Official Title: An Open-Label Extension and Safety Monitoring Study of Moderate to Severe Ulcerative Colitis Patients Previously Enrolled in Etrolizumab Phase II/III Studies

NCT Number: NCT02118584

Document Date: Protocol Version 9: 12-Feb-2019

PROTOCOL

TITLE:	**AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF MODERATE TO SEVERE ULCERATIVE COLITIS PATIENTS PREVIOUSLY ENROLLED IN ETROLIZUMAB PHASE II/III STUDIES**
PROTOCOL NUMBER:	GA28951
VERSION NUMBER:	9
EUDRACT NUMBER:	2013-004435-72
IND NUMBER:	100366
TEST PRODUCT:	Etrolizumab (PRO145223, RO5490261)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 27 November 2013
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	12-Feb-2019 21:05:10

PROTOCOL AMENDMENT, VERSION 9:
RATIONALE

Protocol GA28951 has been amended to align with changes implemented in the parent studies GA29102, GA29103, GA28948, GA28949, and GA28950, as follows:

- Language in the Background section has been amended to align with the other ulcerative colitis studies in the Etrolizumab Phase III Program (Sections 1.2 and 1.3.2).
- The duration of Part 1– open-label extension has been updated to approximately 9 years (Sections 3.1.1.1, 3.1.1.3, and 4.4.3.2 and Figure 1).
- Consistent with the reduction in sample size of some of the parent studies, the maximum number of patients potentially enrolling in this study has been updated to approximately 2100 (Sections 3.1.1.1, 4.1, and 6.1).
- Janus kinase inhibitors have been added to the list of rescue therapies prohibited at any time during the study (Sections 3.1.1.1, 4.1.2, 4.2.2, and 5.1.2).
- References to "Latvia/Lithuania" have been changed to "VHP" to reflect inclusion of all countries participating in the Voluntary Harmonisation Procedure (Section 4.1.1 and Table 1).
- Clarification regarding the reporting of adverse events related to medical device complaints in individuals other than the study patient has been added in Section 4.3.3.3.
- Language in Section 5.4.6.7 has been amended to indicate that a death occurring during Part 2–safety monitoring should be reported directly to the Sponsor, regardless of causality.
- Procedures for adverse event reporting have been updated to clarify that sites are not expected to review patient-reported outcome data for adverse events (Section 5.4.6.12).

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to a Sponsor representative. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL EXTENSION AND SAFETY MONITORING STUDY OF MODERATE TO SEVERE ULCERATIVE COLITIS PATIENTS PREVIOUSLY ENROLLED IN ETROLIZUMAB PHASE II/III STUDIES**
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PHASE:	III
INDICATION:	Ulcerative colitis
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

Safety Objectives

The other safety objectives for this study are as follows:

Part 1 (OLE)

- To evaluate the incidence and severity of infection-related adverse events
- To evaluate the incidence 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

The exploratory objective for this study is as follows:

Part 1 (OLE)

- To evaluate histology 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 active etrolizumab, 105 mg subcutaneous (SC), will be administered every 4 weeks followed by a 12-week safety follow-up.
- 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 1 (OLE) and Part 2 (SM).

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

Number of Patients

The OLE-SM study will be conducted in centers that have participated in the Phase II OLE Study GA27927 and/or the double-blinded Phase III Studies GA28948, GA28949, GA28950, GA29102, and GA29103. The maximum number of patients potentially enrolling in this study will be all patients from the studies; approximately *2100* patients. Patients will be allocated the same subject number they had in the initial Phase II OLE study or Phase III study.

Target Population

Patients must meet the following criteria for study entry:

Part 1 (OLE)

- Patients who were previously enrolled in the Phase II OLE study or a Phase III controlled study and meet the eligibility criteria for treatment with open-label etrolizumab as described in the protocol may enroll in Part 1 (OLE) of the study. These patients must provide written informed consent and comply with the requirements of the OLE-SM protocol.

  Patients not in safety follow-up or PML follow-up within Study GA27927 and whose last dose of etrolizumab is by July 2016 may enroll in Part 1 (OLE) of Study GA28951, if eligible, and receive their first dose in this study 4 weeks after their last dose in Study GA27927. On occasions where this first dose of etrolizumab cannot be administered in accordance with these requirements, the first dose of etrolizumab is to be administered with a maximum delay of 2 weeks (i.e., up to 6 weeks after their last dose of etrolizumab in Study GA27927).

  Eligible patients who exit from Study GA28948 or GA28949 at Week 10 because either they did not achieve clinical remission or they required the use of rescue medication prior to the Week 10 timepoint should not receive their first dose of open-label etrolizumab in Study GA28951 until 2 weeks after the Week 10 timepoint in the Phase III controlled study to allow for adalimumab washout. The first dose of etrolizumab given to these patients entering Study GA28951 should not exceed 4 weeks following the Week 10 timepoint from the Phase III controlled study.

  With the exception of VHP countries participating in GA28949 and Estonia (*participating in GA28948)*: Patients who remain in Study GA28948 or Study GA28949 through Week 14 because they have achieved clinical remission may enroll in Part 1 (OLE) of Study GA28951 at Week 14. The first dose of open-label etrolizumab will be given on Day 1 upon enrollment into Part 1 (OLE) of Study GA28951. The first dose of etrolizumab given to the patients entering Study GA28951 should not exceed 2 weeks following the Week 14 timepoint from the Phase III controlled study.

  With the exception of VHP countries participating in GA28949 and Estonia (*participating in GA28948)*: Eligible patients who receive rescue medication between Weeks 10 and 14 may enroll in Part 1 (OLE) of Study GA28951 at Week 14.

For *VHP countries participating in GA28949* and Estonia (*participating in GA28948)*: Patients who remain in Study GA28948 or GA28949 through Week 14 because they have achieved clinical remission at Week 10 may enroll in Part 1 (OLE) of Study GA28951 at Week 16. The first dose of open-label etrolizumab will be given on Day 1 upon enrollment into Part 1 (OLE) of Study GA28951 (4 weeks after their last etrolizumab/etrolizumab placebo dose or 8 weeks after their last adalimumab/adalimumab placebo dose in Study GA28948 or GA28949). On occasions where the first OLE dose of etrolizumab cannot be administered in accordance with these requirements, the first dose may be delayed by a maximum of 2 weeks (i.e., first OLE dose up to 6 weeks after their last etrolizumab/etrolizumab placebo dose or 10 weeks after their last adalimumab/adalimumab placebo dose in Study GA28948 or GA28949).

For *VHP countries participating in GA28949* and Estonia (*participating in GA28948)*: Eligible patients who receive rescue medication between Weeks 10 and 16 may enroll in Part 1 (OLE) of Study GA28951 at Week 16.

- For women who are not postmenopausal (at least 12 months of non-therapy-induced amenorrhea) or surgically sterile (i.e., absence of ovaries and/or uterus): agreement to remain abstinent or use a highly effective method of contraception during the treatment period and for at least 24 weeks after the last dose of study drug.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use 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 to avoid exposing the embryo to study drug. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Part 2 (SM)

- Patients whose safety follow-up or PML follow-up is not completed within Study GA27927 and patients who had their last dose of etrolizumab in July 2016 in Study GA27927 and are not eligible or choose not to enroll in Part 1 (OLE)
- Patients who participated in one of the etrolizumab Phase III studies (GA28948, GA28949, GA28950, GA29102, and GA29103) and are not eligible or chose not to enroll in Part 1 (OLE)
- Patients who transfer from 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 prior to entering Part 2 (SM).

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

Part 1 (OLE)

- Withdrawal of consent from the Phase II OLE study or any of the Phase III studies
- Patients who discontinued etrolizumab/etrolizumab placebo prior to Week 10 or did not perform the Week 10 visit of the Phase III Studies GA28948, GA28949, GA29102, and GA29103
- Patients who discontinued etrolizumab/etrolizumab placebo prior to Week 14 or did not perform the Week 14 visit of the Phase III Study GA28950

- Inability to comply with the study protocol, in the opinion of the investigator
- Patients not compliant in the Phase II OLE or Phase III studies or did not complete the required washout period for an active comparator in Studies GA28948, GA28949, and GA29103
- Pregnancy or lactation

Exclusion due to Safety Reasons

- Patients who developed an anaphylactic/anaphylactoid or severe allergic reaction to study medication during the Phase II OLE or Phase III studies
- Patients who experienced or have an ongoing serious infection event (except for those listed below) should not receive study drug until the event has completely resolved and treatment with anti-infective medications has been completed
- Patients who experienced a specific de novo or reactivated serious viral infection such as hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV during the Phase II OLE or Phase III studies
- Patients who develop cytomegalovirus (CMV) colitis leading to early treatment discontinuation in the Phase II OLE or Phase III studies
- Patients who develop life-threatening infections during the Phase II OLE or Phase III studies
- 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 the Phase II OLE or Phase III studies
- Receipt of the following since commencement of the Phase II OLE or Phase III controlled studies:

  Any investigational treatment, including investigational vaccines

  Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab), except AZA and 6-MP

  Use of anti-adhesion molecules

  Use of Janus kinase (JAK) inhibitors

  Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF)

  Patients who have previously received rituximab, natalizumab, vedolizumab, or efalizumab may not enter the study

  Immunization with a live/attenuated vaccine
- In the opinion of the investigator, any new (since enrolling in the Phase II OLE or Phase III controlled studies), 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 ulcerative colitis [UC])
- Any patient who developed PML in the Phase II OLE or Phase III studies
- 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 the Phase II OLE study and the Phase III controlled studies. Part 1 (OLE) will continue for up to *approximately 9 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, patients will enter Part 2 for a period of 92 weeks.

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:

- To describe the long-term efficacy of etrolizumab (105 mg SC every 4 weeks) by pMCS clinical remission for patients with UC in Part 1 (OLE)
- To evaluate remission by MCS at Week 108 in Part 1 (OLE)
- To evaluate endoscopic remission by MCS at Week 108 in 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 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 of malignancies
- Incidence of ATAs to etrolizumab
- Incidence and severity of hypersensitivity reaction events

Part 2 (SM)

- Incidence of suspected or confirmed PML events

Exploratory Outcome Measure

The exploratory outcome measure for this study is as follows:

- Histologic appearance of mucosa at Week 108

Investigational Medicinal Products

Test Product

Etrolizumab prefilled syringe (PFS): containing SC formulation, 105 mg given as 0.7 mL of a 150-mg/mL solution 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. Efficacy in Part 1 will be assessed by change from baseline in pMCS and proportion of patients achieving pMCS remission. Additionally, remission and endoscopic remission by MCS at Week 108 will be summarized. All efficacy parameters will be summarized descriptively. Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants, duration of disease, and pMCS will be summarized by use of descriptive statistics.

Further analysis details for Part 1 and Part 2 of the study will be provided in the Statistical Analysis Plan.

Determination of Sample Size

The maximum number of patients enrolled in the OLE-SM study is approximately *2100* (i.e., all patients enrolled in the Phase II OLE protocol and the five UC Phase III protocols). No formal sample size calculations were performed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
5-ASA	5-aminosalicylates
6-MP	6-mercaptopurine
AIS	adenocarcinoma in situ
ATA	anti-therapeutic antibody
AZA	azathioprine
CD	Crohn's disease
CHO	Chinese hamster ovary
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CNS	central nervous system
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
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	Health Insurance Portability and Accountability Act
HSIL	high-grade squamous intraepithelial lesions
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
JAK	*Janus kinase*
JCV	John Cunningham virus
IxRS	interactive voice/Web-based response system
mAb	monoclonal antibody
MAdCAM–Fc	mucosal addressin cell adhesion molecule-fragment crystallizable region

Abbreviation	Definition
MCS	Mayo Clinic Score
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MTX	methotrexate
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OLE	open-label extension
OLE-SM	open-label extension and safety monitoring
QOL	quality of life
PCR	*polymerase chain reaction*
PD	pharmacodynamic
PFS	prefilled syringe
PGA	Physician's Global Assessment
PK	pharmacokinetic
pMCS	partial Mayo Clinic Score
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
RCR	Roche Clinical Repository
SC	subcutaneous
SM	Safety Monitoring
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	tumor necrosis factor
UC	ulcerative colitis
ULN	upper limit of normal

1. BACKGROUND

1.1 BACKGROUND ULCERATIVE COLITIS

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease (IBD) that affects the colon in a diffuse, continuous, and superficial pattern. Approximately 40%–50% of patients have disease limited to the rectum and rectosigmoid colon, 30%–40% have disease extending beyond the sigmoid but not involving the whole colon, and 20% have a total colitis. Proximal spread occurs in continuity without areas of uninvolved mucosa. When the whole colon is involved, the inflammation extends 2–3 cm into the terminal ileum in 10%–20% of patients.

UC is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain and may be complicated by severe bloody diarrhea and toxic megacolon, requiring major and sometimes urgent surgery. UC represents dysregulation of the mucosal immune system in genetically susceptible individuals in response to commensal microbiota and other environmental triggers. The overall incidence of UC ranges from 6.3 to 24.3 cases per 100,000 persons per year, and prevalence ranges from 4.9 to 505.0 cases per 100,000 persons, with the highest estimates in European and Northern American populations (Molodecky et al. 2012). Although the incidence and prevalence vary between regions of the world, both have been increasing in some regions, which may be due in part to better detection and diagnosis, as well as environmental factors such as improved hygiene and Western diet. The disease can affect any age group, but occurrence peaks between the ages of 15 and 35 years.

