nystagmus in lateral gaze, smooth pursuits, and pupillary constriction with convergence. Note: a couple of beats of nystagmus upon extreme lateral gaze is considered normal.

2. Speech

- Observe the patient’s speech output for dysarthria or aphasia.
- Dysarthria is a motor speech disorder. Findings can include “slurred” speech, decreased volume, slow rate of speech, limited tongue, lip, and jaw movement, abnormal rhythm when speaking, changes in vocal quality, and drooling or poor control of saliva.
- Aphasia is a disorder that results from damage to parts of the brain that control language, and can lead to problems with any or all of the following: speaking, listening, reading or writing.

3. Strength

Pronator drift test (Barre maneuver):

- Ask the patient to stand with their feet together and extend their arms out in front of them at 90 degrees (parallel to floor) with palms facing upwards toward the ceiling.
- Ask the patient to close their eyes and keep their arms extended for 15 seconds.
- If either arm drifts downward, upward, or starts to pronate (i.e. thumb turns up), this is considered an abnormal exam.

Gait testing:

- Ask the patient to walk across the room (~10 feet). The patient should have a normal gait, with their left arm swinging forward when the right foot leads, and vice versa. Be certain to note whether there is symmetric arm swinging, because a slight decrease in arm swinging may be an indicator of upper extremity weakness.
- Ask the patient to walk on their heels across the room (~10 feet). Carefully observe whether they have any difficulty maintaining their toes off the ground or loss of balance.

Appendix 8

Worksheet for the PML Neurologic Examination (cont.)

- Ask the patient to walk on their toes across the room (~10 feet). Carefully observe if they have any difficulty maintaining their heels off the ground or loss of balance.

Additional strength testing (ONLY if the patient has any subjective complaints of weakness):

- Test muscle strength of the relevant muscle groups based on the patient's subjective complaints.
- General guidelines for a basic muscle strength exam:
- Upper extremity:
 - Finger grip strength
 - Flexion at elbow
 - Extension at elbow
 - Deltoid strength: Maintain bent arms up (perpendicular to floor) and resist while investigator pushes down
 - Shoulder shrug against resistance
- Lower extremity: (examine while patient is sitting down)
 - Raise thigh (while bent)
 - Straighten leg
 - Flex leg
 - Flex foot
 - Extend foot

4. Coordination

Tandem gait:

- As the patient is looking at his feet, ask them to walk 8 steps with one foot touching in front of the other (demonstrate for them).

Finger to nose:

- Hold your finger out so they need to reach out and lean. Start near the center, and move your finger slowly so that they reach across their body. Make sure they alternate touching your finger and their nose at a good speed. Inability to perform this accurately is considered an abnormal test.

5. Comprehension

- Test ability to follow serial commands
- “Take a piece of paper in your hand, fold it in half, and put it on the floor.”

Appendix 8

Worksheet for the PML Neurologic Examination (cont.)

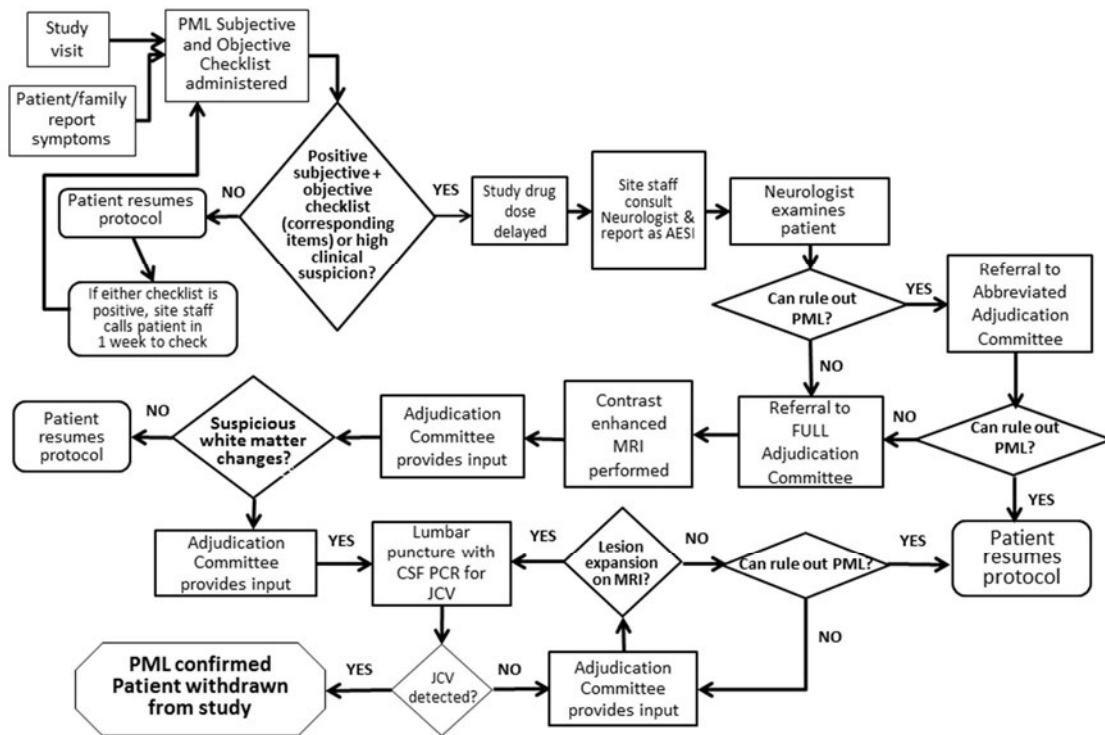
6. Memory and Thinking

- (ONLY if the patient has subjective complaints about their memory or thinking) test the ability of the patient to recall 3 objects over 1 minute with distraction.

7. Sensation

- (ONLY if the patient has subjective sensory complaints) evaluate relevant areas based on the patient's subjective complaints by comparing left vs. right side sensation to cold (e.g. alcohol swab or cold stethoscope) or pinprick (e.g. broken Q-tip). Confirm that the patient is able to feel the sensation symmetrically.

Appendix 9 Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy



Appendix 10

Clinical Criteria for Diagnosing Anaphylaxis

These criteria are taken from a summary report from the second symposium on the definition and management of anaphylaxis, conducted by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network.¹ Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING:

- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
 - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
 - Reduced blood pressure or associated symptoms (e.g., hypotonia, syncope, incontinence)
 - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
 3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
 - Infants and children: low systolic blood pressure (age specific)² or greater than 30% decrease in systolic blood pressure
 - Adults: systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that person's baseline

¹ Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.

² Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Appendix 11 Simple Endoscopic Score for Crohn's Disease (SES-CD)

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. *Gastrointestinal Endoscopy* 2004;60:505–512.