The goals of treatment are to induce and maintain remission, decrease corticosteroid use (as measured by steroid-free remission), induce mucosal healing, reduce hospitalization and surgery, improve quality of life (QOL), and avoid disability. For mildly to moderately active UC, oral and rectal preparations of 5-aminosalicylate (5-ASA) medications are used either alone or together and result in remission in approximately 50% of patients. Patients whose UC fails to respond to 5-ASA drugs or who have moderately to severely active UC often receive conventional therapy, including corticosteroids and immunomodulator therapy (e.g., azathioprine [AZA], 6-mercaptopurine [6-MP], and methotrexate [MTX]). Corticosteroids achieve remission in about 70% of patients, but approximately 20% become steroid dependent and only half maintain steroid-free remission (Faubion et al. 2001). Corticosteroids are also associated with significant side effects, such as infections, osteopenia, glucose intolerance, and adrenal suppression. Immunomodulators, such as 6-MP, AZA, and MTX, have also been used to achieve steroid-free remission, but efficacy in maintaining steroid-free remission is modest (Lobel et al. 2004; Chebli et al. 2010; Mañosa et al. 2011; Khan et al. 2013). In addition, these medications are associated with significant side effects, including hepatotoxicity, pancreatitis, and bone marrow suppression.

Monoclonal antibodies (mAbs) targeting tumor necrosis factor–alpha (TNF-α), such as infliximab and adalimumab, have been used to induce and maintain remission in patients whose immunomodulatory therapy fails, are steroid dependent or refractory, and have moderately to severely active UC. These biologic agents induce remission in up to 40% of patients, but sustained remission is seen in only 10%–20% of patients over 1 year (Rutgeerts et al. 2005; Sandborn et al. 2013). Importantly, TNF inhibitor therapies are associated with serious adverse events, such as bacterial infection, including tuberculosis (TB), disseminated fungal infections, lymphoma, and demyelination (Chang and Lichtenstein 2006). In fulminant steroid-unresponsive colitis, infliximab and (less commonly) cyclosporine are utilized as bridging agents to avoid urgent colectomy. With either therapy, however, treatment failure occurs in approximately 55%–60% of patients (Laharie et al. 2012).

In short, a large proportion of patients with moderately to severely active UC do not maintain a durable response to therapy. Available therapies are associated with significant adverse events and at best achieve sustained remission in only 10%–30% of patients with IBD who have chronic disease (Hanauer et al. 2002; Sandborn et al. 2005). Patients whose disease fails to respond to medical therapy may be treated with total proctocolectomy with an ileal pouch-anal anastomosis. Although surgical intervention may be curative, complications such as chronic pouchitis, fecal incontinence, or decreased female fertility can occur (Bradley and Oliva-Hemker 2012). The current treatments are associated with significant adverse events, resulting in low rates of sustained remission, or are highly invasive.

Consequently, there continues to be a high unmet medical need in moderately to severely active UC. Targeted therapy with an improved safety profile and ability to sustain remission and prevent long-term complications would provide a valuable therapeutic option for these patients.

Part 1 of this study (open-label extension; OLE) investigates the long-term safety of patients with UC who were initially treated in the Phase II OLE (GA27927) or Phase III UC studies (GA28948, GA28949, GA28950, GA29102, and GA29103) and are enrolled into this open-label study for long-term treatment with etrolizumab and safety monitoring.

Part 2 of this study (safety monitoring; SM) includes long-term monitoring for progressive multifocal leukoencephalopathy (PML) for all patients following the last dose of their study medication and the 12-week safety follow-up. Patients who discontinue therapy in this OLE study, OR patients whose safety follow-up or PML follow-up is not completed within the Phase II OLE study, OR patients from the Phase III UC studies who discontinue therapy, or are not eligible for, or choose not to receive open-label etrolizumab, will be monitored for PML within Part 2 (SM) of this protocol.

1.2 BACKGROUND ON ETROLIZUMAB

A new class of molecules targeting the integrin receptors that regulate leukocyte trafficking to specific tissues in the body has been developed for treatment of IBD. Clinical studies have shown evidence of efficacy for these agents, including natalizumab (anti-α4) for Crohn's disease (CD) (Sandborn et al. 2005) and vedolizumab (anti-$\alpha4\beta7$) for UC and CD (Feagan et al. 2005, 2008*); both agents have been approved for their respective indications. Natalizumab and vedolizumab require IV administration, but only vedolizumab is gut-selective. Natalizumab is not gut-selective and is associated with the risk of progressive multifocal leukoencephalopathy (PML).* Etrolizumab distinguishes itself from these molecules by specifically binding the integrin β7 subunit, found in both $\alpha4\beta7$ (Holzmann et al. 1989; Hu et al. 1992) and $\alpha E\beta7$ (Cepek et al. 1993), which regulate trafficking and retention of leukocyte/lymphocyte subsets, respectively, in the intestinal mucosa.

It is important to note that etrolizumab does not bind to $\alpha4\beta1$ (target for natalizumab), which regulates trafficking to both mucosal and non-mucosal tissues, including the CNS. Etrolizumab, therefore, represents a novel gut mucosal–selective anti-trafficking agent whose selectivity may enhance efficacy in UC and eliminate generalized immunosuppression by preferentially targeting trafficking to the gut rather than to other organs and tissues. Data from multiple nonclinical toxicology studies of up to 6 months' duration in adult animals demonstrated no adverse effects in any organ system (including the CNS and hematologic and cardiovascular systems). No adverse events were observed in the embryo-fetal developmental toxicity studies.

Etrolizumab is a humanized mAb based on the human IgG1 subgroup-III V_H, κ subgroup-1 V_L consensus sequences and was constructed using standard recombinant DNA techniques. This recombinant antibody consists of two heavy chains (446 residues) and two light chains (214 residues) and is produced in Chinese hamster ovary (CHO) cells that have been genetically engineered to synthesize the antibody. The protein is manufactured in bioreactors and purified using a series of harvest, purification, and formulation steps. The potency of etrolizumab is determined by an in vitro assay that measures the inhibition of adhesion of $\alpha4\beta7$-expressing cells to mucosal addressin cell adhesion molecule–fragment crystallizable region (MAdCAM-Fc).

Safety assessments for etrolizumab have been completed in the adult Phase I, Phase II, and Phase II open-label extension (OLE) studies without significant safety concerns.

The following is a summary of the etrolizumab safety experience to date:

- There were no observed significant adverse effects in multiple nonclinical toxicity studies of up to 6 months' duration in adult animals or in embryo-fetal developmental toxicity studies. No adverse effects were seen in any organ system (including the CNS and hematologic and cardiovascular systems), no effects were seen in embryo-fetal development, and there was no evidence of increased rates of infection.

- No significant adverse safety signal, including any evidence of increased rates of serious or opportunistic infections, was associated with etrolizumab treatment in the Phase I or Phase II trials in adult patients with moderately to severely active UC who received either single or multiple doses of intravenous (IV) or subcutaneous (SC) etrolizumab.
- No events of PML have been reported in etrolizumab-treated patients.

See the most recent Etrolizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

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

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 4 weeks with regard to adverse events and laboratory abnormalities and to obtain long-term data on the efficacy, immunogenicity, and exposure of etrolizumab. Patients may enroll in this study from:

a) Phase II OLE Study GA27927

b) Phase III controlled studies—namely, Studies GA28948, GA28949, GA28950, GA29102, and GA29103

Patients who complete the last dose of etrolizumab within Study GA27927 by July 2016 will be given the option to continue open-label etrolizumab within Part 1 (OLE) of this study, if eligible.

Eligible patients receiving etrolizumab, placebo, or active comparator (following blinded washout) in the Phase III controlled studies may receive active 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 for the Phase II OLE study and for each of the Phase III controlled studies, respectively, and summarized in Table 1 in this protocol.

Part 2 (Safety Monitoring or "SM")

Part 2 (SM) is designed to monitor for PML in patients who have stopped taking etrolizumab.

a) For patients in Phase II OLE Study GA27927, if the 12-week safety follow-up and 92-week PML follow-up cannot be completed before July 2016, safety follow-up and/or PML follow-up will take place entirely within this study (GA28951) if all health authority/Institutional Review Board (IRB)/Ethics Committee (EC) approvals in the respective country for this study (GA28951) are in place by the time follow-up is scheduled to begin. Otherwise, safety follow-up and/or PML follow-up will first start within Study GA27927 then will be completed within this study (GA28951) once all HA/EC/IRB approvals for this study (GA28951) are obtained.

b) Patients who exit Part 1 (OLE) of this study will then enter Part 2 (SM) for monitoring for events of PML. In addition, given that it is desirable to capture all long-term PML follow-up under a single protocol, all patients from the Phase III studies who do not enroll in Part 1 (OLE) for continued etrolizumab treatment will enroll directly into Part 2 (SM) of this study for extended PML safety monitoring (following completion of the 12-week safety follow-up in the Phase III studies).

1.3.2 Benefit-Risk Assessment

Although effective therapeutic options including TNF inhibitors are available to help patients with moderate to severe ulcerative colitis to reduce the acute symptomatic flares in disease activity, no currently available therapy*, including approved anti-integrins (natalizumab for CD and vedolizumab for UC and CD),* achieves sustained remission in more than 10%–30% of patients with IBD (Hanauer et al. 2002; Sandborn et al. 2005; *Feagan et al. 2013*).

Furthermore, TNF inhibitors are associated with elevated rates of serious bacterial infection, including tuberculosis, and (more rarely) lymphoma and demyelination (Chang and Lichtenstein 2006); commonly associated with neutropenia, anemia, depression, allergic respiratory symptoms, arthralgias, myalgias, tachycardia, and vascular disorders; and very commonly associated with infusion-related reactions, abdominal pain, and nausea (REMICADE Summary of Product Characteristics). Consequently, patients and investigators carefully weigh these benefit-risk tradeoffs both before embarking and while managing long-term treatment with TNF inhibitors.

The recent availability of the gut-selective anti-integrin class of monoclonal antibody treatments may provide potential treatment alternatives to TNF inhibitors and may exhibit a more tolerable safety profile. To establish more effective care standards and understand long-term benefit-risk of etrolizumab, acquisition of robust, long-term data is required.

Etrolizumab distinguishes itself from other anti-integrins on the basis of gut selectivity combined with a dual mechanism of action. *It binds αEβ7 in addition to α4β7 and so regulates retention as well as trafficking of leukocytes/lymphocytes in the intestinal mucosa.*

No clinically significant safety signals have been detected on administration of etrolizumab to patients with moderate to severe UC across a dose range of 0.3–10.0 mg/*kg* IV/SC in the single ascending dose stage and of 0.5–3.0 mg/kg SC and 4 mg/kg IV monthly for 3 doses in the multidose stage of the Phase I study.

The Phase II Study ABS4986g (EUCALYPTUS) and the corresponding OLE study (SPRUCE; Study GA27927) illustrated that a compelling efficacy is achieved with etrolizumab treatment in patients with moderate to severe UC. There was no evidence of increased rates of serious or opportunistic infections and the overall safety profile of etrolizumab was similar to that of placebo. In Phase III, etrolizumab is being assessed for induction and long-term maintenance therapy. Therefore, this study is being conducted to treat patients with etrolizumab in an open-label fashion in order to assess its long-term safety and efficacy.

The non–gut-selective anti-integrin natalizumab has been associated with an increased risk of PML. No events of PML to date have been reported for etrolizumab during the 2-year PML extensive monitoring in the Phase II study, EUCALYPTUS, and the OLE SPRUCE study. Nevertheless, because etrolizumab is also an anti-integrin, albeit with a different subunit target, careful monitoring for possible PML events will be conducted in all studies with an extended period of PML safety monitoring within this protocol.

In summary, there is no known safety risk identified for etrolizumab at this time, but as an investigational medicinal product with limited Phase II data, the full safety profile for etrolizumab will be further characterized as Phase III clinical development progresses. A safety plan is provided in Section 5.1, describing potential risks for etrolizumab and the risk-mitigation strategies to minimize risks for the patients in this trial.

Refer to the most recent Etrolizumab Investigator's Brochure for additional details on clinical and non-clinical studies.

1.3.3 Rationale for Test Product Dosage

Patients enrolling in Part 1 (OLE) of this OLE-SM study from the Phase III etrolizumab studies will receive a dose of etrolizumab that remains unaltered from those studies. Patients enrolling from Phase II OLE Study GA27927 who were receiving a nominal 100-mg dose of etrolizumab (0.7 mL of 150 mg/mL solution via vial and syringe) will receive an actual dose of 105 mg in this study (formulation is a prefilled syringe [PFS] containing 0.7 mL of 150 mg/mL etrolizumab solution, corresponding to delivering a dose of 105 mg etrolizumab per injection). This dose regimen has been demonstrated

to reach full receptor occupancy in the Eucalyptus Phase II clinical study. Of note, no etrolizumab will be administered during Part 2 (SM).

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

2.2 OTHER SAFETY OBJECTIVES

The other safety objectives for this study are as follows:

Part 1 (OLE)

- To evaluate the incidence and severity of infection-related adverse events
- To evaluate the incidence 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

The exploratory objective for this study is as follows:

Part 1 (OLE)

- To evaluate histology 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 active etrolizumab, 105 mg SC, will be administered every 4 weeks followed by a 12-week safety follow-up.
- 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 1 (OLE) and Part 2 (SM).

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

3.1.1.1 Open-Label Extension (Part 1)

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 UC who were enrolled in the Phase II OLE study (GA27927) or the Phase III studies (GA28948, GA28949, GA28950, GA29102, and GA29103) and who meet the eligibility criteria for enrollment into Part 1 (OLE) (see Table 1). All patients will receive open-label etrolizumab in Part 1 (OLE).

Throughout Part 1 (OLE), patients will be monitored for safety by collection of adverse events (both serious and non-serious) and will be monitored for symptoms of PML by administration of the neurologic examination. Efficacy data will consist of Mayo Clinic Score (MCS) at Week 108 and partial Mayo Clinic Score (pMCS) every 4 weeks for the first 3 months and then every 12 weeks thereafter until safety follow-up. Patients will undergo flexible sigmoidoscopy/colonoscopy performed and read by local endoscopist at Week 108 for the assessment of MCS. The local endoscopist will evaluate the endoscopic MCS subscore. In addition, a single paired colonic biopsy sample will be obtained during the procedure to evaluate histology. The paired biopsy sample should be taken from the worst affected segment visualized (up to and including the descending colon). For patients without inflammation on endoscopy, the paired biopsy sample should be taken from the worst affected area visualized in the last endoscopy (up to and including the descending colon).

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 may continue to receive open-label etrolizumab in Part 1 (OLE) until commercial availability in their country, up to *approximately 9 years* after the first patient is enrolled (see Section 3.2), or until the Sponsor's decision to terminate the study, whichever is earlier. 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).

The study population for Study GA27927 consists of patients who are naive to TNF inhibitors and patients who have been previously exposed to TNF inhibitors. Studies GA28948, GA28949, GA29102, and GA29103 enroll patients who are naive to TNF inhibitors. Study GA28950 enrolls patients who have been previously exposed to TNF inhibitors. Protocol design and comparators are provided in Table 1.

Study Drug Administration
Part 1 (OLE)

Patients enrolling from the Phase II OLE or Phase III controlled studies were previously treated with placebo, etrolizumab, infliximab, or adalimumab depending on the study and the group to which the patients were randomized. Patients may also have been receiving concomitant background medication for UC including corticosteroids and/or immunosuppressants.

All patients in Part 1 (OLE) will receive 105 mg etrolizumab every 4 weeks by the SC route. Because a substantial proportion of patients enrolling in this study may be receiving etrolizumab for the first time, all patients will be required to receive their first four doses (Week 0, Day 1–Week 12) of etrolizumab in the clinic setting and to be monitored for 60 minutes following each dose. These in-clinic doses may be administered by the patient if he or she is competent at self-administration following the Phase III controlled study. Patients enrolling from Studies GA27927, GA28948, and GA28949 in which self-administration was not permitted (study medication administered by health care professional [HCP]) may be trained on self-administration of etrolizumab in this study. If patients from Studies GA28950, GA29102, or GA29103 who did not previously self-administer drug at home wish to switch to self-administration, these patients should be trained on self-administration during the first four etrolizumab administrations in this study. Patients may self-administer or have their caregivers administer study treatment in the home setting starting at Week 16, if considered competent to do so by the HCP. Clinic visits during OLE (Part 1) will be every 4 weeks for the first 12 weeks, then every 12 weeks until the patient enters SM (Part 2). If necessary, patients or their HCP may choose to continue administration of study medication in the clinic.

Table 1 Eligibility Criteria for Enrollment into Part 1 of Open-Label Extension and Safety Monitoring Study GA28951

Protocol Number(s)	Title	Eligibility and Timing for Enrollment [a]
GA27927	Phase II open-label extension study to evaluate the long-term safety of etrolizumab in patients with moderate to severe ulcerative colitis	Patients who meet the following criteria: • Patients not in safety follow-up or PML follow-up within Study GA27927 and whose last dose of etrolizumab was during the month of July 2016 may enroll in Part 1 (OLE) of Study GA28951, if eligible, and receive their first dose in this study 4 weeks after their last dose in Study GA27927
GA28948 and GA28949	Phase III, randomized, double-blind, controlled, multicenter study to evaluate the efficacy of (induction of remission) and safety of etrolizumab compared with adalimumab and placebo in patients with moderate to severe active ulcerative colitis who are naive to TNF inhibitors Treatment Arms: etrolizumab, adalimumab, placebo	Patients who performed the Week 10 visit who: • Have not achieved clinical remission at Week 10; may receive their first dose of etrolizumab upon enrollment into Part 1 (OLE) of the OLE-SM study 2 weeks after the Week 10 timepoint in Study GA28948/GA28949 • *With the exception of VHP countries participating in GA28949* and Estonia (*participating in GA28948)*: achieved clinical remission [e] at Week 10 and performed the Week 14 visit; may receive their first dose of etrolizumab upon enrollment into Part 1 (OLE) of the OLE-SM study at Week 14 in Study GA28948/GA28949 • *With the exception of VHP countries participating in GA28949* and Estonia (*participating in GA28948)*: received rescue medication between Week 0 and Week 10, as defined in the GA28948 or GA28949 protocol; patients receiving rescue medication between Weeks 10 and 14 may enroll in Part 1 (OLE) of the OLE-SM study at Week 14 • For *VHP countries participating in GA28949* and Estonia (*participating in GA28948)* only: achieved clinical remission at Week 10 and performed the Week 14 visit; may receive their first dose of etrolizumab upon enrollment into Part 1 (OLE) of the OLE-SM study at Week 16 (4 weeks after the last etrolizumab/etrolizumab placebo dose in Study GA28948/GA28949)

Table 1 Eligibility Criteria for Enrollment into PART 1 of Open-Label Extension and Safety Monitoring Study (GA28951) (cont.)

Protocol Number(s)	Title	Eligibility and Timing for Enrollment a
GA28948 and GA28949 (cont.)		• For *VHP countries participating in GA28949* and Estonia (*participating in GA28948)* only: received rescue medication between Week 0 and Week 10, as defined in the GA28948 or GA28949 protocol; patients receiving rescue medication between Weeks 10 and 16 may enroll in Part 1 (OLE) of the OLE-SM study at Week 16
GA28950	Phase III, randomized, double-blind, placebo-controlled, multicenter study of the efficacy and safety of etrolizumab during induction and maintenance in patients with moderate to severe active ulcerative colitis who have been previously exposed to TNF inhibitors Treatment Arms: etrolizumab, placebo	At end of Induction Phase: • Patients who performed the Week 14 visit who did not meet the criteria for clinical response [b] During the Maintenance Phase • Patients who met the criteria for clinical relapse [c] • Patients receiving rescue medications, as defined in the Study GA28950 protocol All remaining patients at the end of Week 66 visit (completion of Maintenance Phase)
GA29102	Phase III, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy (maintenance of remission) and safety of etrolizumab compared with placebo in patients with moderate to severe active ulcerative colitis who are naive to TNF inhibitors Treatment Arms: etrolizumab, placebo	At the end of the Induction Phase: • Patients who performed the Week 10 visit and who have not achieved clinical response [b] at Week 10 • Patients receiving rescue medications during the Induction Phase, as defined in the GA29102 protocol During the Maintenance Phase: • Patients who met the criteria for clinical relapse [c] • Patients receiving rescue medications, as defined in the GA29102 protocol All remaining patients at the end of Week 62 visit (completion of Maintenance Phase)

Table 1 Eligibility Criteria for Enrollment into PART 1 of Open-Label Extension and Safety Monitoring Study (GA28951) (cont.)

Protocol Number(s)	Title	Eligibility and Timing for Enrollment [a]
GA29103	Phase III, randomized, double-blind, double-dummy multicenter study to evaluate the efficacy and safety of etrolizumab compared with infliximab in patients with moderate to severe active ulcerative colitis who are naive to TNF inhibitors Treatment Arms: etrolizumab, infliximab	Patients who met criteria for disease worsening [d] at any time between Week 10 and Week 54 may enter OLE-SM after an infliximab washout period within Study GA29103 Patients receiving rescue medications, as defined in the GA29103 protocol All remaining patients at the end of Week 54 visit (completion of Maintenance Phase)

MCS = Mayo Clinic Score; OLE = open-label extension; OLE-SM = open-label extension–safety monitoring; pMCS = partial Mayo Clinic Score; SM = safety monitoring; TNF = tumor necrosis factor.

[a] Patients are to receive their first dose of etrolizumab in this protocol 4 weeks after their last dose of study medication in Studies GA27927, GA28950 and GA29102; as specified above for Studies GA28948 and GA28949, and as described in the washout schedule for Study GA29103. On occasions where this first dose of etrolizumab cannot be administered in accordance with these requirements, the first dose of etrolizumab is to be administered with a maximum delay of 2 weeks.

[b] **Definition of Clinical Response:** MCS with ≥ 3-point decrease and 30% reduction from baseline as well as ≥ 1-point decrease in rectal bleeding subscore or an absolute rectal bleeding score of 0 or 1.

[c] **Definition of Clinical Relapse:** Clinical relapse is defined as an increase in pMCS ≥ 3 points compared with induction timepoint (Week 10 or 14) AND absolute pMCS of ≥ 5 AND an endoscopy subscore of ≥ 2.

[d] **Definition of Disease Worsening:** Disease worsening is defined as an increase in pMCS ≥ 3 points from the induction timepoint AND absolute pMCS of ≥ 5 AND an endoscopy subscore of ≥ 2.

[e] **Definition of Clinical Remission:** MCS ≤ 2 with individual subscores ≤ 1.

Number of Patients

The OLE-SM study will be conducted in centers that have participated in the Phase II OLE Study GA27927 and/or the double-blinded Phase III Studies GA28948, GA28949, GA28950, GA29102, and GA29103. The maximum number of patients potentially enrolling in this study will be all patients from the studies; approximately *2100* patients. Patients will be allocated the same subject number they had in the initial Phase II OLE study or Phase III study.

Rescue Therapy That Can Be Given with Study Medication

At any time during the study, patients who have worsening UC may receive concomitant therapy with corticosteroids (IV, oral, or topical). Addition of or increases in doses of 5-ASA (oral or topical) and/or initiation of immunosuppressant treatment (i.e., AZA, 6-MP, or MTX), including patients from Study GA27927, is also permitted during this study at the discretion of the investigator.

Patients who are taking immunosuppressants (i.e., AZA, 6-MP, or MTX) as part of their concomitant treatment in the Phase II OLE and Phase III controlled studies may continue to receive immunosuppressants in OLE-SM study with dose adjustments at the discretion of the investigator. Generally accepted criteria for discontinuation of immunosuppressants 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 reduce dose or discontinue immunosuppressants due to toxicity or any other reason remains at the discretion of the investigator.

Rescue Therapy That CANNOT Be Given with Study Medication

At ANY time during the conduct of the study, use of other immunosuppressive agents including, but not limited to, other anti-integrins, T or B cell depleters (except AZA and 6-MP), TNF inhibitors (including TNF inhibitor biosimilars), anti-adhesion molecules, cyclosporine, tacrolimus, *Janus kinase (JAK) inhibitors,* or investigational agents are prohibited. Patients who do receive such rescue therapies are not allowed to receive further etrolizumab treatment and are to be withdrawn into the 12-week safety follow-up. These patients will then enter Part 2 (SM) of the OLE-SM study for 92 weeks of extended PML monitoring.

Moving from Part 1 (Open-Label Extension) to Part 2 (Safety Monitoring) in this Study

Patients who discontinue treatment with open-label etrolizumab will be requested to enter a post-treatment 12-week safety follow-up, and then be requested to enter Part 2 (SM) of this study. Part 2 (SM) will consist of an additional 92 weeks of extended PML monitoring following the initial 12-week safety follow-up period. See Figure 1 and Figure 2 for schemas of the study and see Section 3.1.1.2.

3.1.1.2 Extended PML Safety Follow-Up (Part 2)

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

- Patients exiting Part 1 (OLE)
- Patients from the Phase II OLE study or the Phase III controlled studies who are not eligible or willing to receive etrolizumab in this study (e.g., due to receipt of prohibited medication)
- Patients whose safety follow-up or PML follow-up is not completed within Study GA27927 by July 2016

Regardless of route of entry, patients will enroll following completion of the 12-week safety follow-up period, which will occur within Part 1 of this study (OLE; for those entering from OLE) or within the Phase III controlled studies (for those enrolling directly from the Phase III studies). Patients from the Phase II OLE study whose safety follow-up is not completed within Study GA27927 by July 2016 will complete their safety follow-up period in this study (GA28951).

3.1.1.3 Study Duration

Part 1 (OLE)

Part 1 (OLE) will continue for up to *approximately 9 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) should 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), either from Part 1 (OLE) or enroll directly from the Phase II OLE study or any of the Phase III studies, the study will last 92 weeks.

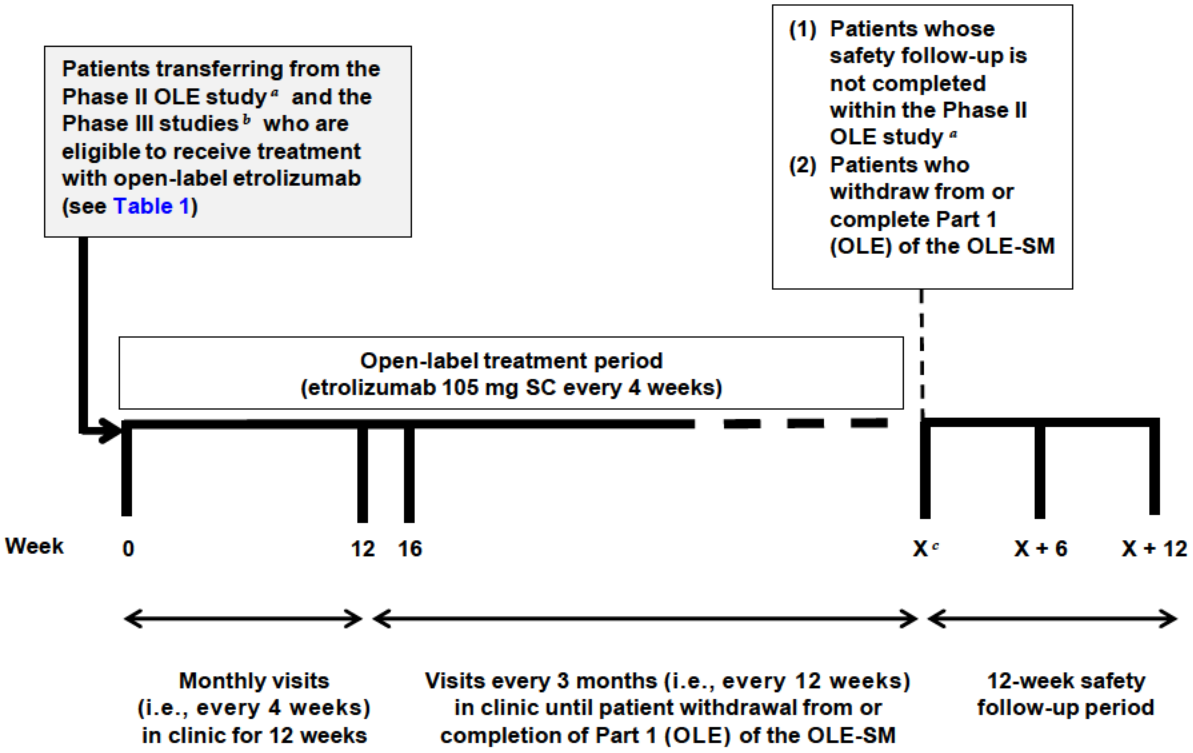
Schedules of Assessments are provided in Appendix 1, Appendix 2, and Appendix 3. The efficacy outcome definitions are given in Table 2.

Table 2 Efficacy Outcome Definitions

Outcome Term	Definition
Endoscopic remission	Endoscopic subscore = 0
MCS	MCS is a composite of 4 assessments, each rated from 0 to 3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment
MCS Remission	MCS ≤ 2, a rectal bleeding score of 0, physician's global assessment of 0–1, stool frequency subscore of 0–1, endoscopy score of 0–1
pMCS	pMCS is a composite of 3 assessments, each rated from 0 to 3: stool frequency, rectal bleeding, and physician's global assessment
pMCS Clinical Remission	pMCS ≤ 2, a rectal bleeding score of 0–1, physician's global assessment of 0–1, stool frequency subscore of 0–1

MCS = Mayo Clinic Score; pMCS = partial Mayo Clinic Score.

Figure 1 Study Schema for Part 1 (OLE) of the OLE-SM Study



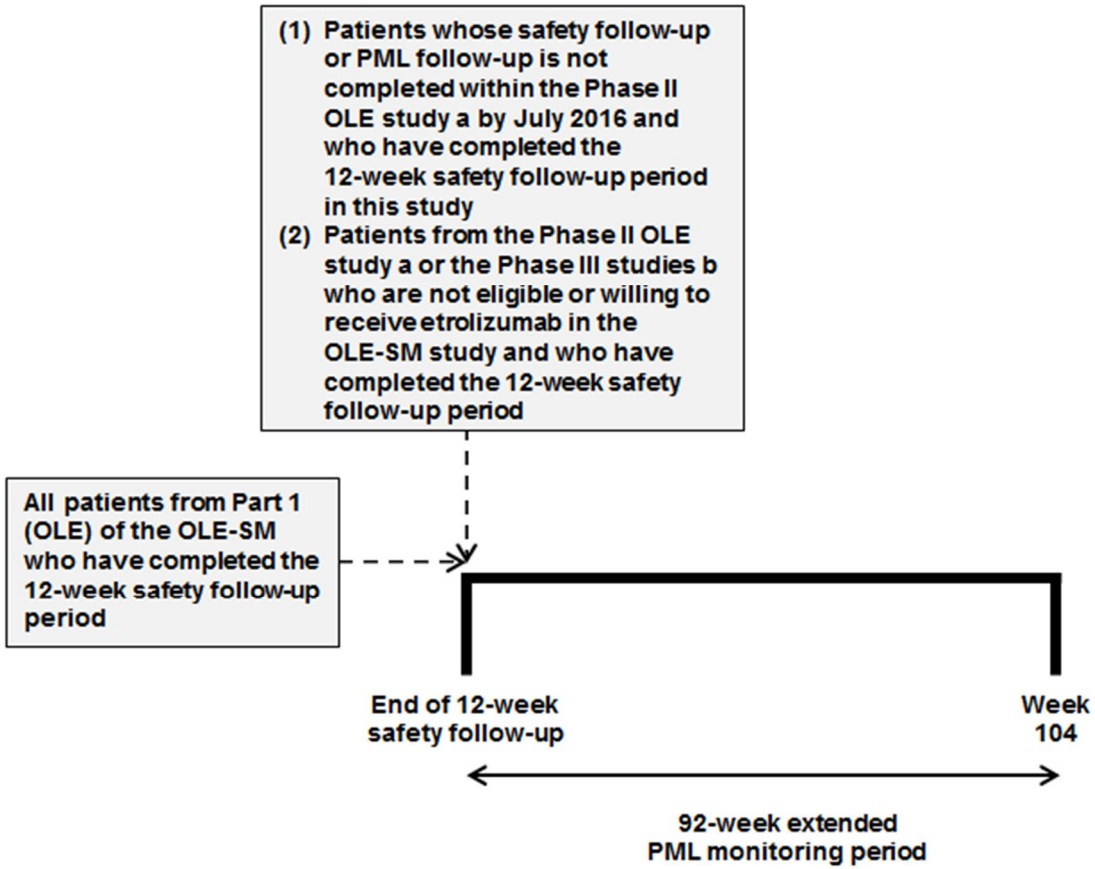
OLE = open-label extension; OLE-SM = open-label extension—safety monitoring study; SC = subcutaneous.

[a] Study GA27927.

[b] Studies GA28948, GA28949, GA28950, GA29102, and GA29103.

[c] Patients may continue to receive open-label etrolizumab in Part 1 (OLE) for up to *approximately 9 years* after the first patient is enrolled, until commercial availability, or until the Sponsor's decision to terminate the study, whichever is earlier.

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



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

[a] Study GA27927.

[b] Studies GA28948, GA28949, GA28950, GA29102, and GA29103.

3.2 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

3.3.1 Efficacy Outcome Measures (Part 1; OLE)

The efficacy outcome measures for this study are as follows:

- To describe the long-term efficacy of etrolizumab (105 mg SC every 4 weeks) by pMCS clinical remission for patients with UC in Part 1 (OLE)
- To evaluate remission by MCS at Week 108 in Part 1 (OLE)
- To evaluate endoscopic remission by MCS at Week 108 in Part 1 (OLE)

3.3.2 Safety Outcome Measures (Part 1; OLE)

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

- Incidence and severity of adverse events
- Incidence of serious adverse events
- Incidence 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 of malignancies
- Incidence of ATAs to etrolizumab
- Incidence and severity of hypersensitivity reaction events

3.3.3 Safety Outcome Measure (Part 2; SM)

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

- Incidence of suspected or confirmed PML events

3.3.4 Exploratory Outcome Measure

The exploratory outcome measure for this study is as follows:

- Histologic appearance of mucosa at Week 108

4. MATERIALS AND METHODS

4.1 PATIENTS

Part 1 (OLE)

Approximately *2100* patients enrolled in the Phase II OLE study (GA27927) and the Phase III studies (GA28948, GA28949, GA28950, GA29102, and GA29103) will be potentially eligible for Part 1 (OLE) of this OLE-SM study. There will be no randomization in this OLE-SM study; all patients entering Part 1 (OLE) will receive open-label etrolizumab.

Part 2 (SM)

Approximately *2100* patients enrolled in the Phase II OLE study and the Phase III controlled studies who provide consent are eligible for Part 2 (SM) of this OLE-SM study.

4.1.1 Inclusion Criteria

Part 1 (OLE)

- Patients who were previously enrolled in the Phase II OLE study or a Phase III controlled study and meet the eligibility criteria for treatment with open-label etrolizumab as described in Table 1 (see Section 3.1.1.1) may enroll in Part 1 (OLE) of the study. These patients must provide written informed consent and comply with the requirements of the OLE-SM protocol.

  Patients not in safety follow-up or PML follow-up within Study GA27927 and whose last dose of etrolizumab is by July 2016 may enroll in Part 1 (OLE) of Study GA28951, if eligible, and receive their first dose in this study 4 weeks after their last dose in Study GA27927. On occasions where this first dose of etrolizumab cannot be administered in accordance with these requirements, the first dose of etrolizumab is to be administered with a maximum delay of 2 weeks (i.e., up to 6 weeks after their last dose of etrolizumab in Study GA27927).

  Eligible patients who exit from Study GA28948 or GA28949 at Week 10 because either they did not achieve clinical remission or they required the use of rescue medication prior to the Week 10 timepoint should not receive their first dose of open-label etrolizumab in Study GA28951 until 2 weeks after the Week 10 timepoint in the Phase III controlled study to allow for adalimumab washout. The first dose of etrolizumab given to these patients entering Study GA28951 should not exceed 4 weeks following the Week 10 timepoint from the Phase III controlled study.

  With the exception of VHP countries participating in GA28949 and Estonia (*participating in GA28948)*: Patients who remain in Study GA28948 or Study GA28949 through Week 14 because they have achieved clinical remission may enroll in Part 1 (OLE) of Study GA28951 at Week 14. The first dose of open-label etrolizumab will be given on Day 1 upon enrollment into Part 1 (OLE) of Study GA28951. The first dose of etrolizumab given to the patients entering

Study GA28951 should not exceed 2 weeks following the Week 14 timepoint from the Phase III controlled study.

With the exception of VHP countries participating in GA28949 and Estonia (*participating in GA28948)*: Eligible patients who receive rescue medication between Weeks 10 and 14 may enroll in Part 1 (OLE) of Study GA28951 at Week 14.

For *VHP countries participating in GA28949* and Estonia (*participating in GA28948)*: Patients who remain in Study GA28948 or GA28949 through Week 14 because they have achieved clinical remission at Week 10 may enroll in Part 1 (OLE) of Study GA28951 at Week 16. The first dose of open-label etrolizumab will be given on Day 1 upon enrollment into Part 1 (OLE) of Study GA28951 (4 weeks after their last etrolizumab/etrolizumab placebo dose or 8 weeks after their last adalimumab/adalimumab placebo dose in Study GA28948 or GA28949). On occasions where the first OLE dose of etrolizumab cannot be administered in accordance with these requirements, the first dose may be delayed by a maximum of 2 weeks (i.e., first OLE dose up to 6 weeks after their last etrolizumab/etrolizumab placebo dose or 10 weeks after their last adalimumab/adalimumab placebo dose in Study GA28948 or GA28949).

For *VHP countries participating in GA28949* and Estonia (*participating in GA28948)*: Eligible patients who receive rescue medication between Weeks 10 and 16 may enroll in Part 1 (OLE) of Study GA28951 at Week 16.

- For women who are not postmenopausal (at least 12 months of non–therapy-induced amenorrhea) or surgically sterile (i.e., absence of ovaries and/or uterus): agreement to remain abstinent or use a highly effective method of contraception during the treatment period and for at least 24 weeks after the last dose of study drug (see Appendix 4).

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use 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 to avoid exposing the embryo to study drug. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Part 2 (SM)

- Patients whose safety follow-up or PML follow-up is not completed within Study GA27927 and patients who had their last dose of etrolizumab by July 2016 in Study GA27927 and are not eligible or choose not to enroll in Part 1 (OLE)
- Patients who participated in one of the etrolizumab Phase III studies (GA28948, GA28949, GA28950, GA29102, and GA29103) and are not eligible or chose not to enroll in Part 1 (OLE)
- Patients who transfer from 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 prior to entering Part 2 (SM).

4.1.2 Exclusion Criteria

Part 1 (OLE)

- Withdrawal of consent from the Phase II OLE study or any of the Phase III studies
- Patients who discontinued etrolizumab/etrolizumab placebo prior to Week 10 or did not perform the Week 10 visit of the Phase III Studies GA28948, GA28949, GA29102, and GA29103
- Patients who discontinued etrolizumab/etrolizumab placebo prior to Week 14 or did not perform the Week 14 visit of the Phase III Study GA28950
- Inability to comply with the study protocol, in the opinion of the investigator
- Patients not compliant in the Phase II OLE or Phase III studies or did not complete the required washout period for an active comparator in Studies GA28948, GA28949, and GA29103
- Pregnancy or lactation

Exclusion Due to Safety Reasons

- Patients who developed an anaphylactic/anaphylactoid or severe allergic reaction to study medication during the Phase II OLE or Phase III studies
- Patients who experienced or have an ongoing serious infection event (except for those listed below) should not receive study drug until the event has completely resolved and treatment with anti-infective medications has been completed
- Patients who experienced a specific de novo or reactivated serious viral infection such as hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV during the Phase II OLE or Phase III studies
- Patients who develop cytomegalovirus (CMV) colitis leading to early treatment discontinuation in the Phase II OLE or Phase III studies
- Patients who develop life-threatening infections during the Phase II OLE or Phase III studies

- 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 the Phase II OLE or Phase III studies
- Receipt of the following since commencement of the Phase II OLE or Phase III controlled studies:

  Any investigational treatment, including investigational vaccines

  Use of agents that deplete B or T cells (e.g., alemtuzumab or visilizumab), except AZA and 6-MP

  Use of anti-adhesion molecules

  Use of JAK inhibitors

  Use of cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil (MMF)

  Patients who have previously received rituximab, natalizumab, vedolizumab, or efalizumab may not enter the study

  Immunization with a live/attenuated vaccine
- In the opinion of the investigator, any new (since enrolling in the Phase II OLE or Phase III controlled studies), 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 UC)
- Any patient who developed PML in the Phase II OLE or Phase III studies
- Any patient with neurological symptoms where suspected PML has not been ruled out

Part 2 (SM)

- No exclusion criteria

4.2 CONCOMITANT MEDICATION AND TREATMENT ASSIGNMENT

Part 1 (OLE)

In Part 1 (OLE), all patients will receive 105 mg etrolizumab every 4 weeks by the SC route. Because a substantial proportion of patients enrolling in this study may be receiving etrolizumab for the first time, all patients will be required to receive their first four doses of etrolizumab (i.e., Week 0, Day 1–Week 12) in the clinic setting and to be monitored for 60 minutes following each dose. These in-clinic doses may be administered by the patient if he or she is competent at self-administration following the Phase III controlled study.

Patients enrolling in this study from Studies GA27927, GA28948, and GA28949 (study medication administered by HCP) may be trained on self-administration of etrolizumab in this study. If patients from the Phase II OLE study or any Phase III study who did not previously self-administer drug at home wish to switch to self-administration, these

patients are to be trained during the first four administrations. Starting at Week 16, patients may self-administer or have their caregivers administer study treatment in the home setting, if considered competent to do so by the HCP. Clinic visits during OLE (Part 1) will be every 4 weeks for the first 12 weeks, then every 12 weeks until the patient enters SM (Part 2). If necessary, patients or their HCP may choose to continue administration of study medication in the clinic.

Part 2 (SM)

In Part 2 (SM), no study drug will be administered.

4.2.1 Concomitant Therapy

4.2.1.1 Permitted Concomitant Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, preventative vaccines, vitamins, nutritional supplements) used by a patient from the start of the study to completion/early withdrawal from treatment. During Part 1 (OLE), all concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). During Part 2 (SM), the use of concomitant therapies will not be required to be documented in the eCRF.

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

4.2.1.2 Requirements Regarding Concomitant Therapy for Ulcerative Colitis

Part 1 (OLE)

- Patients who are taking immunosuppressants as part of their concomitant treatment in the Phase II OLE or Phase III controlled studies may continue to receive immunosuppressants in the OLE-SM study with dose adjustments at the discretion of the investigator. Generally accepted criteria for discontinuation of immunosuppressants 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 reduce dose or discontinue immunosuppressants due to toxicity or any other reason remains at the discretion of the investigator.
- All sites, including U.S. sites in Phase II OLE study, may initiate immunosuppressant treatment (i.e., AZA, 6-MP, or MTX) in their patients during this study at the discretion of the investigator.

At any time during the study, patients may receive concomitant therapy with corticosteroids (IV, oral, or topical) or 5-ASA (oral or topical).

Part 2 (SM)

There are no requirements regarding concomitant therapies during Part 2 (SM) of this study. 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.

4.2.2 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) following 12-week safety follow-up.

- Any investigational treatment including investigational vaccines
- Use of lymphocyte-depleting agents (e.g., alemtuzumab or visilizumab), except AZA and 6-MP
- Use of cyclosporine, tacrolimus, sirolimus, or MMF
- Use of natalizumab, vedolizumab, efalizumab, or rituximab
- Use of TNF inhibitors (including TNF inhibitor biosimilars)
- Use of anti-adhesion molecules (e.g., anti-MAdCAM-1)
- *Use of JAK inhibitors*

Part 2 (SM)

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

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Etrolizumab

Part 1 (OLE)

Etrolizumab will be supplied by the Sponsor as a liquid formulation in PFSs and is administered as a SC injection. Each 1–mL PFS will contain 150 mg/mL of etrolizumab (0.7 mL nominal volume). Etrolizumab 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 parenteral administration and contains no preservatives.

Study drug packaging will be overseen by the Sponsor's Clinical Trial Supplies Department and will be a labeled with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labeling 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, quantity, integrity of seals, and temperature conditions and report any deviations or product complaints to the monitor upon discovery.

The study drug must be stored according to the details on the product label. The drug label indicates the storage temperature. PFSs of study medication should be refrigerated at 2°C–8°C and protected from excessive light and heat. 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 (up to 30°C). If a PFS 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 PFSs with study drug will be stored at room temperature 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 labeling of the study drug will be provided in the protocol-supporting documents.

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

4.3.1.2 Concomitant Therapy and Treatments

Please refer to product label, local prescribing dosage, administration, and compliance information for the formulation, packaging, and handling details of agents prescribed as concomitant therapy for UC.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Etrolizumab

Part 1 (OLE)

All patients will receive one 0.7-mL injection with use of a PFS device once every 4 weeks. The device is a 1-mL long glass syringe with a staked-in stainless steel needle. The needle is a 27G ½" thin-wall design. The needle-safety device is a standard design (SSI X100L), and the device is fitted with a custom-designed plunger rod and an extended finger flange.

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

Study site HCPs will be trained on the use of the PFS device and SC administration of study medication into the thigh, abdomen, or upper arm.

Patients Self-Administering for the First Time in this Protocol

As mentioned in Section 4.2, in order to monitor for any possible hypersensitivity reactions in patients who would receive their first active etrolizumab dose upon enrolling in the OLE-SM study, etrolizumab administration is to be conducted in the clinic setting for the first four drug administrations. Patients who are to self-administer for the first time in this study will be trained in the use of the device by an HCP and be given 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. The upper arm, abdomen, or thigh site may be used by the caregiver. Note: The upper arm site is not to be used for patient administration of study treatment.

For the initial 4 dose administrations, study medication is to be administered under close supervision of the HCP in a setting where medications and resuscitation facilities are available. The first two treatments (each 0.7 mL delivered via PFS; Week 0 [Day 1] and Week 4) will be administered by the HCP and observed by the patient (and/or caregiver). The following two treatments (Week 8 and Week 12) will be administered by the patient (or caregiver) and observed by the HCP in the clinic setting. Following the first four study treatment administrations, patients will be monitored for acute hypersensitivity reactions for at least 1 hour after the end of the injection.

Epinephrine must be readily available for immediate use if required to treat anaphylaxis. Adjunctive medications such as parenteral diphenhydramine and inhaled bronchodilators can also be used IN ADDITION to epinephrine if necessary. Resuscitation equipment should also be available. 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. 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 an e-diary to record drug administration and return of used and unused medication syringes (see Appendix 8). 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 HCP/patient cannot administer study medication on the scheduled dosing day, study medication is to be administered within a window of +3 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. Any potential deviation from this window is to be discussed with the Medical Monitor for the study.

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

The recommended injection sites are the front of the middle thighs and the lower part of the abdomen below the navel except for the 2-inch area directly around the navel. Patients should place themselves in a comfortable position before self-administering study drug. As previously recommended, caregivers responsible for administering the injection should utilize the outer area of the upper arm, abdomen, or thigh. 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 5.1.1.3) should be documented on the appropriate Adverse Event eCRF page. Patients administering at home should be taught to report any injection-site reactions as adverse events (e.g., redness and/or swelling).

For dosage and administration of concomitant therapy for UC see Section 4.2.1.2 and for compliance see Section 4.3.3.1.

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.

4.3.3 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.

4.3.3.1 Assessment of Compliance Part 1 (OLE)

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

Home injection: An e-diary will be provided to patients to record home injections. Patients will be asked to return all unused PFS 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 e-diary via an online portal. However, patients should bring the e-diary to the clinic during each visit.

Sharps containers for any used PFS 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 4.3.3. 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 (Section 4.3.3.2). The investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Sponsor.

4.3.3.2 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 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 4.3.3.3).

4.3.3.3 Reporting of Prefilled Syringe Complaints/Events Part 1 (OLE)

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 within 24 hours of the investigator becoming aware of the event. 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 the medical device complaint results in an adverse event, an Adverse Event eCRF must be completed and submitted through the electronic data capture (EDC) system immediately (i.e., no more than 24 hours after learning of the event). 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 5.4.1. If the medical device complaint results in an adverse event to an individual other than the study patient *(e.g. nurse at the site or relative/caregiver during a home administration)*, the device complaint must be reported on the PD103 IMP deviation form. The adverse event must be reported to the Sponsor as a spontaneous adverse event *(see Section* 5.4.6).

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 Description of Study Assessments in Part 1 (OLE)

On the final visit of the Phase II OLE or Phase III controlled study, patients should have had procedures and laboratory assessments performed as part of their withdrawal visit. Therefore, to minimize burden on the patient, results from the single set of procedures and laboratory assessments from the final visit of the Phase II OLE or Phase III controlled study will be used for analysis and data sets for the first visit of the OLE-SM study, with the exception of ATA samples, which must be collected at Week 0 if the Week 0 visit occurs >7 days after the final visit of the Phase II OLE or Phase III controlled study. Only 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.

4.4.1.1 Physical Examinations

A partial physical examination will be performed at Day 1 of the OLE-SM study and recorded as “normal” or “abnormal” at the times indicated in the Schedule of Assessments. 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 the parent study (i.e., the Phase II OLE study or a Phase III controlled study) will be stated as unresolved in those studies and reopened in Study GA28951. The adverse event will be reported in Study GA28951 with the start date and adverse event term identical to those in the Phase II OLE study or the Phase III controlled study. The adverse event severity (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade) should be evaluated by the investigator at the start of Part I (OLE) and recorded in the "AE initial NCI CTCAE grade" field of the Adverse Event eCRF for Study GA28951. The most extreme NCI CTCAE grade for the event should also be recorded, taking into account the severity of the event since it was first reported during the parent study.

4.4.1.2 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 at the indicated timepoints in the Schedule of Assessments (see Appendix 1) before study drug administration at clinic visit only.

4.4.1.3 Ulcerative Colitis Disease Activity Assessments

Efficacy will be assessed with use of the MCS (at Week 108) and pMCS at the indicated timepoints in the Schedule of Assessments (see Appendix 1). The MCS has a range of 0–12, whereas the pMCS has a range of 0–9, with higher scores indicating more severe

disease. The MCS is a composite of four assessments, each rated from 0–3: stool frequency, rectal bleeding, endoscopy, and physician's global assessment (PGA). The pMCS is a composite of three assessments, each rated from 0–3: stool frequency, rectal bleeding, and PGA (see Appendix 5).

One of the components of the MCS is the endoscopic subscore. At Week 108, for the assessment of the MCS (i.e., that requires endoscopy), every effort should be made to schedule the endoscopy on the same day as the study visit. If this is not possible, endoscopy should be performed within 2 weeks prior to the day of the visit. The endoscopy score should be considered when determining the PGA (as applicable), a component of the MCS.

The symptoms of UC must be recorded in the e-diary at specified timepoints throughout the study. To help characterize the clinical profile of etrolizumab, the stool frequency and rectal bleeding components of the pMCS will be collected daily during the initial 12 weeks. After the Week 12 visit, the stool frequency and rectal bleeding components of the pMCS (performed every 12 weeks) and MCS (for the Week 108 assessment) will be collected daily for 4 weeks prior to clinic visit and the PGA component of the MCS/pMCS will be determined at study visits. The format of the MCS/pMCS questions may change when they are converted to electronic format. The questions will be translated as required in the local language.

In order to ensure instrument validity and that data standards meet health authority requirements, the stool frequency and rectal bleeding components of the MCS/pMCS, when completed at the sites, should be administered at the investigational site prior to the completion of other assessments and before the patient receives any disease-status information or study drug during that visit.

The e-diary entries will be reviewed by site personnel during study visits, including early withdrawal from treatment visit and any unscheduled visit(s) due to disease exacerbation. Because the colonoscopy/flexible sigmoidoscopy and bowel cleansing preparations may interfere with the assessment of patient-reported symptoms, e-diary entries used to calculate the complete MCS should not correspond to days of bowel preparation or endoscopy or the day following the endoscopy. Further details and examples of stool frequency and rectal bleeding subscore derivation are provided in Appendix 5. Appendix 5 also outlines procedures to follow in the event of e-diary malfunction or loss.

Flexible Sigmoidoscopy/Colonoscopy with Colonic Biopsies

Patients are to prepare their bowel prior to the flexible sigmoidoscopy colonoscopy/procedures. Medications used for bowel preparation should be recorded on concomitant medications pages of the eCRF.

Flexible sigmoidoscopy (or full colonoscopy, if required) will be performed on all patients at Week 108 in Part 1(OLE) of the study and/or at withdrawal from the study if the

withdrawal visit is prior to the Week 108 visit (see Appendix 1). The endoscopic procedure will be performed by local endoscopist who will evaluate the endoscopic MCS subscore.

Each patient entered into the study will have one paired colonic biopsy sample taken during this flexible sigmoidoscopy/full colonoscopy. The paired biopsy sample should be taken from the worst affected segment visualized (up to and including the descending colon). For patients without inflammation on endoscopy, the paired biopsy sample should be taken from the worst affected area visualized in the last endoscopy (up to and including the descending colon). This paired biopsy sample will be placed in formalin at the sites.

Necrotic areas of ulcerated mucosa should be avoided during biopsy. Original location (colonic segment and endoscopic depth) of biopsy specimen should be clearly indicated.

Progressive Multifocal Leukoencephalopathy Assessment

Study site personnel and patients will be educated regarding the signs and symptoms of PML. Close monitoring during the course of the study for any new symptoms or signs suggestive of PML will be performed, with 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 by a qualified HCP and will be performed as indicated on the Schedule of Assessments (see Appendix 6).

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 event should be expeditiously reported as an adverse event of special interest within 24 hours (see Section 5.3 and Appendix 7 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) performed 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 John Cunningham virus (JCV) by PCR. If JCV is detected, the patient should be treated as a PML case, permanently discontinue study drug, and transfer to safety follow-up.

Dosing with etrolizumab can only be resumed in patients where PML has been ruled out. See Appendix 7 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 neurologic examination 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 Phase II OLE or blinded Phase III studies) will be requested to continue to be monitored for PML for an additional 92 weeks by enrolling in the Part 2 (SM) portion of the this study; thus, providing a total of 2 years PML follow-up after the last dose of study medication (see Section 4.4.1.6 for details of assessments in Part 2 [SM]).

4.4.1.4 Laboratory Assessments

Laboratory assessments will be performed as indicated on the Schedule of Assessments (see the Study Flowchart in Appendix 1 and Appendix 2). With the exception of urine pregnancy tests, all laboratory investigations will be performed by a central laboratory. Urine pregnancy tests will be performed at specified subsequent visits or in the patient's home. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

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)
- Serum chemistries, including liver function tests (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)
- C-reactive protein (CRP)
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test performed at monthly intervals. Pregnancy tests are to be conducted at home on a monthly basis when drug administration is in the home setting and the outcome of the pregnancy test should be recorded on an e-diary. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

- Serum samples will be collected for the detection and characterization of ATAs. ATA samples will be analyzed using validated assays. ATA samples may also be utilized for exploratory PD biomarker assessments or assessment of etrolizumab concentrations.
- Serum samples will be collected for monitoring the etrolizumab concentration (PK) during the long-term dosing period. PK samples will be analyzed using validated assays.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.4.1.7), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Colon biopsy samples (formalin and RNA later) will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

4.4.1.5 Electrocardiograms

A 12-lead electrocardiogram (ECG) with formal readings will be taken at the end of each year of treatment as indicated on the Schedule of Assessments. The patient should be supine for 10 minutes before the measurement is taken.

4.4.1.6 Medication Use and Compliance

Following each home administration of study medication, the patient is to record the location of each injection and whether the injection was successfully administered. The e-diary will automatically collect date and time information for when the patient completes the study medication administration report. Note that details of the study medication administration are to be entered directly into the eCRF following clinic administrations.

4.4.1.7 Samples for Roche Clinical Repository

Overview of the Roche Clinical Repository

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

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. Any residual colonic biopsy sample will be transferred to the RCR in consenting patients. RCR specimens will be used to achieve the following objectives:

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

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

For patients who have consented to donate samples to the RCR, any residual or not entirely consumed colonic biopsy sample obtained at Week 108 and residual serum samples (see Appendix 1 for specific collection timepoints) will be stored in the RCR and will be destroyed no later than 15 years after the date of final closure of the associated clinical database.

Potential applications of RCR samples include these samples being assayed for mRNA expression, genetic variation, and other biomarker(s) that predict response or toxicity to etrolizumab.

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Reference Manual or Laboratory Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. 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 provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

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

Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GA28951 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GA28951.

Monitoring and Oversight

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

4.4.2 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 telephone calls 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 call, the patient will be asked to come into the clinic for a neurologic examination, including administration of the PML Objective Checklist (see Appendix 6). The PML Algorithm (see Appendix 7) 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 5.1.1.1.1).

4.4.3 Timing of Study Assessments

4.4.3.1 Assessments during Treatment

Part 1 (OLE)

Written informed consent for participation in the study must be obtained before performing any study-specific tests or evaluations. For patients enrolling into Part 1, 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 the Phase II OLE or Phase III studies 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.

All patients would have received hands-on training in use of the e-diary and tablet in the Phase III controlled studies and will continue to document compliance for etrolizumab administration. Patients enrolling in Part 1 (OLE) are to record their stool frequency and rectal bleeding in the e-diary daily during the initial 12 weeks for the pMCS. After the Week 12 visit, the stool frequency and rectal bleeding components of the pMCS (performed every 12 weeks) and MCS (for the Week 108 assessment) will be collected by the patient daily for 4 weeks prior to clinic visit assessment. 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 assessments will be available.

See the Study Flowchart provided in Appendix 3 for the assessments to be performed during the safety monitoring period.

4.4.3.2 Assessments at Study Completion/Early Withdrawal from Treatment Visit/Early Withdrawal

Part 1 (OLE)

Part 1 (OLE) of OLE-SM study (during which patients receive treatment with open-label etrolizumab) will continue for up to *approximately 9 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.

After completion of Part 1 of the study and availability of commercial etrolizumab, patients who do not go on to receive commercial etrolizumab (via a prescription) should enter the 12-week safety follow-up in Part 1 (OLE) and then enter Part 2 (SM) for PML follow-up.

Discontinuation during the OLE (Part 1)

Patients who discontinue treatment for any reason will be asked to complete the early withdrawal from treatment visit for the OLE (Part 1; see Appendix 1). The early withdrawal from treatment visit will be followed by a 12-week safety follow-up consisting of one telephone call 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). Patients who discontinue before entering safety follow-up will be asked to return to the clinic for an early withdrawal visit (see Appendix 2).

Discontinuation during the 12-Week Safety Follow-Up Period of OLE (Part 1)

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 (Part 2)

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.

4.4.3.3 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, 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 e-diary and assessment of pMCS if e-diary data is available
- Recording of concomitant medications and procedures
- Collection of adverse events and serious adverse events
- Clinical chemistry and hematology and CRP, 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.

4.5 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 Discontinuation from Study Drug

Part 1 (OLE)

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

- Pregnancy
- Anaphylaxis or other severe hypersensitivity reaction
- 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

- Specific serious infection (see Section 5.1.1.1 for details on serious infection):

  Any patient who experiences a specific de novo or reactivated serious viral infection, such as HBV, HCV, HIV, should discontinue study drug.

  Patients who develop life-threatening infections during the study should discontinue study drug.
- Use of any prohibited medication as a concomitant therapy (see Section 4.2.2)

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 4.4.3.2) 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 4.4.1.6). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

4.5.1.2 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 appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.5.1.3 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 Council for 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) that focuses on PML safety monitoring in patients off etrolizumab.

5.1 SAFETY PLAN (PART 1 OPEN-LABEL EXTENSION)

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 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

Etrolizumab is an investigational drug that demonstrated a safety profile similar to placebo in the Phase II study, EUCALYPTUS. Given the relatively limited size of Phase II studies, the full safety profile will be further characterized during the Etrolizumab Phase III program. The safety plan for this study is designed to ensure patient safety and mitigate potential risks, including specific eligibility criteria, monitoring, and management strategy as described below.

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

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-α4 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.

PML has not been attributed to vedolizumab, which selectively impedes lymphocyte trafficking into gut tissue by specifically blocking only the α4β7 integrin and not the α4β1 integrin, *despite extensive treatment exposure* (Dotan 2017).

Etrolizumab targets cells expressing the β7 integrin (α4β7 and αEβ7 cells) and not α4β1 cells. Despite the lack of theoretical or experimental evidence for a specific role of β7 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 the Phase III trials. There have been no cases of PML in patients treated with etrolizumab.

Patient Selection and PML Education

No known interventions can reliably prevent PML or adequately 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, efalizumab, vedolizumab, rituximab, B- or T-cell–depleting agents (e.g., alemtuzumab or visilizumab), cyclosporine, anti-adhesion molecules, 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 study, 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 (see Appendix 6; 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 event should be expeditiously reported to the Sponsor as an adverse event of special interest within 24 hours (see Section 5.5.2 and Appendix 7 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 7 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 6 (Worksheet for the PML Neurologic Examination) and Appendix 7 (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 placebo-treated patients 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 specific de novo or reactivated serious viral infection, such as HBV, HCV, or HIV, during the Phase II OLE or Phase III studies should not be enrolled in Part 1 of this study. Similarly, patients who developed CMV colitis leading to early treatment discontinuation in the Phase II OLE or Phase III studies should be excluded.

Patients who experienced or have an ongoing serious infection event (except for those listed below) 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 other 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 specific 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, one serious adverse event of hypersensitivity (Grade 2) has been reported. No anaphylactic, anaphylactoid, or severe hypersensitivity reactions were observed; however, anaphylaxis 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 the Phase II OLE or Phase III studies will be excluded from participation in Part 1 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 the randomized studies may receive their first active etrolizumab dose upon enrolling in the OLE-SM study. After each of these four injections, the patient must be monitored for 60 minutes. Epinephrine must be readily available for immediate use if required to treat

anaphylaxis. Adjunctive medications such as parenteral diphenhydramine and inhaled bronchodilators may be used IN ADDITION to epinephrine if necessary. Resuscitation equipment should also be available. Site personnel must be able to detect and treat such reactions.

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 or 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 9 (Clinical Criteria for Diagnosis Anaphylaxis).

5.1.1.3 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 $will$ be given guidance on reporting injection-site reactions when administering drug at home or after the patient leaves the clinic.

5.1.1.4 Hepatic Effects

Background

Liver toxicity has been reported with other drugs that target α4 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.

5.1.1.5 Malignancies

Background

There have been no reports of malignancy or 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 trial 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 the Phase II OLE or Phase III studies, including AIS, HSIL, or CIN of Grade >1 or colonic dysplasia, are to be excluded from the study.

Monitoring and Management

Investigators should remain vigilant for signs or symptoms of cancer 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, producing the potential for allergic reactions. On the basis of 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 Schedule of Assessments) 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 the Phase II OLE or Phase III studies 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 approximately 5 half-lives (approximately 12 weeks) after final study drug administration.

5.1.2 Risks Associated with Worsening of Ulcerative Colitis

The worsening of UC may result in the use of rescue medications. In severe cases, worsening of UC may lead to hospitalization and, at worst, colectomy.

At any time during the study, patients who have worsening of their UC will be permitted to receive additional therapy with steroids (IV, oral, or topical). Addition of or increases in doses of 5-ASA (oral or topical) and/or immunosuppressants (i.e., AZA, 6-MP, or MTX) will also be allowed if clinically indicated by the Principal Investigator.

Rescue therapy with TNF inhibitors (including TNF inhibitor biosimilars), cyclosporine, tacrolimus, sirolimus, MMF, anti-adhesion molecules, *JAK inhibitors,* natalizumab, vedolizumab, efalizumab, rituximab, other lymphocyte-depleting agents (except AZA and 6-MP), 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.

See Section 4.4.3.3 and Appendix 1 for the schedule of assessments to be performed in the event of worsening of UC, which may lead to an unscheduled visit.

5.2 SAFETY PLAN (PART 2 SAFETY MONITORING)

PML Monitoring Part 2 (SM)

Following the 12-week safety follow-up period in either the Phase II OLE or Phase III controlled studies or in Part 1 (OLE) of the OLE-SM, 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. If there are any signs or symptoms suggestive of PML identified on the subjective checklist during the telephone call, the patient will be asked to come into the clinic for a neurologic examination, including administration of the PML Objective Checklist (see Appendix 3). Any signs or symptoms suggestive of PML or cases of suspected PML (see Appendix 6) should be documented, 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 Sections 5.1 and 5.3.3, and Appendix 7 (PML algorithm). 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. 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; 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 6) will be documented and handled as described in Section 5.1.1.1.1 and Appendix 7 (PML algorithm).

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 5.4.6.8 and 5.4.6.9
- 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., invasive procedures such as biopsies)

5.3.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

All 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). 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 5.4.6.10)
- 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.

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 (see Section 5.4.6.6)

- 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 Sampson's Criteria in Appendix 9)

  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 7 PML algorithm and Section 5.1.1.1.1, above)

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 4.3.3.3).

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 the Phase II OLE or Phase III controlled studies will be stated unresolved in those studies and reopened in Study GA28951. The adverse event will be reported in Study GA28951 with the start date and adverse event term identical to those in the parent study (i.e., the Phase II OLE study or a Phase III controlled study). The severity (NCI CTCAE grade) should be evaluated by the investigator at the start of Part I (OLE) and recorded in the "AE initial NCI CTCAE grade" field of the Adverse Event eCRF for Study GA28951. The most extreme NCI CTCAE grade for the event should also be recorded, taking into account the severity of the event since it was first reported during the parent study.

Adverse events reported as ongoing at the end of Part 1 (OLE) (i.e., the end of the 12-week safety follow-up) will be recorded as unresolved.

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), investigators are not required to actively monitor patients for adverse events after the patient completes the 12-week safety follow-up in Part 1 (OLE). However, if they become aware of any serious adverse events that are believed to be related to prior study drug treatment, these should be reported to the sponsor (see Section 5.7). 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. The investigator is not required to actively monitor patients for other adverse events in Part 2 (SM); however, if he or she becomes aware of any other non-PML serious adverse events that are believed to be related to any prior study drug treatment, these should be reported to the Sponsor.

The investigator should report such events directly to Roche or its designee either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting form with use of the fax number or email 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 (Version 4.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 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 4). 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 re-introduction 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 4 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	Adverse events will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 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.

5.4.6.1 Diagnosis versus Signs and Symptoms

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 separately 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.

Other Adverse Events

For adverse events other than injection-site reactions, 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.

5.4.6.2 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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.

5.4.6.3 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 (NCI CTCAE grade) of the event should be recorded at the time the event is first reported during Study GA28951. If a persistent adverse event becomes more severe, the most extreme NCI CTCAE grade should also be recorded on the Adverse Event eCRF. For adverse events reported as ongoing at the end of a parent study (i.e., the Phase II OLE study or a Phase III controlled study), the severity (NCI CTCAE grade) should be evaluated by the investigator at the start of Part 1 (OLE) and recorded in the "AE initial NCI CTCAE grade" field of the Adverse Event eCRF for Study GA28951. The most extreme NCI CTCAE grade for the event should also be recorded, taking into account the severity of the event since it was first reported during the parent study.

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 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 separately on the Adverse Event eCRF.

5.4.6.4 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:

- 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
- 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 cholecystitis), only the diagnosis (i.e., cholecystitis) 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 only be recorded once on the Adverse Event eCRF (see Section 5.4.6.3 for details on recording persistent adverse events).

5.4.6.5 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:

- 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
- Clinically significant in the investigator’s judgment

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.4.6.3 for details on recording persistent adverse events).

5.4.6.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.4.6.4) 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).

5.4.6.7 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 UC.

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

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

Part 2 (SM)

If the investigator is made aware of an event of death, it should be reported directly to the Sponsor either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.6.8 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 the Phase II OLE or Phase III studies will be stated unresolved in those studies and reopened in Study GA28951.

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").

5.4.6.9 Lack of Efficacy or Worsening of Ulcerative Colitis

Medical occurrences or symptoms of deterioration that are anticipated as part of UC 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 UC on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated ulcerative colitis" or "worsening of ulcerative colitis").

5.4.6.10 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.

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

- 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.

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

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

5.4.6.11 Adverse Event Associated with 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 error in administration of study drug is not itself an adverse event, unless it results in an adverse event.

Any study drug overdose or error in administration of study drug (e.g., dosing outside of the allowed window and injection without completion of full volume administration) should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or error in administration of study drug (e.g., dosing outside of the allowed window and injection without completion of full volume administration) 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).

5.4.6.12 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. *Sites are not expected to review the PRO data for adverse events.*

5.5 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR DURING PART 1 AND PART 2

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 further details)
- Adverse events of special interest (see Section 5.5.2 for further details)
- Pregnancies (see Section 5.5.3 for further 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 IRB/EC.

5.5.1 Emergency Medical Contacts

Medical Monitor Contact Information

Primary Contact

Medical Monitor: [redacted] M.B., Ch.B.
Primary: [redacted]
Secondary: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the $IQVIA$ Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with an $IQVIA$ 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 EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Part 2 (OLE)

Reports of non-PML serious adverse events, that the investigator becomes aware of and believes to be related to prior study drug treatment will be reported via a direct report to the Sponsor either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

Instructions for reporting post-study adverse events are provided in Section 5.7.

5.5.3 Reporting Requirements for Pregnancies

5.5.3.1 Pregnancies in Female Patients

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.

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), 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 exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.5.2).

5.5.4 Reporting Requirements for Medical Device Complaints

See Section 4.3.3.3 for reporting requirements for medical devices.

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

5.7 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) 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), investigators are not required to actively monitor patients for adverse events after the end of the 12-week safety follow-up period; however, if he or she becomes aware of any serious adverse events that are believed to be related to prior study drug treatment, these 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 emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to the 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)

Post-study adverse event information for Part 2 will be reported the same as for patients in Part 1 who do not enter Part 2 (SM) (see Section 5.7.1).

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 with use of 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 Investigational

New Drug (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’)."

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Because of the non-comparative character of the study, no statistical tests are planned. Efficacy in Part 1 will be assessed by change from baseline in pMCS and proportion of patients achieving pMCS remission. Additionally, remission and endoscopic remission by MCS at Week 108 will be summarized. All efficacy parameters will be summarized descriptively. Demographic and baseline characteristics such as age, sex, race, region, use of corticosteroids and immunosuppressants, duration of disease, and pMCS will be summarized by use of descriptive statistics.

Further analysis details for Part 1 and Part 2 of the study will be provided in the Statistical Analysis Plan.

6.1 NUMBER OF PATIENTS

The maximum number of patients enrolled in the OLE-SM study is approximately *2100* (i.e., all patients enrolled in the Phase II OLE protocol and the five UC Phase III protocols). No formal sample size calculations were performed.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enrolled in Part 1 and Part 2 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. The data will also be summarized by origin of the patient (i.e., by original Phase II OLE protocol or Phase III controlled protocol).

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 urinalysis), 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. Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade.

Analyses will be performed for:

- Systemic hypersensitivity events

  Specific analyses will be performed for anaphylactic reactions with use of the anaphylactic reaction Sampson's criteria (see Appendix 9).
- 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, 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 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 with use of 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 will be collected electronically through use of electronic devices provided by an electronic patient-reported outcome (ePRO) vendor. The electronic device, e-diary, is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with 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 patient-reported outcomes [PRO]), 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. 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 such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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 MCS (with the exception of endoscopy data) and pMCS symptom data.

A central laboratory (i.e., Roche or a vendor) 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 and to randomize patients to study drug.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

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

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

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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

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 Weeks, Starting at Day 1 of Week 0 (± 3 days)				Clinic Visit at Every 12 Weeks, Starting at Day 1 of Week 0 (± 3 days)	Clinic Visit at Every 48 Weeks, Starting at Day 1 of Week 0 (± 7 days)	Clinic Visit at Week 108 (–14 days)	Unscheduled Visit [c]	Early Withdrawal from Treatment Visit [d]
	0 [a, b]	4	8	12					
Informed consent	x								
Review eligibility criteria	x								
Vital signs (BP, pulse rate)	x			x	x	x	x		x
ECG	x					x			x
Concomitant medications	x	x	x	x	x	x	x	x	x
Adverse events [e]	x	x	x	x	x	x	x	x	x
Limited/symptom driven physical examination, including GI	x	x		x	x	x	x	x [c]	x
PML neurologic examination [f]	x			x	x	x	x	x [c]	x
Partial Mayo Clinic Score (pMCS) [g]		x	x	x	x	x		x	x [h]
Mayo Clinic Score (MCS) [i]							x		x [j]

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

	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 Weeks, Starting at Day 1 of Week 0 (± 3 days)				Clinic Visit at Every 12 Weeks, Starting at Day 1 of Week 0 (± 3 days)	Clinic Visit at Every 48 Weeks, Starting at Day 1 of Week 0 (± 7 days)	Clinic Visit at Week 108 (–14 days)	Unscheduled Visit [c]	Early Withdrawal from Treatment Visit [d]
Part 1 (OLE)	0 [a, b]	4	8	12					
Flexible sigmoidoscopy (or colonoscopy, IF REQUIRED) with colonic biopsies [k]							x [l]		x [j]
Pregnancy test [m]	x	x	x	x	x	x	x		x
Hematology [n]	x			x	x	x	x	x [c]	x [h]
Chemistry [o]	x			x	x	x	x	x [c]	x [h]
Hepatitis B DNA [p]	x			x	x	x	x		
Serum (CRP)	x					x		x [c]	x [h]
Etrolizumab administration	x	x	x	x	x	x	x		
Etrolizumab PK sample (serum) [q]	x			x		x	x		
Anti-therapeutic antibody sample (serum) [q]	x			x		x	x	x [c]	x [h]

ATA = anti-therapeutic antibody; BP = blood pressure; CRP = C-reactive protein; ECG = electrocardiogram; eCRF = electronic case report form; GI = gastrointestinal; LFT = liver function test; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy.

Note: All assessments and blood draws are to be conducted prior study medication administration. All visit intervals based on Day 1 of Week 0.

[a] Day 1 of Week 0.

[b] Week 0 procedures and laboratory assessments that have been collected as part of the final visit for the Phase II OLE and Phase III controlled studies do not need to be repeated, with the exception of ATAs, which must be collected at Week 0 if the Week 0 visit occurs >7 days after the final visit of the Phase II OLE or Phase III controlled study.

[c] 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). pMCS to be conducted if patient experiences disease worsening and if stool frequency and rectal bleeding are available in the e-diary. Assessments corresponding to items noted in this column should be recorded on the eCRF.

[d] 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.

[e] 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.

[f] PML neurologic examination consists of the PML Subjective Checklist and the PML Objective Checklist. Administer before other assessments, as per Appendix 5.

[g] Rectal bleeding assessment + stool frequency assessment + physician's global assessment. Patients are to complete the e-diary for the stool frequency and rectal bleeding score daily during the initial 12 weeks for the pMCS. After the Week 12 visit, the stool frequency and rectal bleeding components of the pMCS (performed every 12 weeks) and MCS (for the Week 108 assessment) will be collected by the patient daily for 4 weeks prior to clinic visit. The Week 0 pMCS score is derived from data collected as part of the final visit from the Phase II OLE or the Phase III controlled studies.

[h] Not required if unscheduled visit leads to withdrawal and assessment previously conducted at unscheduled visit.

[i] Endoscopy, rectal bleeding assessment, stool frequency assessment, Physician's Global Assessment. Patients are to complete the e-diary on a daily basis for 3 weeks prior to clinic visit for the stool frequency and rectal bleeding score (for MCS).

[j] If early withdrawal visit is prior to Week 108 visit, then flexible sigmoidoscopy/colonoscopy with biopsies and full MCS should be conducted if e-diary data are available. If early withdrawal visit is after the Week 108 visit, then flexible sigmoidoscopy/colonoscopy with biopsies should not be conducted, but pMCS should be conducted if e-diary data are available.

[k] The flexible sigmoidoscopy/colonoscopy should be conducted on the day of the clinic visit or within 14 days prior to the clinic visit.

[l] Each patient entered into the study will have one paired colonic biopsy sample (2 samples) taken during flexible sigmoidoscopy/colonoscopy procedure at Week 108 and placed in formalin and then paraffin embedded. The paired biopsy sample should be taken from the worst affected segment visualized (up to and including the descending colon). For patients without inflammation on endoscopy, the paired biopsy sample should be taken from the worst affected area visualized in the last endoscopy (up to and including the descending colon). In RCR consenting patients only, any residual or not entirely consumed colonic biopsy sample obtained at Week 108 will be stored in the RCR and will be destroyed no later than 15 years after the date of final closure of the associated clinical database. Original biopsy location and endoscopic depth should be clearly indicated.

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

[m] 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. Patient is to report the pregnancy test result via e-diary. Patients must be 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.

[n] 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.

[o] 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.

[p] Only enrolled patients who were hepatitis B core antibody positive in the Phase III study of origin should have hepatitis B DNA measured at these timepoints.

[q] Samples are to be collected prior to dose administration at all timepoints indicated (see footnote ''b'') 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 etrolizumab PK measurement and ATAs should be drawn and sent to the central laboratory. ATA samples may also be utilized for exploratory PD assessments or assessment of drug concentrations.

Appendix 2
12-Week Safety Follow-Up (Part 1, OLE)
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	
Partial physical examination		x	
PK sampling (serum)		x	
Anti-therapeutic antibody sample (serum) [e]		x	
PML neurologic examination [f]		x	

ATA = anti-therapeutic antibody; PK = pharmacokinetic; PML = progressive multifocal leukoencephalopathy.

[a] Week 6 study assessments are to be made by telephone call 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 termination 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 etrolizumab PK and ATAs should be drawn and sent to the central laboratory. ATA samples may be used for PK and/or exploratory PD assessments.

[f] PML neurologic examination consists of the PML Subjective Checklist and the PML Objective Checklist. Administer before other assessments as per Appendix 5.

Appendix 3
Extended Progressive Multifocal Leukoencephalopathy Safety Monitoring (Part 2, SM) 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 Symptom-Driven Unscheduled Telephone Call [b] OR Early Termination [c]	Unscheduled Visit [d]
PML Subjective Checklist (telephone only)	x	
PML Objective Checklist [e]		x
Adverse event reporting to the Sponsor [f]	x	x

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

Note: The extended PML monitoring period is to be conducted for patients completing or discontinuing from OLE-SM Part 1 AND for patients entering OLE-SM Part 2 from blinded Phase III studies after completion of 12-week safety follow-up in the Phase III studies AND for patients entering OLE-SM Part 2 from the Phase II OLE study (GA27927).

[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). The extended PML monitoring period telephone calls 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] Unscheduled telephone call represents a call that is not as per Schedule of Assessments and it is symptom driven.

[c] 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).

[d] Unscheduled visit represents a visit that is not as per Schedule of Assessments and it is symptom driven.

[e] If there are any signs or symptoms suggestive of PML identified on the subjective checklist during the telephone call, the patient will be asked to come into the clinic for a neurologic examination, including administration of the PML Objective Checklist.

[f] Investigators are not required to actively monitor patients for adverse events; however, if he or she becomes aware of any other serious adverse events that are believed to be related to prior study drug treatment, these should be reported directly to Roche or its designee either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form with use of the fax number or email address provided to the investigators. The investigator may become aware of such events at these timepoints or via other means, but the data are not to be collected routinely.

Appendix 4
Childbearing Potential, Pregnancy Testing, and Contraception

All women of childbearing potential (including those who have had a tubal ligation) will have 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.

All female 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
- 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 because friction between the two can result in either product failing)

Appendix 4
Childbearing Potential, Pregnancy Testing, and Contraception (cont.)

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, and postovulation methods) and withdrawal are not acceptable methods of contraception.

Appendix 5
Mayo Clinic Score Measurement

Mayo Clinic Score (MCS) is a composite endpoint with four components. The score ranges from 0 to 12 with higher scores indicating more severe disease.

The Mayo Clinic components are as follows:

STOOL FREQUENCY

0 = Normal number of stools for this patient

1 = 1 to 2 stools more than normal

2 = 3 to 4 more stools than normal

3 = 5 or more stools than normal

Subscore 0–3

RECTAL BLEEDING

0 = No blood in stool

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passed

Subscore 0–3

ENDOSCOPY

0 = Normal or inactive disease

1 = Mild disease (erythema, decreased vascular pattern, mild friability)

2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)

3 = Severe disease (spontaneous bleeding, ulceration)

Subscore 0–3

PHYSICIAN'S GLOBAL ASSESSMENT

0 = Normal (Subscores are 0)

1 = Mild disease (Subscores are mostly 1s)

2 = Moderate disease (Subscores are 1 to 2)

3 = Severe disease (Subscores are 2 to 3)

Subscore 0–3

Appendix 5
Mayo Clinic Score Measurement (cont.)

DATA COLLECTION REQUIREMENTS

Data will be collected on e-diary and other electronic media; during conversion to these media the format of the questions may change.

- A CRITICAL DATA POINT TAKEN AT BASELINE FROM THE PREVIOUS STUDY IS THE PATIENT'S NORMAL NUMBER OF STOOLS. This is defined as the number of stool passed when a patient is in remission/not in flare. This is to be taken from the most recent available data in the patient's medical notes or taken during patient interview at screening in the Phase II and Phase III controlled study.
- Normal number of stools is to be rounded up (e.g., normal number of stools = 1–2 would be rounded to 2).
- The NORMAL number of stools is to be recorded on the e-diary and made visible to the patient to assist with their scoring relative to this number.

  NOTE: Data recorded during bowel preparation procedures and day of endoscopy are to be ignored (bowel preparation and endoscopy procedure days are to be loaded onto the e-diary by the patient and excluded from the MCS calculation).

1. Stool frequency

- Stool frequency is to be recorded during the study in the e-diary. E-diary entries are to be made daily during the initial 12 weeks. After the 12-week visit, the stool frequency component of the partial Mayo Clinic Score (pMCS; performed every 12 weeks) and MCS (for the Week 108 assessment) will be collected daily for 4 weeks prior to clinic visit.
- The stool frequency is to be compared with the patient's normal stool frequency and is entered as a score between 0 and 3 (see 1 above) (e.g., a patient normally has 1 stool per day and today has 4 stools; therefore, the patient has 3 stools more than "normal," which yields a value of 2 for that day).
- The stool frequency will be defined as the passage of solid or liquid fecal material. Episodes of incontinence count. A non-productive trip to the bathroom or the simple passage of gas DO NOT COUNT as stool.
- The stool frequency value for endpoint assessment will be calculated as the average (rounded to the nearest integer) from the three most recent stool frequency scores that were entered in the e-diary prior to the clinic visit (and prior to endoscopy) and prior to the days devoted to bowel preparation and endoscopy.

2. Rectal bleeding

- Rectal bleeding is to be recorded during the study in the e-diary. E-diary entries are to be made daily during the initial 12 weeks. After the 12-week visit, the rectal bleeding component of the pMCS (performed every 12 weeks) and MCS (for the Week 108 assessment) will be collected daily for 4 weeks prior to clinic visit.

Appendix 5
Mayo Clinic Score Measurement (cont.)

- The rectal bleeding score is to be categorized from 0–3 according to the definition given in 2 above.
- The rectal bleeding value for endpoint assessment will be determined by the worst of the three most recent rectal bleeding scores that were entered in the e-diary prior to the clinic visit and prior to the days devoted to bowel preparation and endoscopy.
- Patients are to be instructed to ignore any blood which is caused by menstruation or hemorrhoids.

3. Endoscopy Subscore

- This score is provided by the local endoscopy reading as a subscore of 0 to 3.
- Findings on endoscopy will be documented by photographic evidence.
- The score will be based upon the worst affected segment visualized (up to and including the descending colon).

4. Physician's Global Assessment

The physician's global assessment WILL:

- Be based on the patient's overall status
- Reflect how the patient is doing at present. Assessment SHOULD NOT reflect past disease severity or complexity or the number/kinds of medicines the patient is receiving

Be based on the:

- Rectal bleeding score, stool frequency score, and endoscopic evaluation
- Patient's recollection of abdominal discomfort and general sense of well-being
- Patient's performance status, fecal incontinence, and mood
- Physician's observations and physical exam findings
- Reflect disease activity NOT disease severity (e.g., do not automatically give a high PGA to patients with pancolitis or severe/complicated disease or patients requiring multiple medications

The physician's global assessment will be provided by the Investigator as a score of 0 to 3 and entered into the tablet.

Appendix 5
Mayo Clinic Score Measurement (cont.)

CALCULATION OF THE MAYO CLINIC SCORE

1. Mayo Clinic Score assessment will be performed at Week 108 and at early withdrawal if the early withdrawal visit occurs prior to Week 108, as outlined in the protocol Schedule of Assessments.
2. MCS Remission

   MCS ≤ 2, a rectal bleeding score of 0, physician's global assessment of 0–1, stool frequency subscore of 0–1, endoscopy score of 0–1
3. Endoscopic remission

   Endoscopic subscore $= 0$

PARTIAL MAYO CLINIC SCORE

The pMCS is identical to the MCS BUT EXCLUDES THE ENDOSCOPY SUBSCORE

- Timepoints for pMCS can be found in the protocol Schedule of Assessments
- pMCS is also required if a patient experiences disease worsening

E-DIARY MALFUNCTION OR LOSS

The help desk for the e-diary vendor (CRF Health) should be contacted in the event of e-diary malfunction or loss. Until a working e-diary can be provided to the patient, site staff should, after the e-diary malfunction or loss, retrospectively collect the previous day's stool frequency and rectal bleeding subscores from the patient via telephone interview within the next working day following the e-diary failure or loss. These data will then be transcribed into a data clarification form within CRF Health's TrialManager system for approval.

REFERENCE

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study. N Engl J Med 1987;317:1625–9)

Appendix 6
Worksheet for the PML Neurologic Examination

PML SUBJECTIVE AND OBJECTIVE CHECKLISTS OF NEUROLOGIC ASSESSMENTS TO MONITOR FOR PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IN THE ETROLIZUMAB 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 and Appendix 2). 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 6
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?				• Test visual fields and ocular motility
2. Have you been experiencing any persistent difficulty speaking or having your speech understood by others?				• Casual observation of speech output for dysarthria or aphasia.
3. Have you been experiencing any persistent weakness in an arm or a leg?				• Test for pronator drift (Barre maneuver). • Assess gait. • Test muscle strength *(only if indicated).*
4. Have you noticed yourself regularly bumping into things or having difficulty writing?				• Observe tandem gait and finger to nose.
5. Have you regularly been experiencing difficulty understanding others?				• Test ability to follow serial commands.
6. Have you had persistent problems with your memory or thinking?				• Recall of 3 objects over 1 minute with distraction *(only if indicated).*
7. Have you been experiencing any persistent numbness or other loss of sensation?				• Test sensation side to side with either pinprick or cold *(only if indicated).*

Appendix 6
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 finding
		YES	NO	
1. Visual fields and ocular motility	• **Visual Field Testing** • **Ocular Motility Testing**			
2. Speech	• **Observe the patient's speech output for dysarthria or aphasia.**			
3. Strength	• **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			
4. Coordination	• **Observe tandem gait and finger to nose**			
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."**			
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 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)			

Appendix 6
Worksheet for the PML Neurologic Examination (cont.)

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.
- 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)

Appendix 6
Worksheet for the PML Neurologic Examination (cont.)

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.
- 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.

Appendix 6
Worksheet for the PML Neurologic Examination (cont.)

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.
- 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).

Appendix 6
Worksheet for the PML Neurologic Examination (cont.)

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."

6. Memory and Thinking

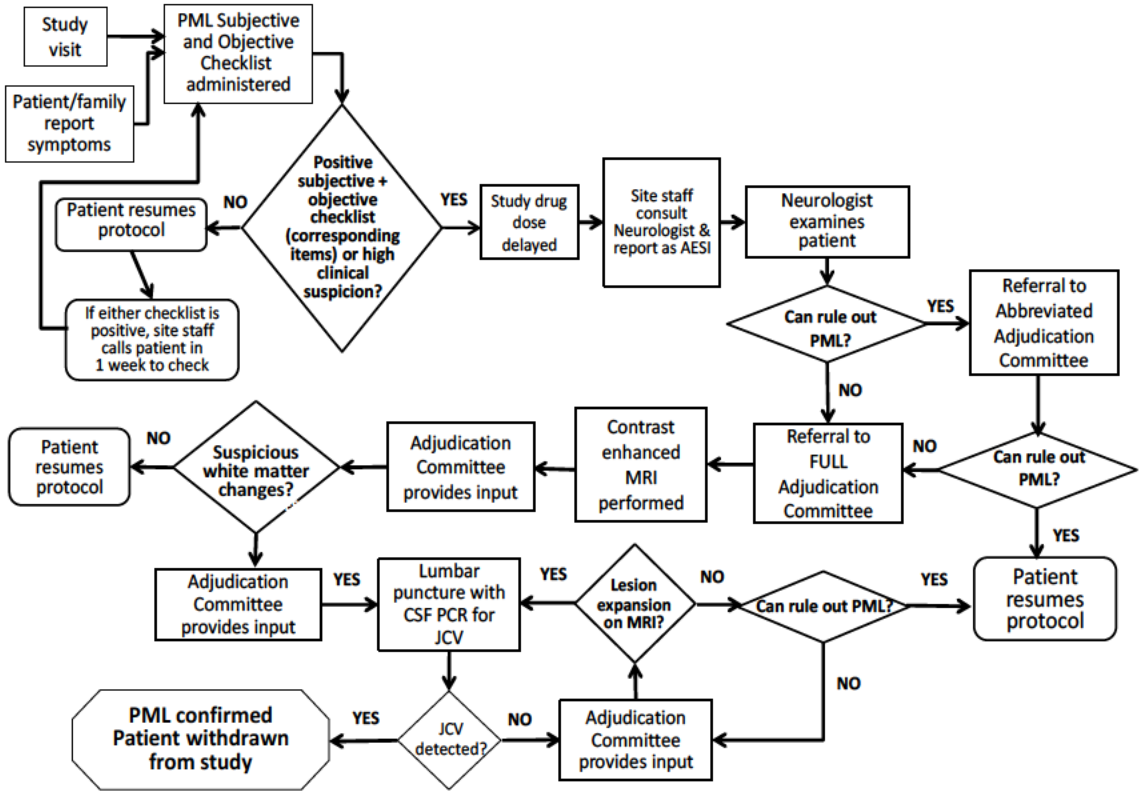
- *(ONLY* if the patient has subjective complaints about their memory or thinking) test the ability of the patient to recall 3 objects over 1 minute with distraction.

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 7
Algorithm for the Evaluation of Progressive Multifocal Leukoencephalopathy

- If there is a positive finding on the PML Subjective or Objective Checklist, this should be appropriately documented.
- 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):
  - **Report as an AESI within 24 hours**
  - **Urgently refer the patient to a neurologist**
  - **Suspend dosing of drug until PML can be ruled out**



Appendix 8
Patient Daily Diary

PATIENT DIARY CARD
FORMAT MAY CHANGE DURING THE SWITCH TO ELECTRONIC FORMAT

PATIENT NUMBER

Monthly Record of Study Medication Injections

Week	Date/Time of Injection dd-mmm-yyyy e.g. 30/Sep/2013 (24 h clock) e.g. 14:00	Location of Injection	Information About Your Injection
0 Day 1	INJECTION 1 Date: __ __/__ __ /__ __ __ __ Time: ___:___ ☐ Injection done at clinic ☐ Injection administered by caregiver	☐ thigh ☐ arm ☐ abdomen	☐ Injection not done ☐ Less than full amount of pre-filled syringe injected ☐ Incorrectly injected medication* ☐ OTHER COMMENTS:
4	INJECTION 2 Date: __ __/__ __ /__ __ __ __ Time: ___:___ ☐ Injection done at clinic ☐ Injection administered by caregiver	☐ thigh ☐ arm ☐ abdomen	☐ Injection not done ☐ Less than full amount of pre-filled syringe injected ☐ Incorrectly injected medication* ☐ OTHER COMMENTS

An incorrectly administered injection is defined as

- an SC injection which was given intermuscularly
- an SC injection was given to a body site that is not allowed per protocol (namely a site other than thigh, arm or abdomen)

If you experience any side effects following your injection please remember to describe these to the study staff the next time you speak with them

RESULT OF PREGNANCY TEST
DATE PREGNANCY TEST CONDUCTED --/---/----
PREGNANCY TEST RESULT: POSITIVE ☐ NEGATIVE ☐ NOT DONE ☐

Appendix 9
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

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[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 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.